REACTIONS OF 4-CHLORO-2,6-DIMETHOXYPYRIMIDINE AND 2-CHLOROTHIAZOLE WITH CARBANION NUCLEOPHILES

by

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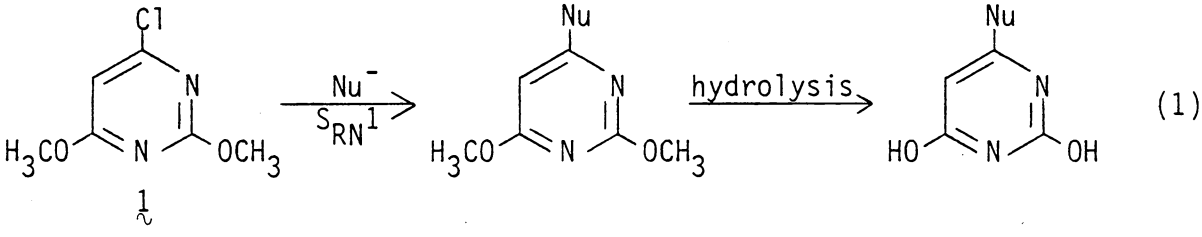
I. INTRODUCTION

This dissertation describes the results of a study of the scope and limitations of $S_{RN}1$ (nucleophilic substitution via a radical-chain process) reactions of 4-chloro-2,6-dimethoxypyrimidine (1) and 2-chlorothiazole (2) with selected carbanion nucleophiles.

Prior to the present work only two reports dealing with $S_{RN}1$ reactions of monohalogenated pyrimidines with carbanion nucleophiles had appeared in the literature.[1,2] Thus, one of our major goals was to extend the knowledge of $S_{RN}1$ reactions involving this biologically important class of heterocycles.[3] We were particularly interested in using 1 as a substrate, since it represents a potentially convenient precursor to 6-substituted uracils as shown in eq 1.



(1)

Only one example of a reaction of 2-chlorothiazole with carbanion nucleophiles[4] and only one report of the behavior of halogenated π-excessive heteroaromatics (2-and 3-bromothiophenes[5]) as substrates in $S_{RN}1$ reactions have appeared in the literature.

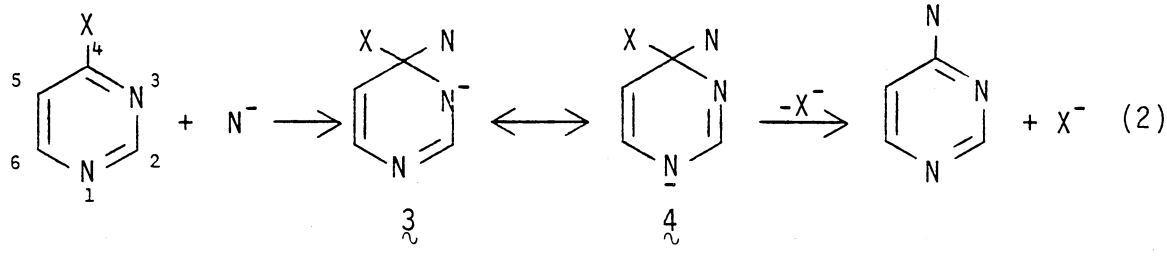
The following historical section constitutes a brief survey of traditional nucleophilic substitutions involving halogenated pyrimidines and thiazoles. This is intended to serve as a background against which the rationale and results of the present investigation may be viewed.

II. HISTORICAL

(A) MECHANISMS FOR NUCLEOPHILIC AROMATIC SUBSTITUTION IN HALOGENATED PYRIMIDINES

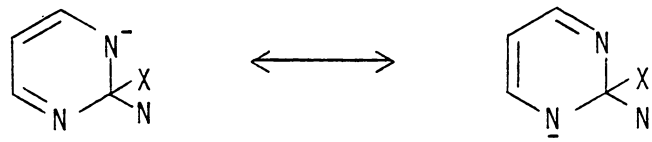
The various mechanisms of nucleophilic substitution for pyrimidines containing appropriate leaving (nucleofugal[6]) groups differ according to the position and nature of the leaving group, the nucleophile, and reaction conditions.

AE_n (Normal Addition-Elimination) Mechanism. Reactions of 2-and 4-halogenopyrimidines with nucleophiles most often proceed via the SnAr, or normal addition-elimination (AE_n), mechanism as shown in eq 2 for a generalized negative nucleophile, N^-, reacting with a 4-halopyrimidine. This reaction pathway involves rate-determining addition of N^- to the



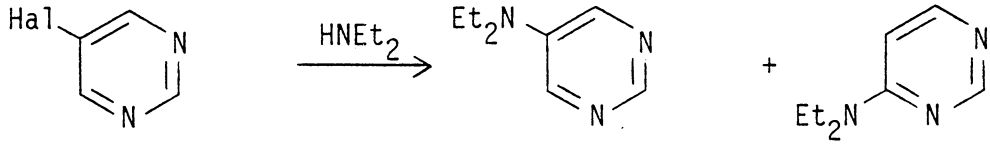
(2)

carbon bearing the nucleofugal[6] halogen to form an intermediate σ-complex, which is stabilized by direct delocalization of negative charge onto the ring nitrogens as illustrated by resonance forms 3 and 4. Elimination of halide ion then completes the substitution process. Similar heteroatom stabilization of σ-complexes obtained from 2-halopyrimidines is illustrated by resonance structures 5 and 6.



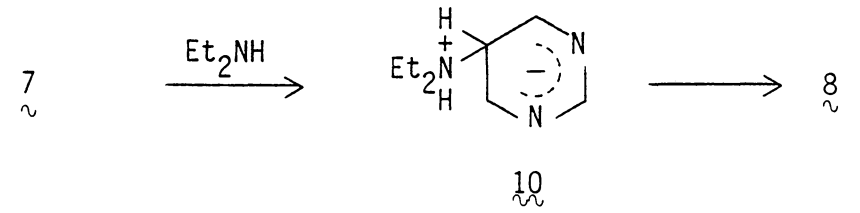
5 ⟷ 6

Since 5-halogenopyrimidines cannot yield analogous N-stabilized complexes, nucleophilic displacements of 5-substituents take place more slowly than substitution at positions 2 and 4. In addition, such reactions are often more mechanistically complex. For example, reaction of 5-halogenopyrimidines (7) (halogen = Cl or Br) with diethylamine at 130°C formed ipso substitution product 8 and cine product 9 (eq 3).[7,8,9] The ratio of 8 to 9 varied with the halogen (82:18 for



7 → 8 + 9 (3)

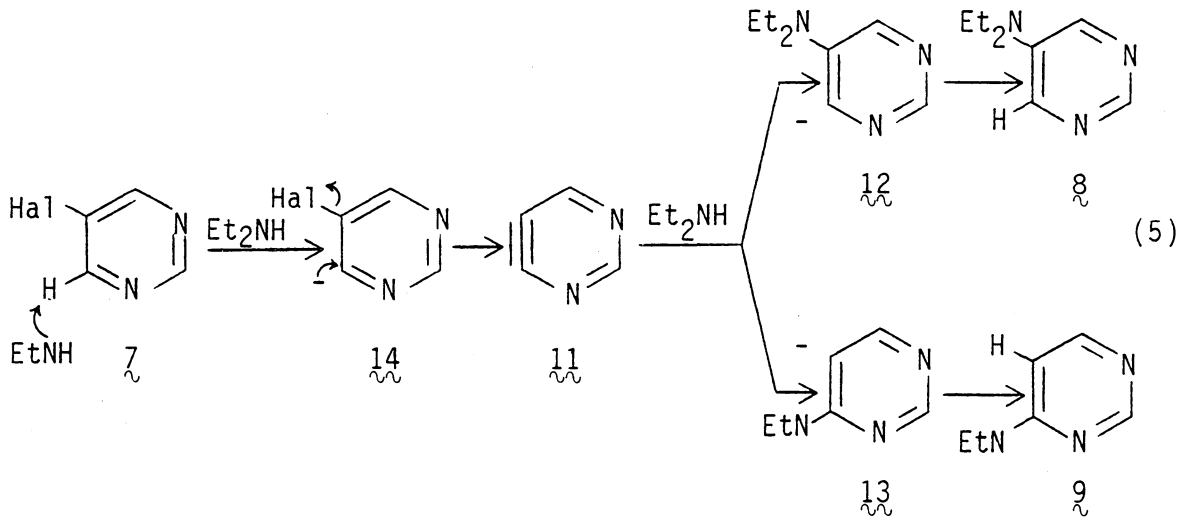
Hal=Cl and 40:60 for Hal=Br). Formation of ipso product 8 implicates an SnAr mechanism involving σ-complex 10 (eq 4).



(4)

Hetaryne (EA) Mechanism. Formation of cine substitution product 9 as shown in eq 3 provides evidence that a hetaryne mechanism competes with direct AE_n displacement of halide.

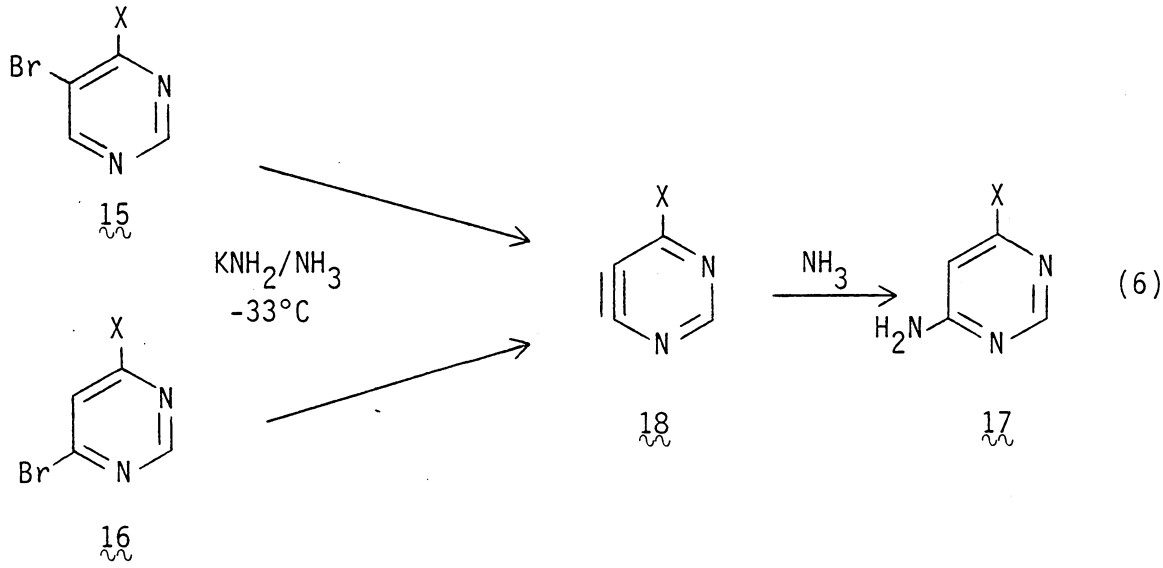
In this elimination-addition process, the nucleophile abstracts the hydrogen adjacent to the halogen leaving group. Elimination of halide then can occur to form 4,5-pyrimidyne 11 (eq 5). The hetaryne



(5)

intermediate (11) can now add Et_2NH to form aryl anions 12 and 13 . followed by protonation, which results in overall substitution of the leaving group. The participation of the EA mechanism in the reaction of bromopyrimidine 7 with diethylamine was deduced from interception of hetaryne 11 by aniline to form 4- and 5-anilino derivatives, and by complete absence of the cine substitution product, 9, when ethanol was present in the reaction mixture. Ethanol presumably protonates intermediate 14.

In 1964 and 1968, van der Plas and coworkers studied the reactions of 5-bromo-4-X-pyrimidine 15 (X = $-C_6H_5$, $-OCH_3$, -OH) and 4-bromo-6-X-pyrimidine 16 (X = C_6H_5, t-butyl) with potassium amide in liquid ammonia[10,11,12] (eq 6). For both the 4- and 5-bromopyrimidines

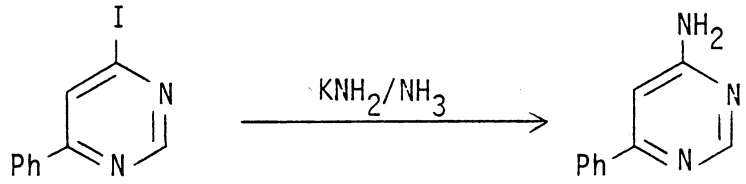


(6)

the sole product formed was the 6-amino-4-X-pyrimidine (16). When substrates 15 and 16 containing deuterium at the 6- and 5-position, respectively, were treated with potassium amide in liquid ammonia the resulting product, 17, contained no deuterium. Thus, these investigators

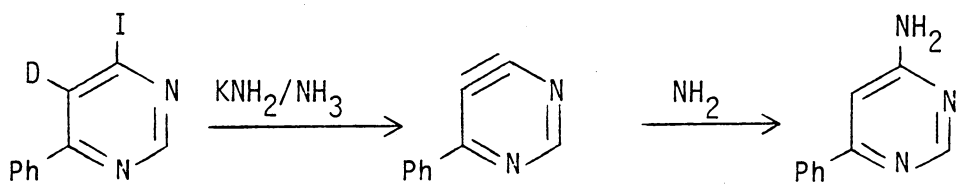
concluded that 17 was formed from 15 and 16 via the EA mechanism involving common hetaryne 18.

In 1972, Valk and van der Plas found that 4-iodo-6-phenylpyrimidine (19) reacted with potassium amide in liquid ammonia to yield 4-amino-6-phenylpyrimidine (20) via the EA mechanism (eq 7).[13] Evidence for this mechanism was obtained by allowing 5-deutero-4-iodo-6-phenylpyrimidine



19 20 (7)

(21) to react with potassium amide in liquid ammonia (eq 8).

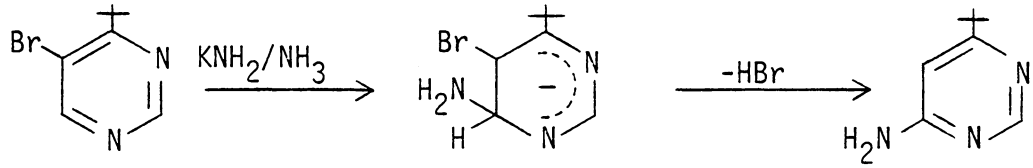


21 23 22 (8)

Substitution product 22 was found to contain no deuterium, thus supporting the intermediacy of aryne 23 in the formation of 22 from 21.

AE_a (Abnormal Addition-Elimination) Mechanism. As mentioned in the previous section, van der Plas and coworkers had concluded that the reaction of 4-substituted 5-bromopyrimidine (15) with potassium amide in

liquid ammonia to yield 17 occurred via the aryne mechanism. However, in 1974, 1977 and 1978 these investigators demonstrated that formation of rearranged (cine) product took place through an abnormal addition-elimination (AE_a) mechanism as shown in eq 9.[14,15,16] Evidence

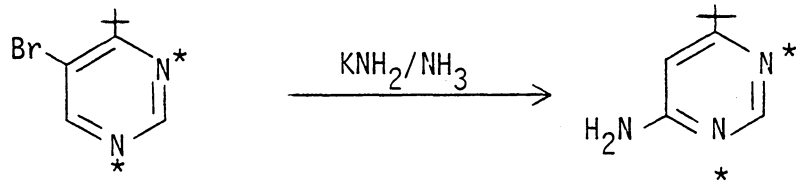


(9)

24 25 26

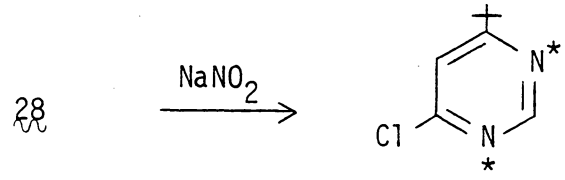
for this was based on the discovery that ^1H NMR studies from the reaction of 5-bromo-4-t-butyl-pyrimidine (24) with potassium amide in liquid ammonia showed the existence of σ-adduct 25.[14] The absence of deuterium in the final product 26 when substrate 24 containing deuterium at C-6 was treated with potassium amide in liquid ammonia results from elimination of DBr from a deuterated intermediate analogous to 25.

S_N(ANRORC) Mechanism. In addition to the AE_a mechanism that was shown to be operating in reactions of 5-bromo-4-substituted pyrimidines with potassium amide in liquid ammonia, a ring-opening, ring-closure mechanism was also demonstrated to be responsible for the formation of 26.[15,16] Thus, ^{15}N-labelled 5-bromo-4-t-butylpyrimidine (27) containing 6% excess ^{15}N distributed equally between the two ring nitrogens was allowed to react with potassium amide in liquid ammonia at -33°C for 24 h to form 28 (eq 10). Compound 28 was then diazotized to yield 29 (eq 11)



27 28 (10)

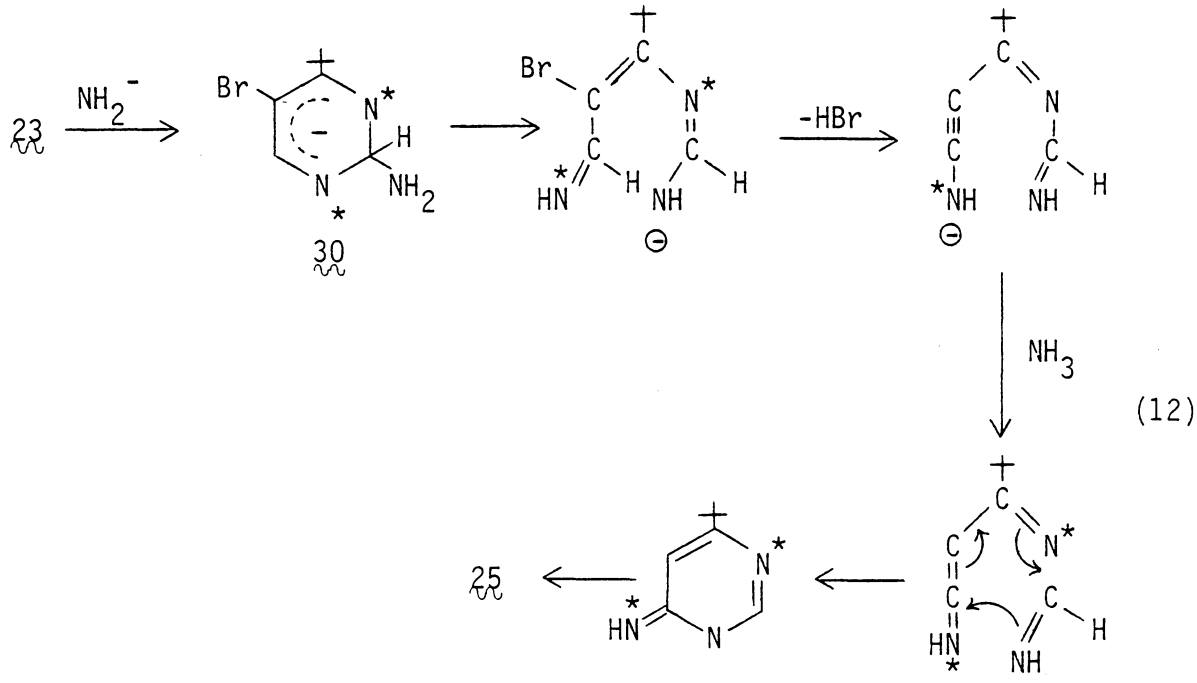
and the amount of excess ^{15}N-label in compound 29 was shown to be approximately one-half of that present in 27 and 28; thus, showing that the



29 (11)

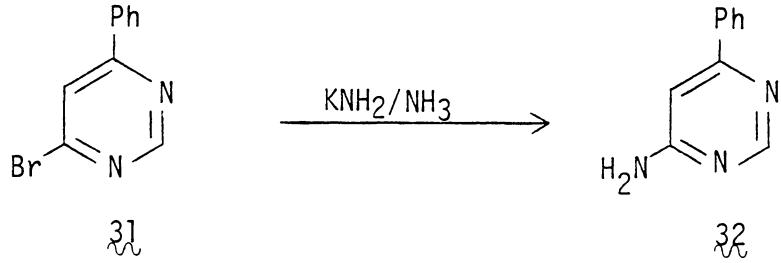
formation of 28 had occurred by the S_N(ANRORC) (addition of the nucleophile, ring opening ring closing) mechanism. In this mechanism, cleavage of the N(1)-C(2) bond occurs in the C(2) σ-adduct (30) followed by elimination of hydrogen bromide and recyclization (eq 12).

Additional work was conducted by van der Plas and coworkers on the reactions of 4-bromo-6-substituted pyrimidine (16) with potassium amide in liquid ammonia.[13,17] They had originally reported that these reactions yielded compound 17 via the aryne mechanism.[11] As in the reactions of 5-bromo-4-substituted pyrimidines (15) with potassium amide



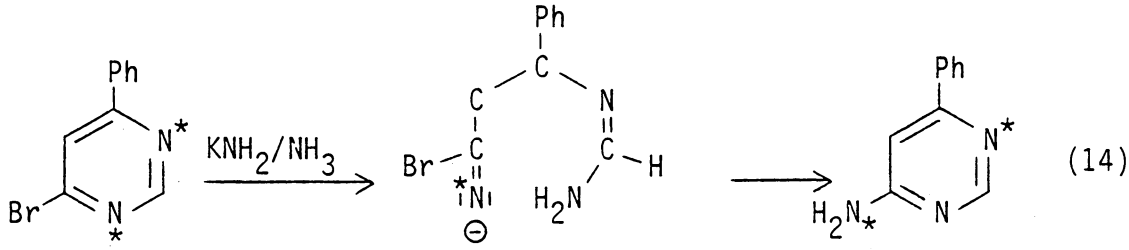
(12)

in liquid ammonia,[11] ^{15}N-labeling experiments showed that the reactions of 4-bromo-6-substituted pyrimidines with potassium amide in liquid ammonia also proceed by the S_N(ANRORC) mechanism.[17] Using ^{15}N-labeling, Valk and van der Plas showed that conversion of 4-bromo-6-phenylpyrimidine (31) into 4-amino-6-phenylpyrimidine (32) with potassium amide in liquid ammonia involved initial attack of amide ion at position 2 of 31 followed by ring opening and ring closure to give the 4-amino product 32 (eq 13).[13] If the reaction of 6-phenyl



(13)

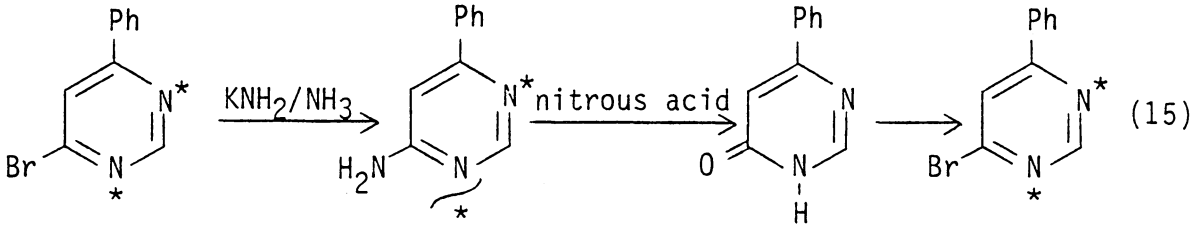
derivative of 1(3)-^{15}N-labelled 4-bromopyrimidine (33) with potassium amide in liquid ammonia proceeded by the S_N(ANRORC) mechanism to give 34, the amount of the ^{15}N-label in the pyrimidine ring should be approximately one-half of that in 33 (eq 14). To gain support for this, 33



(14)

33 34

which contained 6.0% excess ^{15}N was treated with potassium amide in liquid ammonia to yield the 4-aminopyrimidine 35 (eq 15). The

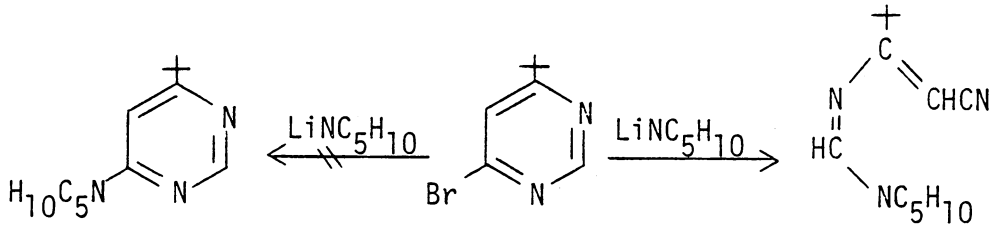


(15)

33 35 36 37

4-aminopyrimidine was then treated with concentrated nitrous acid followed by treatment with phosphoryl bromide to give 37. By mass-spectrometric determination, compounds 35 and 37 were found to contain 6.0% and 3.5% of excess ^{15}N, respectively, thus showing that the formation of 32 from 31 had occurred by the S_N(ANRORC) mechanism.[17]

In another study by van der Plas, 4-bromo-6-t-butylpyrimidine (16) was reacted with lithium piperidide in piperidine/ether.[18] From this reaction, no 6-piperidino-4-t-butylpyrimidine (38) was obtained. Instead, 2-aza-4-cyano-1-piperidino-1,3-butadiene (39) was the only product isolated (eq 16). Instead of displacing bromine, the lithium

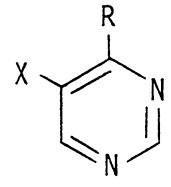


38 16 39 (16)

piperidide had attacked position 2 of the pyrimidine ring, followed by ring opening with loss of bromide ion.

A detailed description of the S_N(ANRORC) mechanism may be found in the 1978 review by van der Plas.[19]

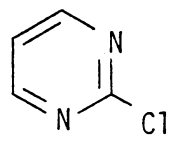
$S_{RN}1$ Mechanism. Three studies have appeared in the literature dealing with the $S_{RN}1$ reaction of pyrimidines 40, 41, and 42 with carbanion nucleophiles.[1,2,20] The first by Oostveen and van der Plas dealt with the reactivity of 4-substituted-5-halogenopyrimidines (40) towards the enolates of acetone, acetophenone, and pinacolone.[1] The second study described reactions of 2-chloropyrimidine (41) and 4-chloro-2,6-dimethoxypyrimidine (1) with the enolates of acetone, pinacolone, and diisopropyl ketone.[2] The most recent study by Wolfe



R = C_6H_5
X = Br,Cl

40

and coworkers dealt with the reaction of 2,6-dichloropyrimidine (42) with the carbanion of phenylacetonitrile.[20]



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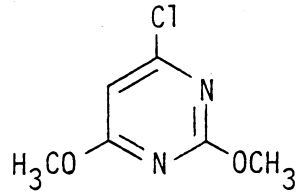

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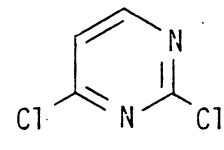
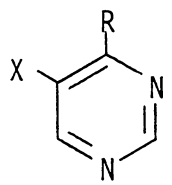
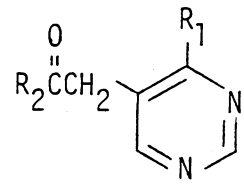


42

Oostveen and van der Plas found that irradiation of 5-bromo-4-phenylpyrimidine (40a) with the enolate of acetone with near ultraviolet light in liquid ammonia for 75 min produced 5-acetonyl-4-phenylpyrimidine 43a in 30% yield. 5-Chloro-4-phenylpyrimidine (40b) showed essentially the same reaction behavior. When identical experiments were conducted in the presence of 10 mol % of di-tert-butyl nitroxide (DTBN), a known radical-trapping agent[21], no reaction occurred.





40a: R = C_6H_5, X = Br

40b: R = C_6H_5, X = Cl

43a: R_1 = C_6H_5, R_2 = CH_3

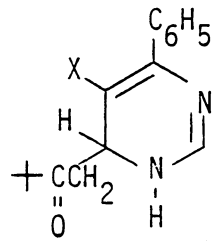
43b: R_1 = C_6H_5, R_2 = C_6H_5

43c: R_1 = C_6H_5, R_2 = t-Bu

The substitution product, 5-phenacyl-4-phenylpyrimidine (43b), was obtained in 60% yield by photostimulated reaction of 40a with the enolate of acetophenone. This reaction failed to give 40b when it was conducted in the presence of 10 mol % of DTBN.

The enolate ion of pinacolone reacted differently towards 40a. With no photostimulation, 5-(2-oxo-3,3-dimethylbutyl)-4-phenylpyrimidine (43c) and 5-X-1,6-dihydro-6-(2-oxo-3,3-dimethylbutyl)-4-phenylpyrimidine (44a), or (44b) were isolated in yields of 40, 60, and 32%, respectively. Irradiating 40a in the presence of pinacolone enolate increased the yield of 43c to 65% at the expense of 44a.

In 1981, Wolfe and coworkers found that the photostimulated reaction of potassioacetone with 2-chloropyrimidine (41) for 15 min produced the substitution product 45 (15%), 2-aminopyrimidine (46), and intractable polymeric material (Scheme I).[2] When 41 was reacted under photostimulation in the presence of the potassium enolate of pinacolone,



44a: X = Br

44b: X = Cl

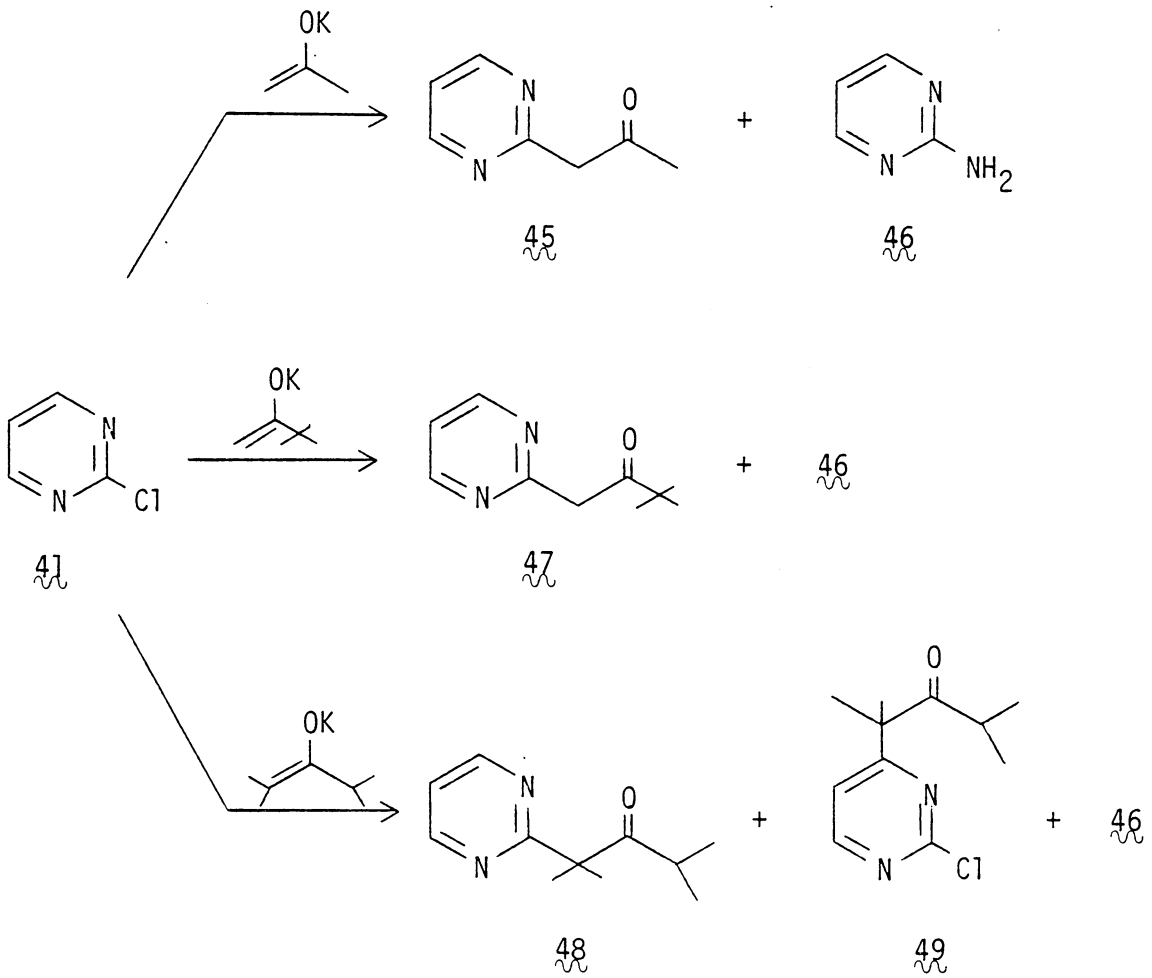
substitution product 47 was formed in 32% yield, along with 46 (4%) and uncharacterized resinous material. Irradiating 41 and the potassio salt of diisopropyl ketone for 15 min yielded ketone 48 in 88% yield.

When each of the above reactions were conducted without illumination, only trace amounts of each of the substitution products (45, 47, and 48) were obtained. For the acetone enolate, 2-aminopyrimidine (46) (88%) was the major product. Pinacolone enolate produced a mixture of unstable products, which polymerized during chromatography. Diisopropyl ketone yielded 50% of recovered 41, plus ketone 49 (17%).

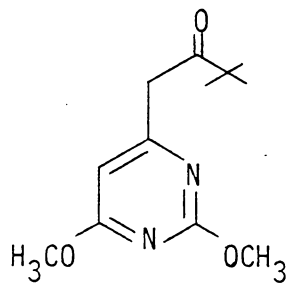
When the photostimulated reactions of 41 with each of the three ketone enolates were repeated in the presence of DTBN, complete inhibition of the formation of 45, 47 and 48 was observed; thus, supporting the existence of a radical-chain mechanism for these reactions.

To study the success of substitution at the 4-position, 4-chloro-2,6-dimethoxypyrimidine (1) was photostimulated in the presence of pinacolone enolate.[2] Substitution product 50 was obtained in nearly

Scheme I



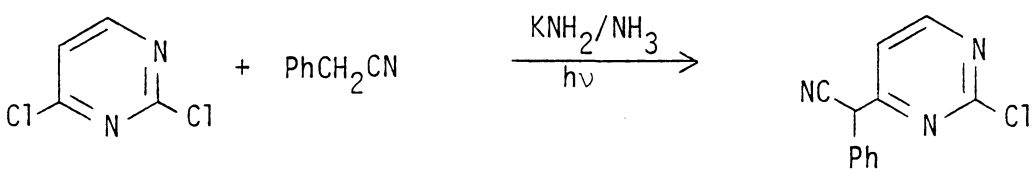
quantitative gc yield. Treatment of 1 with pinacolone enolate in the dark



50

returned 80% of (1), while inhibition with 20 mol % DTBN produced ketone 50 in only 6% yield.

In 1982, Wolfe and coworkers found that the photostimulated reaction of 2,6-dichloropyrimidine (42) with the carbanion of phenylacetonitrile gave a 58% yield of monosubstitution product 51 (eq 17), while the dark reaction gave only unreacted 42.[20] Support for the radical-chain



42 51 (17)

nature of the photostimulated reaction involving 42 was obtained by the complete inhibition by DTBN.

The photoassisted substitution reactions of pyrimidines 40, 41, 42 and 1 are all assumed to occur via a radical-chain ($S_{RN}1$) mechanism. When these reactions with carbanion nucleophiles were conducted in the presence of di-t-butylnitroxide (DTBN), the yields of the substitution

products (43a, 43b, 43c, 45, 47, 48, and 51) were dramatically decreased. This nonrearranging radical chain mechanism is the one that Bunnett discovered in 1970[22] for phenyl halides, and resembles the electron-transfer mechanism for nucleophilic substitution in certain aliphatic systems proposed by Kornblum and Russell.[23,24] For this radical chain mechanism, Bunnett suggested the designation, $S_{RN}1$, which stands for substitution, radical-nucleophilic, unimolecular.[22] Scheme II shows this mechanism as applied to 2-chloropyrimidine with ketone enolates.

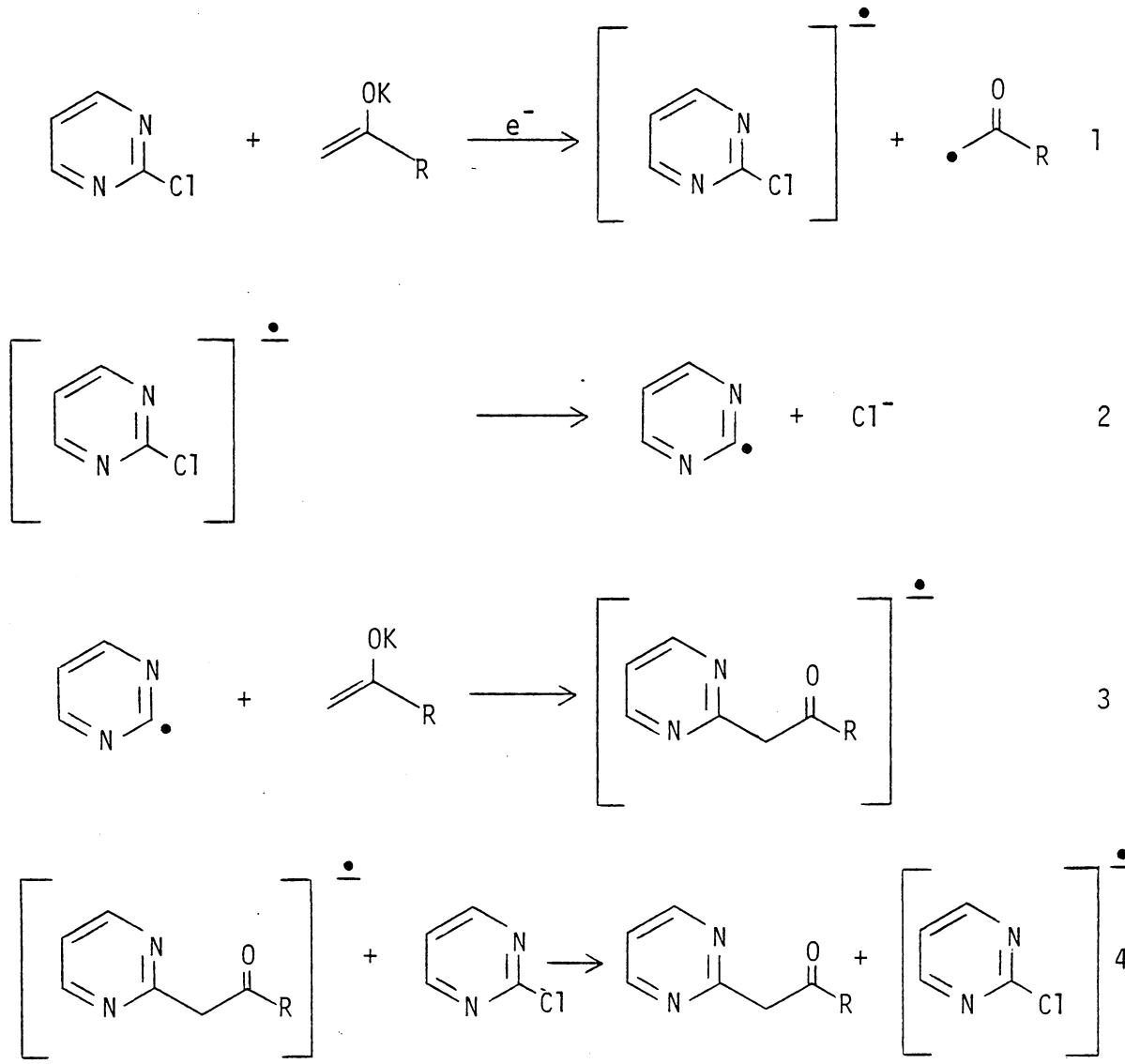
In step 1 of the $S_{RN}1$ reaction (Scheme II), an electron is transferred from the enolate to the aromatic substrate to produce a 2-chloropyrimidine radical anion. Steps 2 through 4 are the propagation steps for this mechanism. In step 2, the radical anion decomposes to give the 2-pyrimidinyl radical and chloride ion. This radical then combines with the ketone enolate in step 3 to form the radical anion of the substitution product. In the last step, the radical anion of the substitution product transfers an electron to 2-chloropyrimidine to form the 2-chloropyrimidinyl radical anion, which can then reenter the chain as in step 2. A detailed treatment of the $S_{RN}1$ reaction, may be found in recent reviews by Bunnett[25] and Rossi[26].

(B) EXAMPLES OF SPECIFIC NUCLEOPHILIC SUBSTITUTION REACTIONS INVOLVING HALOGENATED PYRIMIDINES

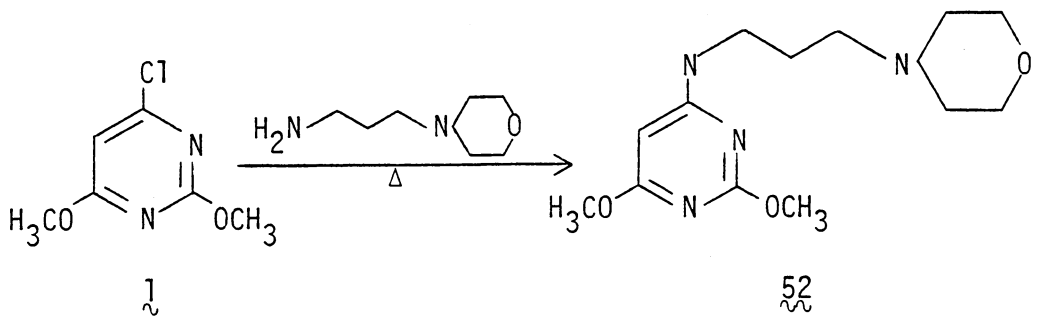
In general, the relative positional order of halide displaceability in halopyrimidines is 4->2->5.[27]

Aminolysis. Aminolysis of alkoxychloropyrimidines usually leads to displacement of the halogen and not the alkoxy group.[28] For example,

Scheme II

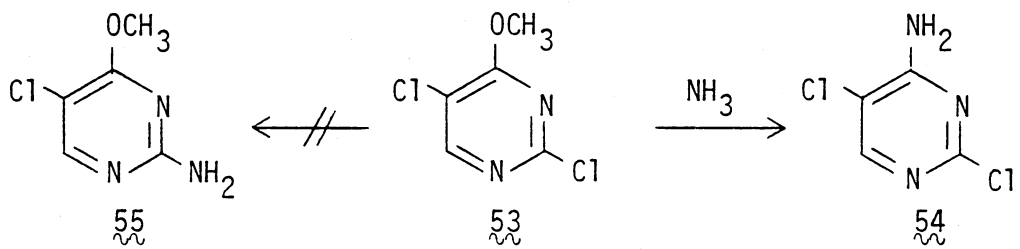


4-chloro-2,6-dimethoxypyrimidine (1) gives 2,4-dimethoxy-6-(γ-morpholinopropyl)aminopyrimidine (52) in refluxing ethanolic amine (eq 18).[29] However, 2,5-dichloro-4-methoxypyrimidine (53) in liquid ammonia



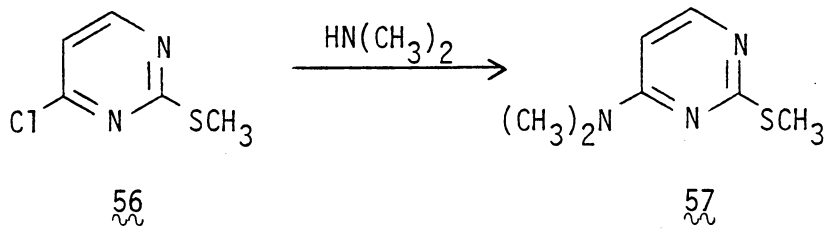
(18)

at 20°C or in methanolic ammonia at 80°C gives 4-amino-2,5-dichloropyrimidine (54) rather than the 2-amino isomer (55) (eq 19).[30]



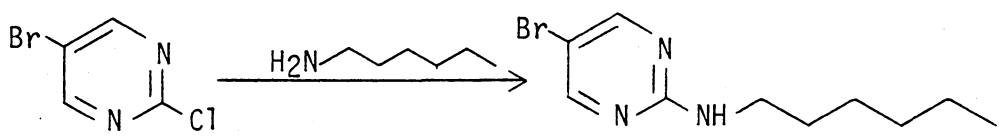
(19)

Chloroalkylthiopyrimidines are convenient intermediates because the chlorine group can be aminolysed with no affect on the alkylthio group, which can then be removed by Raney nickel or hydrolyzed to an hydroxy group. An example of this is the conversion of 4-chloro-2-methylthiopyrimidine (56) into 4-dimethylamino-2-methylthiopyrimidine (57) (eq 20).[31]



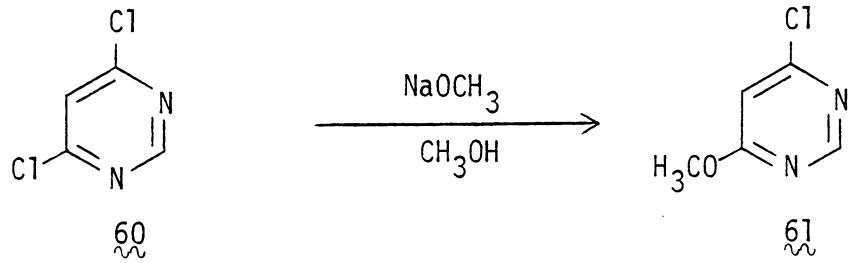
56 57 (20)

A bromine or chlorine atom attached to C-5 of the pyrimidine ring has a mild activating effect on other halogen substituents. For example, 5-bromo-2-chloropyrimidine (58) can be converted to 5-bromo-2-hexylamino-pyrimidine (59) in 94% yield (eq 21).[31]



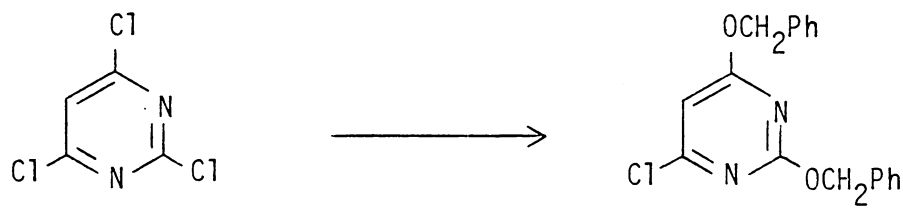
58 59 (21)

Replacement of 2-, 4-, and 6-Halogens by Alkoxy Groups. Reaction of 2-, 4-, or 6-halogenated pyrimidines with an alkoxide ion (sodium alkoxide in the appropriate alcohol) yields the alkoxypyrimidine derivative. It is possible to achieve selectivity in attacking a di- or trichloropyrimidine with alkoxide by controlling the reaction conditions, as well as the amount, concentration, or type of alkoxide ion. This is illustrated by the conversion of 4,6-dichloropyrimidine (60) into 4-chloro-6-methoxypyrimidine (61) (80%) (eq 22)[32] and by the



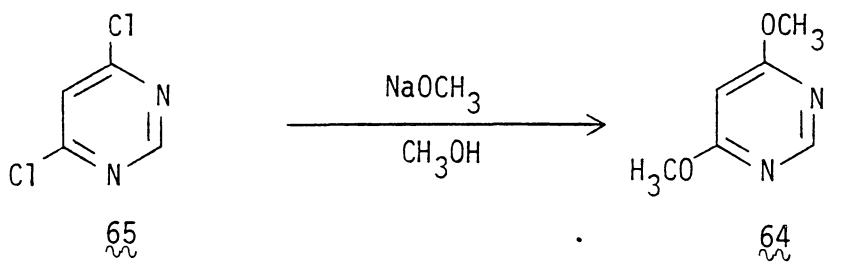
60 61 (22)

conversion of 2,4,6-trichloropyrimidine (62) into 2,4-dibenzyloxy-6-chloropyrimidine (63) (eq 23).[33] Complete alkoxylation of di- or



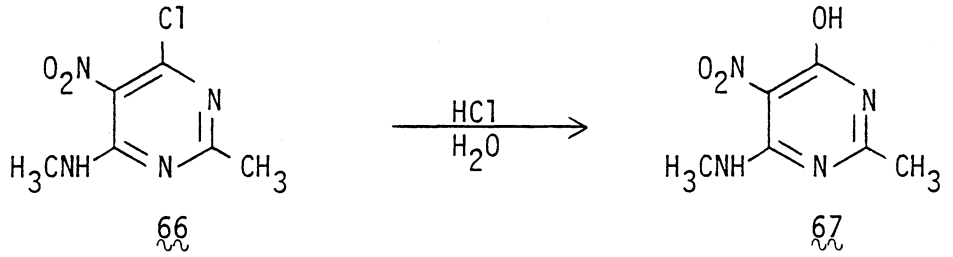
62 63 (23)

trichloropyrimidines is exemplified by the preparation of 4,6-dimethoxy-pyrimidine (64) from 4,6-dichloro-pyrimidine (65) (eq 24).[33]



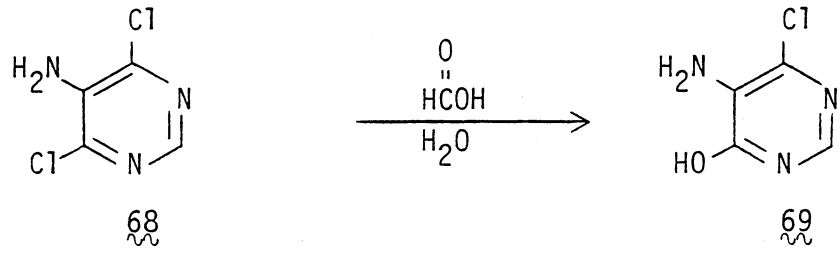
65 64 (24)

Replacement of 2-, 4-, and 6-Halogens by Hydroxy Groups. Direct hydrolysis of a chloropyrimidine to an hydroxypyrimidine can be accomplished under either acidic or alkaline conditions. Alkaline hydrolysis is the method of choice, and monohydrolysis of a di- or trihalogenopyrimidine is possible. Examples of acid hydrolysis include the conversion of 4-chloro-2-methyl-6-methylamino-5-nitropyrimidine (66) into 4-hydroxy-2-methyl-6-methylamino-5-nitropyrimidine (67) by means of refluxing 10 N HCl[34] (eq 25), and by the conversion of



66 67 (25)

5-amino-4,6-dichloropyrimidine (68) into 5-amino-4-chloro-6-hydroxypyrimidine (69) by means of boiling 98% formic acid[35] (eq 26).



68 69 (26)

An example of alkaline hydrolysis may be found in the production of 4-chloro-2,6-dihydroxypyrimidine from 2,4,6-trichloropyrimidine (2.5 N-alkali at 100°C for 1 h).[36]

Replacement of 2-, 4-, and 6-Halogens by Mercapto Groups. Several examples of the use of alcoholic or aqueous sodium hydrogen sulfide in converting a chloropyrimidine into a mercaptopyrimidine include the preparation of 2-amino-4-mercaptopyrimidine from 2-amino-4-chloropyrimidine[37], the preparation of 4-mercapto-6-methoxypyrimidine from 4-chloro-6-methoxypyrimidine[38], and the preparation of 4-dimethylamino-2-mercapto-5-methylpyrimidine from 4-dimethylamino-2-chloro-5-methylpyrimidine[39].

Replacement of 2-, 4-, and 6-Chloro Substituents by Hydrazino-, Hydroxyamino-, Azido-, and Related Groups. Hydrazine reacts readily with chloropyrimidines to form a variety of hydrazino-substituted pyrimidines. Two such examples include the formation of 4-hydrazino-2,6-dimethylpyrimidine from 4-chloro-2,6-dimethylpyrimidine (aqueous hydrazine at 60°)[40], and the formation of 4,6-hydrazinopyrimidine from 4,6-dichloropyrimidine (ethanolic hydrazine at 80°)[41].

Treatment of 4-chloro-2,6-dihydroxypyrimidine with warm ethanolic hydroxylamine yields 2,4-dihydroxy-6-hydroxyaminopyrimidine[42].

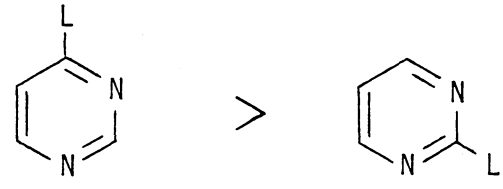
Nucleophilic displacement has also been used to make some azidopyrimidines. For example, 4-amino-2-chloro-5-nitropyrimidine and sodium azide in refluxing ethanol produced 4-amino-2-azido-5-nitropyrimidine.[43] Also, 5-amino-4,6-dichloropyrimidine gave 5-amino-4-azido-6-chloropyrimidine on treatment with sodium azide in dimethylformamide.[44]

Reactions of Halogenated Pyrimidines with Carbanion Nucleophiles.

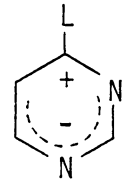
Reactions of 4-phenyl-5-halogenated pyrimidines (40a-b) (Cl, Br),[1] 2-chloropyrimidine (41),[2] 4-chloro-2,6-dimethoxypyrimidine (1),[2] and 2,6-dichloropyrimidine (42)[20] with certain carbanion nucleophiles via the $S_{RN}1$ reaction have been discussed earlier. In each case, good to excellent yields of the respective substitution products were formed.

(C) RELATIVE REACTIVITY OF NUCLEOFUGAL GROUPS AT VARIOUS RING POSITIONS IN PYRIMIDINE

Nucleophilic substitution in pyrimidines is based on the principle that reactivity is greatest para to the activating nitrogen unless specific ortho-directing effects intervene.[27] In pyrimidines, the most



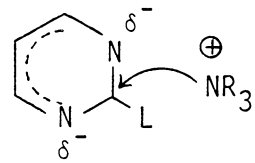
reactive positions for nucleophilic substitution are either between the two centers of high electron density, C-2, or opposite one and adjacent to the other such center, C-4. The activation energy is postulated to be slightly lower for transition states in which the electron-rich centers, (nucleophile and ring-nitrogen) are farthest apart (position-4 > position-2).[31] A second factor in determining comparative positional reactivity is the localization energy required to produce transition state 70. The localization energy will be lower when a nitrogen atom is



70

at the center of the anionic resonating pentadienoid system of transition state 70 than when it is at the end of such a system.

A shift in the relative reactivity of 4-versus 2-substituted pyrimidines can be accomplished by increasing the rate of reaction at the 2-position. One method of accomplishing this is by increasing the electrostatic attraction between an anionic nucleophile and a cationic substrate. A similar effect is observed by the electrostatic attraction between unlike charges in a zwitterionic transition state such as 71. This arises with uncharged nucleophiles such as tertiary nitrogen bases.

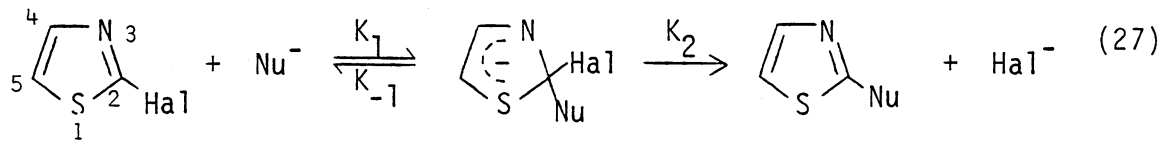


71

(D) MECHANISM FOR NUCLEOPHILIC AROMATIC SUBSTITUTION IN HALOGENOTHIAZOLES

AE_n (Normal Addition-Elimination) Mechanism. During the 1970's,

Bosco and coworkers published a series of papers dealing with the reactivity of 2-, 4-, and 5-halogenothiazole derivatives toward certain nucleophiles.[45-51] In each case, the substitution product was produced via a S_NAr mechanism as shown in eq 27 for a 2-halogenothiazole. All of the reactions followed a second-order kinetic rate law, first order with respect to each reactant. Electron withdrawing groups accelerate



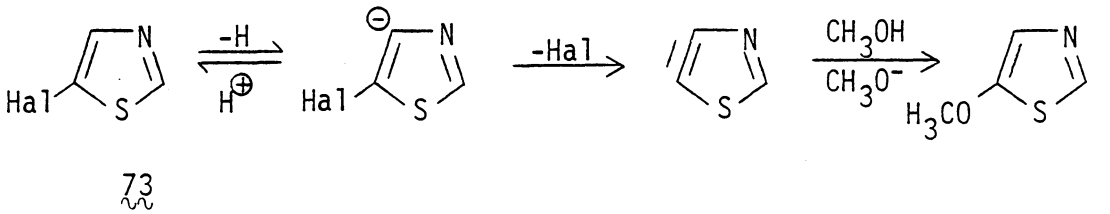
(27)

72

substitution by stabilizing σ-complex 72, while electron releasing groups decrease the rate of substitution. For example, changing from 2-chloro-5-methylthiazole to 2-chloro-5-nitrothiazole produced an increase of 10^9 rate units with alkoxide nucleophiles.

In 1978, Forlani and Todesco found that the steric bulk of alkoxide nucleophiles affects the rate of reaction with 2-halogenothiazoles.[50] The order was found to be as follows: $MeO^- > i\text{-}PrO^- > t\text{-}BuO^-$. However, for 4-halogenothiazoles steric effects are not important ($MeO^- < i\text{-}PrO^- < t\text{-}BuO^-$); therefore, the rate in the latter series parallels the basicity (nucleophilicity) of the alkoxide.

Hetaryne (EA) Mechanism . An elimination-addition pathway as shown in eq 28 was found not to be in operation for nucleophilic substitution reactions of 5-halogenothiazoles (halogen = Cl or Br) (73) with sodium methoxide, thiophenoxide, and thiomethoxide for the following reasons.



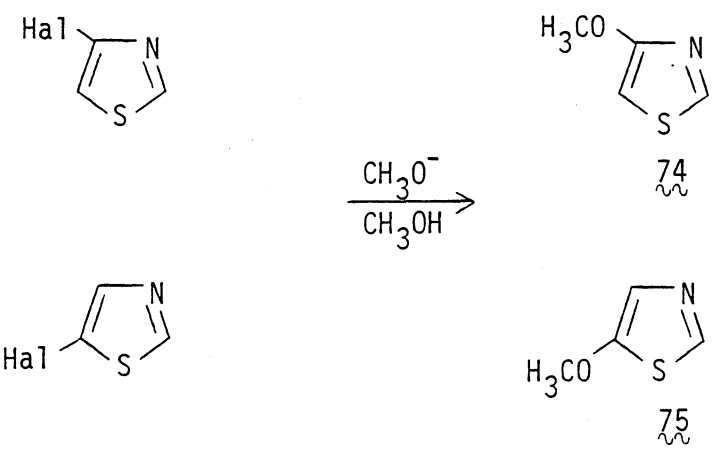
(28)

73

First, there was no H-D exchange at position-4 and, secondly, there was no cine isomer found.[50] A radical mechanism was ruled out by the observation that addition of a large excess of azobenzene caused no change in the kinetics.[50]

(E) EXAMPLES OF SPECIFIC REACTIONS INVOLVING HALOGENOTHIAZOLES

Replacement of Halogens by Alkoxy Groups. In addition to the specific examples mentioned in the previous section for 2-halothiazoles, Bosco and coworkers found that 4-halogenothiazoles and 5-halogenothiazoles (Hal = Cl, Br) react with methoxide in methanol to yield almost quantitatively the expected 4-methoxythiazole (74) and 5-methoxythiazole (75) (eq 29). To obtain more information on



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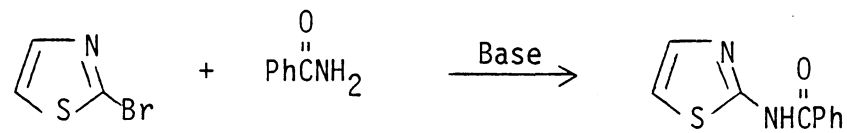
(29)

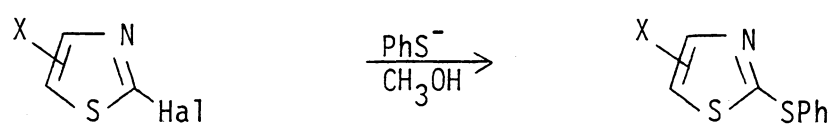
the reactivity of chlorothiazoles, they studied the reaction of 2-chloro-4(5)-X-substituted thiazoles (X = H, 4-CH_3, 4-Cl, 4-C_6H_5, 5-Cl, 5-CH_3, 5-NO_2) with methoxide ion in methanol.[52] The substituted thiazoles reacted with sodium methoxide quantitatively to yield the corresponding 2-methyl ethers.

Replacement of Halogens by Amides. In 1941, Jensen and coworkers found that 2-bromothiazole (76) reacts with benzamide to give 2-benzamidothiazole (77) (eq 30).[53]



76 77 (30)

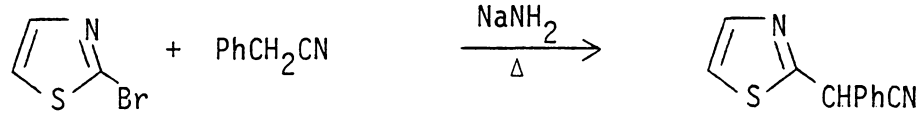
Replacement of Halogens by Thiolates and Thiophenol. Bosco and coworkers found that 2-halogenothiazoles with X-substituents in positions 4 and 5 (X = -H, -CH_3, -Ph, -Cl, or -NO_2) reacted with benzenethiolate ion in methanol to produce the 2-substituted products (78) (eq 31).[45] Yields for these reactions were between 55-100%, depending on the



78 (31)

X-substituent. In 1974, the same researchers investigated the reaction between 2-halogeno-X-substituted thiazoles (X = same as above) and substituted thiophenols.[49] They found that the 2-halogenothiazoles reacted with thiophenols at 50° in methanol to yield the expected substitution products.

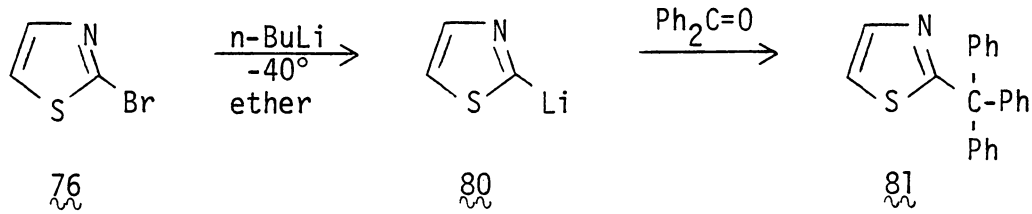
Replacement of Halogen by Carbanion Nucleophiles. The only example in the literature involving the reaction of halogenothiazoles with carbanion nucleophiles is illustrated in eq 32.[4] Thus,



76 79 (32)

α-phenyl-(2-thiazolyl)acetonitrile (79) was obtained in 87% yield from the reaction of 2-bromothiazole (76) and phenylacetonitrile with $NaNH_2$ in refluxing toluene.

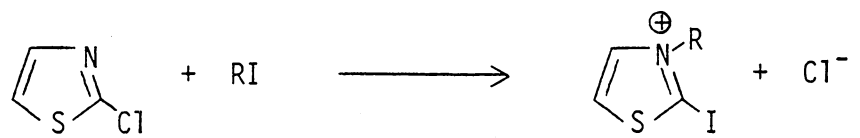
Metal Halogen Exchange. 2-Halogenothiazoles react with n-butyllithium in ether at -40°C to produce the corresponding thiazolyllithium compound (80), which can then react with carbonyl compounds to give the expected condensation products.[54] As shown in eq 33, carbinol (81) can be obtained from lithium derivative (80) and benzophenone.[55]



76 80 81 (33)

Reduction of 2-Halogenothiazole. The halogen in position-2 can be easily replaced by hydrogen using zinc and acetic acid[56] or tin and hydrochloric acid.[57] Catalytic reduction can be accomplished by using potassium hydroxide or triethylamine with Raney nickel catalyst.[58]

N-alkylation of Halogenothiazoles. The halogenothiazoles undergo N-alkylation by reaction with various alkyl halides.[59] Halogen exchange occurs simultaneously with the alkylation (eq 34).



(34)

Electrophilic Substitution Reaction of Halogenothiazoles. All of the halogenothiazoles react slowly in electrophilic substitution reactions such as nitration and sulfonation.[60] This is due to the electron-withdrawing power of the halo substituent and of the ring nitrogen.

(F) REACTIVITY OF HALOGENOTHIAZOLES

Halogens bonded to the thiazole ring show different degrees of nucleofugal reactivity, which depend on the position of attachment and on the reagents used. Table I shows a comparison of reactivity of some 2-halogenothiazoles with selected nucleophiles. It may be seen that the relative reactivity (F > Cl > Br > I) is that expected fron an S_NAr mechanism in which the most electronegative halogen facilitates rate-determining σ-complex formation.

Positions 4- and 5- are also activated towards nucleophilic substitution as reported by Todesco et al.[45] As shown in Table II, no simple relationship exists between nucleophilic reactivity and charge density.[60] The thiazole residue itself shows a net electron-withdrawing effect in all positions as shown by the fact that thiazole carboxylic acids are all more acidic than the benzoic acid.[61] With methoxide ion in methanol, the reactivity sequence is 5-chlorothiazole > 2-chlorothiazole > 4-chlorothiazole, but with thiophenoxide ion the sequence is 2 > 4 > 5.[60] When more crowded and basic alcohols are used, the order of reactivity is reversed. Using t-butoxide in t-butanol causes the 4-chlorothiazole to be more reactive than the 2-chloro isomer.[46]

There is a sharp decrease in reactivity of 2-halogeno-X-substituted thiazoles in going from electron-withdrawing to electron-releasing substituents. For example, changing from 2,5-dichlorothiazole to 2-chloro-4-methylthiazole caused an approximate ten-fold decrease in rate with alkoxide nucleophiles. For 2,4-dichlorothiazole and 2,5-dichlorothiazole, no displacement of halogen ion by alkoxide nucleophile

Table I

Relative Reactivities of 2-Halogenothiazoles

Compound	Nucleophile			Ref.
	MeO^- in MeOH	PhS^- in MeOH	PhSH in MeOH	
2-Fluorothiazole	2.2×10^3	2.67×10	----	61,61
2-Chlorothiazole	1.00	1.00	1.00	61,51,48
2-Bromothiazole	1.30	3.91	4.89	61,61,49
2-Iodothiazole	4.91×10^{-1}	2.51	----	61,61

Table II

Reactivity Ratios of Halogenothiazoles With Different Nucleophiles

Halogen	MeO^- in MeOH	EtO^- in EtOH	$i\text{-}PrO^-$ in i-PrOH	$t\text{-}BuO^-$ in t-BuOH	PhS^- in MeOH	Ref.
2-Cl						51,46,46,46,48
4-Cl	0.074	0.59	3.9	42	--	51,46,46,46,--
5-Cl	2.3	--	--	--	--	51,--,--,--,--
2-Br	1.3	--	--	--	3.9	51,--,--,--,46
4-Br	0.16	--	--	--	0.36	51,--,--,--,46
5-Br	2.8	--	--	--	0.20	51,--,--,--,46

from C-4 or C-5 was observed even at 70-80% conversion.

The nucleophilic reactivity of 2-halogeno-X-thiazoles is strongly affected by the presence of substituents -X. When -X-is able to fully carry the negative charge, one sees a strong increase in reactivity. For example, 5-nitro-2-chlorothiazole is 10^8 times more reactive than 2-chlorothiazole.[60]

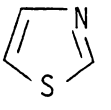
There is little information in the literature about substituent effects on the nucleofugal reactivity of halogens in positions 4- and 5-. The reactivity of the halogen in position 5- seems to be increased by an amino group in position 2. Reactions of neutral nucleophiles such as thiourea, thiophenols, and mercaptans with 5-halogenothiazole easily yield substitution products.[62,63]

In the reaction of 2,4- or 2,5- dihalogenothiazoles with anionic nucleophiles, the 2-halogen reacts first.[49] The halogen in the 2-position is activated strongly by the aza group and also by the other halogen. The metal reduction of 2,4-dichlorothiazole or 2,5-dichlorothiazole proceeds exclusively in position 2.

(G) MISCELLANEOUS REACTIONS OF THIAZOLE

The following classes of reactions are discussed since they have a bearing on our findings with 2-chlorothiazole. Most reactions of basic nucleophiles with thiazole itself involve the abstraction of a ring proton by the nucleophile followed by the addition of an electrophile to the intermediate. Two types of hydrogen replacement reactions will be discussed next. The first is base induced hydrogen-deuterium exchange, and the second is hydrogen-metal exchange.

Hydrogen-Deuterium Exchange Reactions. Thiazole (82) undergoes H-D exchange at position-2 10^5 to 10^{10} times more slowly than in cations such as (83). No evidence has been presented for deprotonation at C-4 of 82 or cations such as 83. The protons on carbons 2 and 5 in 82 exchange at



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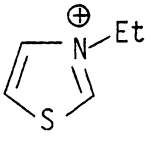
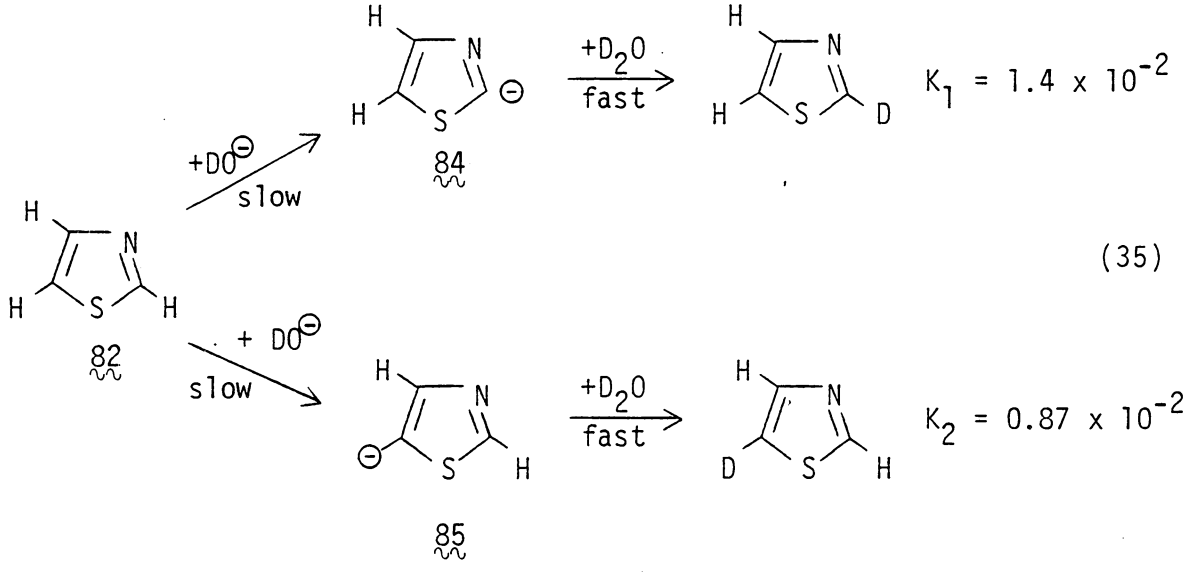


83

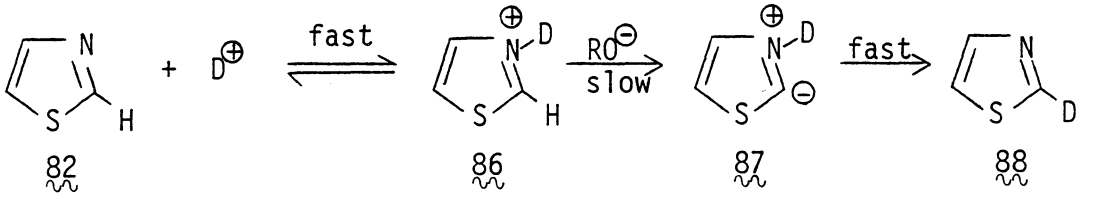
about the same rate.[64] Derbez found the absolute second-order rates of exchange by ^1H NMR and determined the ratio of the rate constants K_1 and K_2 for exchange at positions 2 and 5, respectively, to be 1.31 (eq 35).[64] These findings gave further support to the theory that stabilization



(35)

of the forming anions 84 and 85 is caused by overlap with an unfilled d orbital on the adjacent sulfur.[65]

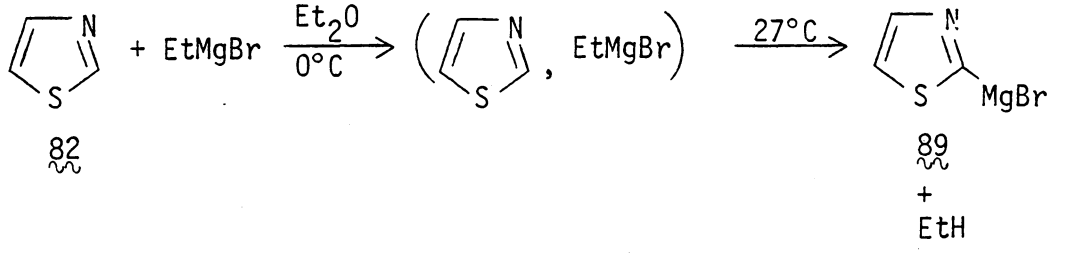
In 1970, Olofson et al. published the results of their work on thiazole (82).[66] They hypothesized the existence of two exchange mechanisms, which depend on pD. The first mechanism operates between pD0 and pD11 (eq 36). In this addition-elimination process, the conjugate



82 86 87 88 (36)

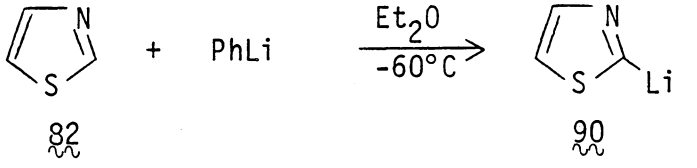
acid, 86, of thiazole (82) is formed in a preequilibrium step. In the second step, the proton on carbon-2 of 86 is abstracted to produce ylide 87, which then undergoes trans deuteration to produce compound 88. Under these acidic conditions, 86 exchanges only the proton at C-2 to yield exclusively 2-deuterothiazole 88. Under more basic conditions (pD > 12), the mechanism illustrated in eq 35 predominates, and the rate increases very rapidly with pD.[67] Between pD 12.2 and 13.4, the ratio of K_1/K_2 decreases from 12.4 to 1.8.

Hydrogen-Metal Exchange Reactions. In the presence of organometallic bases, thiazole will undergo hydrogen-metal interconversion. As illustrated in eq 37, ethylmagnesium bromide reacts with thiazole to form an insoluble complex that yields thiazol-2-ylmagnesium bromide (89) on heating.[68]



(37)

Thiazole also reacts with phenyllithium to produce thiazol-2-yllithium (90) (eq 38).[69,70] As shown in eqs 37 and 38, the most

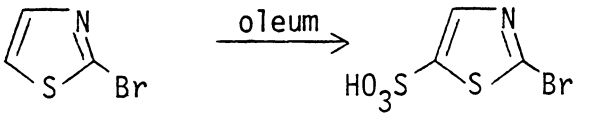


(38)

reactive position in thiazole toward metalation by Grignard or organolithium reagents is the 2-position.

Electrophilic Substitution. Despite thiazole's "π excessive character", it is resistant to electrophilic substitution due to deactivation of the heterocyclic nucleus by the ring nitrogen. Electrophilic substitution will occur in thiazole derivatives only when the ring is activated by the presence of electron-releasing groups. Electron-releasing groups attached to carbon-2 promote 5-substitution if that position is open. If the 5-position is blocked, then substitution occurs on C-4. The most effective electron-releasing groups are the

hydroxy and amino groups. As shown in eq 39, relatively deactivated thiazole derivatives, 2-bromothiazole (76) and 2,5-dibromothiazole (91), will undergo sulfonation in oleum at about 200°C in the presence of mercuric sulfate.[71] At low temperatures (0°C), 2-aminothiazoles (92) can



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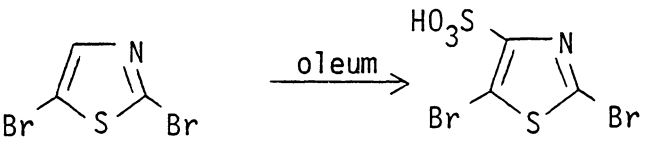
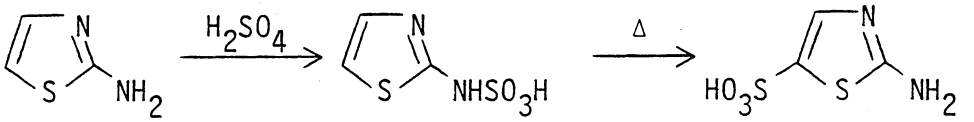


91

be sulfonated to give 2-sulfamic acid (93) which rearranges to 2-amino-5-sulfonic acid (94) on heating (eq 40).[72,73]



92 93 94 (40)

(H) RATIONALE FOR THE PRESENT STUDY

As discussed in the previous sections, only three studies have been conducted that deal with $S_{RN}1$ reactions of halogenated pyrimidine ring systems.[1,2,20] Moreover, even though many different types of nucleophiles have been shown to undergo the $S_{RN}1$ reaction with aromatic substrates, at the present time only ketone enolates have been studied with halopyrimidines. The mild conditions of the $S_{RN}1$ reaction and the generally good yields found with ketone enolate nucleophiles in the pyrimidine series suggested that the synthetic potential of this substitution mechanism warranted further investigation. To accomplish this, we used compound 1 to gain further insight into the $S_{RN}1$ reactivity of halopyrimidines. Since only the enolate from pinacolone had been used in $S_{RN}1$ reactions with 1, we also wanted to learn what other types of nucleophiles would enter into this radical-chain substitution reaction with 1. The nucleophiles studied include carbanions stabilized by four functional groups. By using nucleophiles containing various functional groups, one could show the versatility of the $S_{RN}1$ reaction with respect to nucleophiles. The nucleophiles employed in the present include the enolates of acetone, pinacolone, diisopropyl ketone, acetophenone, ethyl phenylacetate, and N,N-dimethylacetamide, and carbanions derived from acetonitrile, phenylacetonitrile, and propionitrile.

In searching the literature, one finds only one example of the $S_{RN}1$ reaction of π-excessive substrates (2- and 3-bromothiophenes)[74]. In order to gain insight into this largely unknown area of $S_{RN}1$ chemistry we chose to use 2-chlorothiazole (2) as a readily available and illustrative

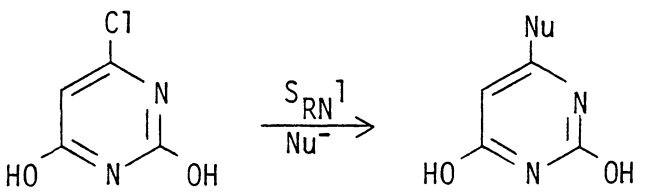
substrate. The biological activity of thiazole derivatives also made 2 an attractive system for investigation.[60] The nucleophiles studied with 2 include the enolates of acetone, pinacolone, diisopropyl ketone, acetophenone, and N,N-dimethylacetamide and carbanions derived from acetonitrile, propionitrile and phenylacetonitrile.

In the following sections, reactions of 4-chloro-2,6-dimethoxypyrimidine (1) and 2-chlorothiazole (2) with the nucleophiles listed above will be presented and discussed.

III. Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) and Related Systems with Carbanion Nucleophiles

RESULTS

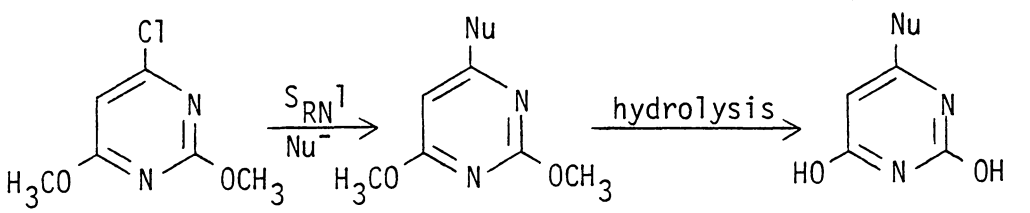
Initially, we thought that substituted uracils, 96, might be prepared by an $S_{RN}1$ reaction of 6-chlorouracil (95) with various carbanion nucleophiles (eq 41). However, we also suspected that ionization of the acidic



95 96 (41)

uracil protons might make substrate 95 reluctant to accept an electron, thereby preventing initiation of the desired radical-chain process. Indeed, irradiation of chlorouracil (95) and potassioacetone for 2 h in liquid ammonia yielded diacetone alcohol and recovered 95 (Expt 11).

Since 6-chlorouracil (95) failed to react in the desired $S_{RN}1$ fashion, it seemed that substrate 1 might function as a precursor to uracils as shown in eq 42. This appeared to be attractive because 1 had



1 97 96 (42)

earlier been shown to undergo clean $S_{RN}1$ substitution with pinacolone enolate. Consequently, we undertook an investigation of reactions of 1 with a series of carbanion nucleophiles.

Ketone Enolates. The first series of nucleophiles to be investigated were the enolates of pinacolone, acetone, diisopropyl ketone, and acetophenone, which were prepared by reaction of the appropriate ketone with potassium amide in liquid ammonia.

Since the yield of substitution product 50 derived from the originally reported $S_{RN}1$ reaction of 1 with pinacolone enolate had been determined only by gc analysis, we repeated the reaction to determine how effective it would be for preparative purposes. The photoassisted reaction of 1 with the potassium enolate of pinacolone in liquid ammonia for 15 min gave a 69% isolated yield of ketone 50 and 6% of recovered 1 (Table III, Expt 12). When the same reactants were denied illumination (dark reaction), a quantitative recovery of 1 was obtained (Expt 13).

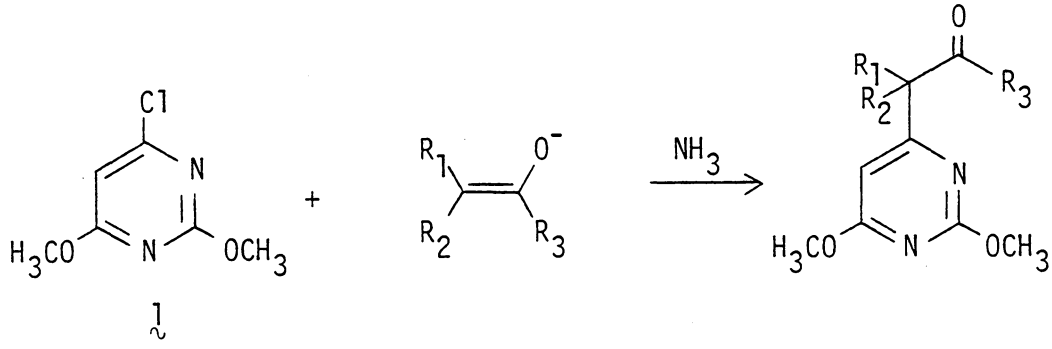
Treatment of 1 with excess potassioacetone with photostimulation for 15 min yielded 75% of ketone 98a and 8% of unreacted 1, while a 15 min dark reaction produced only 9% of substitution product 98a and 90% of recovered 1 (Expts 14 and 15) (eq 43).

Exposure of 1 to the potassium enolates of acetone or diisopropyl ketone in the presence of 10 mol % of the radical scavenger, di-tert-butyl nitroxide (DTBN) resulted in complete recovery of 1 after 15 min of irradiation (Expts 16 and 21). When the lithium enolate of acetone was generated by means of lithium diisopropylamide (LDA) in THF and treated with 1 for 4 h under irradiation, a quantitative recovery of 1 was

TABLE III

Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) with Ketone Enolates

Expt.	Enolate From	Reaction Conditions	Reaction Time (min)	Product	Product Yield, %	Recovered 1, %
12	Pinacolone	KNH_2/NH_3,hν	15	50	69	6
13	Pinacolone	KNH_2/NH_3,dark	15	50	0	100
14	Acetone	KNH_2/NH_3,hν	15	98a	75	8
15	Acetone	KNH_2/NH_3,dark	15	98a	9	90
16	Acetone	KNH_2/NH_3,DTBN,hν	15	98a	0	100
17	Acetone	LDA/THF,hν	240	98a	0	100
18	Acetone	LDA/THF,HMPA (30 mmol),hν	360	98a	0	100
19	Diisopropyl Ketone	KNH_2/NH_3,hν	15	98b	52	4
20	Diisopropyl Ketone	KNH_2/NH_3,dark	15	98b	48	42
21	Diisopropyl Ketone	KNH_2/NH_3,DTBN,hν	15	98b	0	100
22	Diisopropyl Ketone	KNH_2/NH_3,pDBN,dark	15	98b	0	100
23	Acetophenone	KNH_2/NH_3,hν	15	98c	0	100



(43)

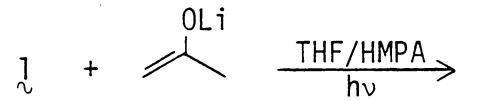
50: $R_1=R_2=H$; $R_3=t$-Bu

98a: $R_1=R_2=H$; $R_3=CH_3$

98b: $R_1=R_2=CH_3$; $R_3=CH(CH_3)_2$

98c: $R_1=R_2=H$; $R_3=Ph$

obtained (Expt 16). Attempted photostimulated reaction of 1 with acetone enolate generated by means of LDA in THF in the presence of 30 mmol of hexamethylphoramide (HMPA) for 6 h also gave a quantitative recovery of 1 (Expt 18) (eq 44).

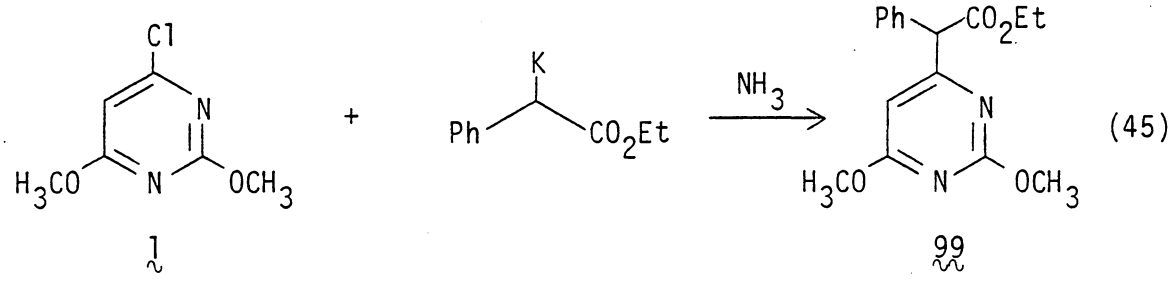


(44)

Photostimulated reaction of 1 with the potassium enolate of diisopropyl ketone in liquid ammonia for 15 min yielded 52% of substitution product 98b and 4% of unreacted 1, while a dark reaction gave a 48% yield of 98b and a 42% yield of recovered 1 (Expts 19 and 20).

Attempted photostimulated reaction of 1 with the potassium enolate of acetophenone returned 100% of unreacted 1 (Expt 23).

Ethyl Phenylacetate Enolate. Photoassisted reaction of 1 with the potassium enolate of ethyl phenylacetate, prepared by means of potassium amide in liquid ammonia, for 15 min yielded 71% of substitution product 99 and 25% of unreacted 1, while a dark reaction produced only 3% of 99 and 60% of unreacted 1 (eq 45) (Table IV, Expts 24 and 25). Exposure of



(45)

1 to the potassium enolate of ethyl phenylacetate in the presence of 10 mol % of DTBN under photostimulation gave a 59% yield of 99 and a 27% yield of 1 (Expt 26). However, increasing the amount of DTBN to a full equivalent decreased the yield of 99 to 22% (Expt 27). When the period of photostimulation was reduced from 15 to 5 min, the reaction of 1 with ethyl phenylacetate enolate gave 99 in 60% yield, while a 5 min dark reaction gave 99 in 46% yield (Expts 28 and 29). Photostimulated reaction of 1 with the lithium enolate of ethyl phenylacetate, generated by LDA in THF, for 4 h gave a 50% yield of 99, while a dark reaction of the same duration gave a 32% yield of 99 (Expts 30 and 31).

N,N-Dimethylacetamide Enolate. Although other investigations have found that carboxamide enolates react with haloarenes under $S_{RN}1$ conditions[74], neither the photostimulated nor the dark reactions of 1 with the potassium enolate of N,N-dimethylacetamide in liquid ammonia

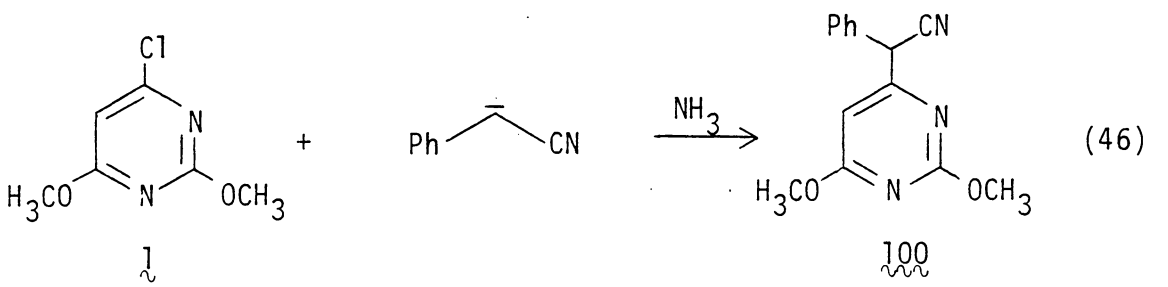
TABLE IV

Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) with Ethyl Phenylacetate Enolate

Expt.	Reaction Conditions	Reaction Time (min)	Product	Product Yield, %	Recovered 1, %
24	KNH_2/NH_3,hν	15	99	71	25
25	KNH_2/NH_3,dark	15	99	3	60
26	KNH_2/NH_3/hν,DTBN(10 mol %)	15	99	59	27
27	KNH_2/NH_3,hν,DTBN(1 equiv)	15	99	22	65
28	KNH_2/NH_3,hν	5	99	60	21
29	KNH_2/NH_3,dark,DTBN(1 equiv)	5	99	46	21
30	LDA/THF,dark	240	99	32	62
31	LDA/THF,hν	240	99	50	44

proved to be successful (Expts 34 and 35). In both cases, the sole reaction product was a black, intractable tar.

Nitrile Carbanions. The next class of nucleophiles studied were the carbanions of phenylacetonitrile, acetonitrile, and propionitrile, which were generated by either potassium amide in liquid ammonia or by LDA in THF. Photostimulated reaction of 1 with potassiophenylacetonitrile in liquid ammonia for 15 min gave a 68% yield of substitution product 100 and a 29% yield of unreacted 1, while a dark reaction gave a 63% yield of 100 (eq 46) (Table V, Expts 38 and 39). Exposure of 1 to potassiophenylacetonitrile in the



1 100 (46)

presence of 10 mol % DTBN for 15 min in the dark gave a 54% yield of 100 and a 35% yield of recovered 1 (Expt 40). Increasing the amount of DTBN to a full equivalent had no significant effect, in that a 51% yield of 100 was obtained (Expt 42). When the reaction time was changed from 15 to 5 min, a dark reaction of 1 with phenylacetonitrile carbanion in liquid ammonia gave a 59% yield of 100 (Expt 43). Exposure of 1 to the phenylacetonitrile carbanion generated by potassium amide in liquid ammonia in the presence of 10 mol % DTBN for 5 min produced 71% of

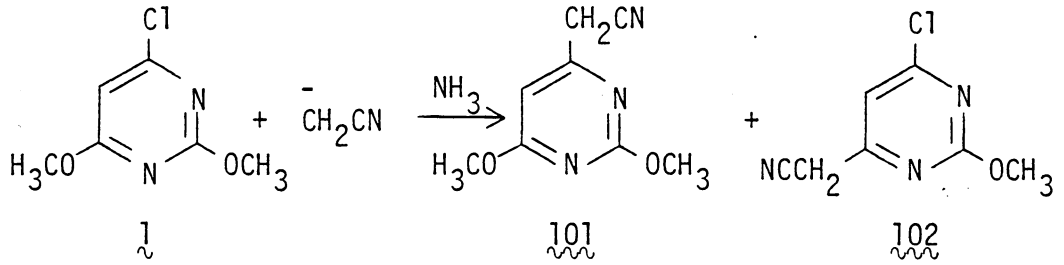
TABLE V

Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) with Phenylacetonitrile Carbanion

Expt.	Reaction Conditions	Reaction Time (min)	Product	Product Yield, %	Recovered 1, %
38	KNH_2/NH_3,hν	15	100	68	29
39	KNH_2/NH_3,dark	15	100	63	--
40	KNH_2/NH_3,DTBN (10 mol %),dark	15	100	54	35
41	KNH_2/NH_3,p-DNB (10 mol %),dark	15	100	79	3
42	KNH_2/NH_3,DTBN(1 equiv),dark	15	100	51	8
43	KNH_2/NH_3,dark	5	100	59	--
44	KNH_2/NH_3,DTBN,dark	5	100	71	--
45	LDA/THF,hν	240	100	75	17
46	LDA/THF,dark	240	100	50	13

100 (Expt 44). Photostimulated reaction of the lithium enolate of phenylacetonitrile, prepared by means of LDA in THF, for 4 h, gave a 75% yield of 100, while a similar dark reaction gave a 50% yield of 100 (Expts 45 and 46).

Treatment of 1 with potassioacetonitrile, prepared by means of potassium amide in liquid ammonia, under photostimulation for 15 min, gave 101 resulting from displacement of chloride, along with 102, which arose by displacement of methoxide, in yields of 7% and 45%, respectively. A dark reaction produced 101 and 102 in yields of 26% and 58%, respectively (eq 47) (Table VI, Expts 47 and 48).



1 101 102 (47)

The photoassisted reaction of 1 with acetonitrile carbanion, generated by means of n-butyllithium in THF, for 4 h produced 101 (18%) and 102 (69%), while an analogous dark reaction gave 101 (12%) and 102 (46%) (Expts 49 and 50).

When 5 mol % of acetone was used as a potential entraining agent in liquid ammonia, the photostimulated reaction of 1 with acetonitrile carbanion didn't change the relative distribution of products, in that a 30% yield of 101 and a 55% yield of 102 were obtained (Expt 51).

TABLE VI

Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) with Acetonitrile Carbanion

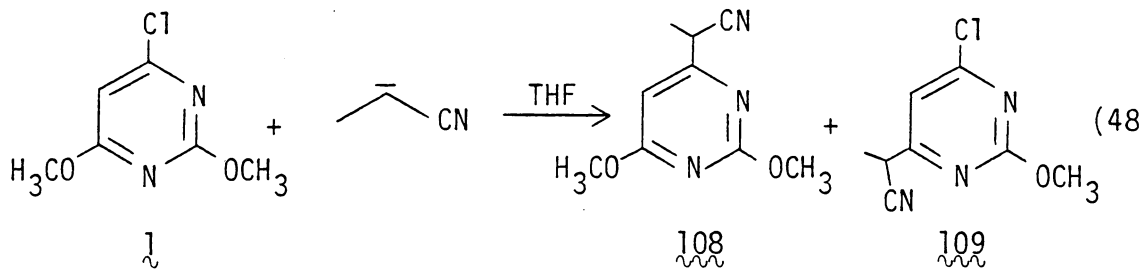
Expt.	Reaction Conditions	Reaction Time (min)	Products	Product Yield,% 101	102	Recovered 1 %
47	KNH_2/NH_3,hν	15	101, 102	7	45	--
48	KNH_2/NH_3,dark	15	101, 102	26	58	4
49	n-BuLi/THF,dark	240	101, 102	12	46	35
50	n-BuLi/THF,hν	240	101, 102	18	69	--
51	KNH2/NH3,hν,5 mol % 	15	101, 102	30	55	--

Pyrimidine 102, formed from the reactions of 1 with acetonitrile carbanion generated by potassium amide in liquid ammonia or by LDA in THF was shown to contain only one methoxy group and a chlorine atom by ^1H NMR and mass spectrometry. The integrated ^1H NMR spectrum revealed the presence of only three methoxy protons, thereby showing that only one methoxy group was present. The mass spectrum gave conclusive evidence that 102 contained a chlorine atom, in that the spectrum had both a peak at 183 (relative intensity = 100), which corresponds to the M+ fragment of 102, and a M+2 peak at 185 (relative intensity = 28). Displacement of the methoxy group at carbon-6 rather than at carbon-2 was supported by ^{13}C NMR analyses. Table VII contains the reported ^{13}C δ-values for pyrimidine (103)[75], plus the δ values observed for 1, 2,4-dimethoxypyrimidine (104), 2-methoxypyrimidine (105), 2-chloropyrimidine (106), 2,4-dichloro-pyrimidine (107), and 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102). The δ-values for C-2 of pyrimidine and the substituted pyrimidines listed in Table VII are the farthest downfield since it is flanked by the two ring nitrogens. In comparing the δ-values of C-4 and C-6 for pyrimidine (103) with those of 102, one observes the values are larger (more deshielded) for 102, thus showing that C-4 and C-6 of 102 have electron-withdrawing groups attached to them. The δ-value of C-4 for 102 is the same as the δ-value of C-4 in 2,4-dichloropyrimidine (107) (160.9); therefore, C-4 of 102 must still have the chlorine atom attached to it. The δ-values for C-2 of 102 and 1 are approximately the same, thereby showing that the methoxy group in 102 is still attached to C-2. In addition to the δ-values for the ring carbons of 102 listed in Table VII, the ^{13}C NMR

spectrum of 102 also shows three other peaks. One peak (δ = 54.9) corresponds to the methoxy carbon. The δ-value for this carbon corresponds well to the δ-values of the methoxy carbon for the other pyrimidines listed in Table VII. Apparently, the peak at 28.1 ppm for 102 corresponds to the methylene carbon of the acetonitrile group. Finally, the peak at 115.1 ppm arises from the carbon of the nitrile function.

The photostimulated and dark reactions of 1 with the lithium carbanion of propionitrile in THF for 5 h gave similar results to that of the reactions of 1 with the lithium carbanion of acetonitrile in that two products (108 and 109) arising from chloride and methoxide displacement were formed. However, the reactions of 1 with propionitrile carbanion, gave different ratios for these two types of products than observed with the acetonitrile carbanion.

Thus, photostimulated reaction of 1 with the lithium carbanion of propionitrile in THF favored displacement of chloride to produce a 58% yield of 108 and a 27% yield of 109, while a dark reaction gave yields of 45% and 19% of 108 and 109, respectively (eq 48) (Table VIII, Expts 52 and 53).



1 108 109 (48)

TABLE VII

^{13}C δ-Values for Pyrimidine and Substituted Pyrimidines

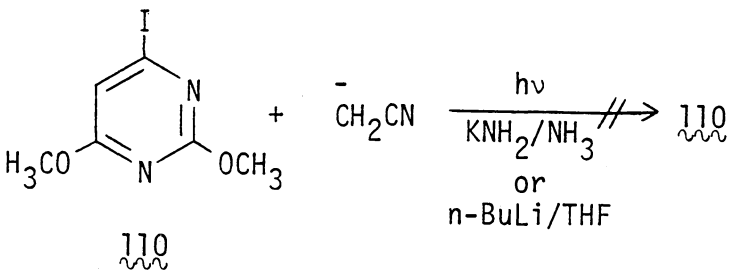
Pyrimidines	δ-Values (ppm) C-2	C-4	C-5	C-6	CH_3
Pyrimidine (103)	159.5	157.4	122.1	157.4	----
4-Chloro-2,6-dimethoxypyrimidine (1)	172.2	164.8	100.8	161.2	55.2,54.3
2,4-Dimethoxypyrimidine (104)	171.5	165.5	102.0	158.3	54.6,53.7
2-Methoxypyrimidine (105)	164.9	158.6	114.3	158.6	54.1
2-Chloropyrimidine (106)	161.6	159.6	119.7	159.6	----
2,4-Dichloropyrimidine (107)	162.5	160.9	120.3	159.9	----
4-Chloro-6-cyanomethyl-2-methoxypyrimidine (102)	171.1	160.9	106.5	161.1	54.9

TABLE VIII

Reactions of 4-Chloro-2,6-Dimethoxypyrimidine (1) with Propionitrile Carbanion

Expt.	Reaction Conditions	Reaction Time (min)	Products	Product Yield,% 102	109	Recovered 1 %
52	n-BuLi/THF,hν	300	102, 109	58	27	4
53	n-BuLi/THF,dark	300	102, 109	45	19	35

Attempted Reactions of 2,4-Dimethoxy-6-Iodopyrimidine (110) with Acetonitrile Carbanion. Once it was established that certain carbanion nucleophiles would enter into $S_{RN}1$ reactions with 4-chloro-2,6-dimethoxypyrimidine (1) to give good yields of the respective substitution products, we decided to study the effect of changing the halide on the pyrimidine ring. Attempted photostimulated reaction of iodopyrimidine 110 with acetonitrile carbanion in liquid ammonia for 15 min gave only unreacted 110 in quantitative yield (Expt 54). Using n-butyllithium in THF, an attempted 4 h photostimulated reaction of 110 with acetonitrile carbanion once again gave only unreacted 110 in quantitative yield (Expt 55) (eq 49).

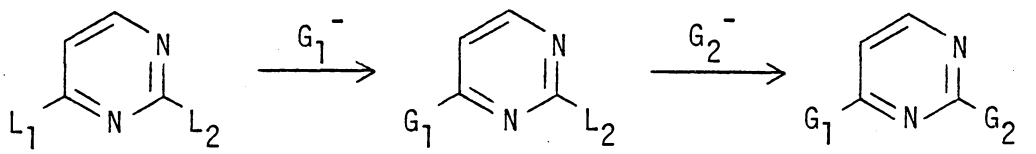


(49)

Attempted Reactions of 2-Chloro-4-Methoxypyrimidine (111) and 2,4-Dimethoxypyrimidine (104) with Carbanions of Pinacolone and Acetonitrile.

The reaction of 1 with acetonitrile and propionitrile carbanions established that a methoxy group as well as a chlorine group could be displaced. From these results, we wondered what effect if any the chlorine atom on C-4 had on the displacement of the methoxy group at C-6. We also wondered if it would be possible to observed selective displacement of leaving groups from the pyrimidine ring. For example, under one set of reaction conditions would it be possible to displace group L_1 from the

pyrimidine ring, then by altering the reaction conditions would it be possible to displace L_2 (eq 50). If this was synthetically possible, then



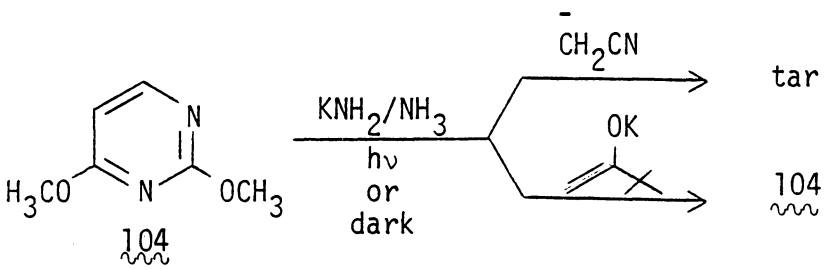
(50)

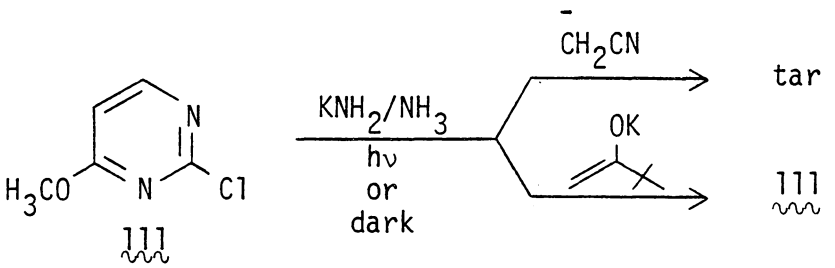
it would be a useful method for sequentially introducing different functionality onto the pyrimidine ring. To study the possibility of selective displacement of groups from the pyrimidine ring, we reacted 2-chloro-4-methoxypyrimidine (111) and 2,4-dimethoxypyrimidine (104) with the carbanions of acetonitrile and pinacolone in liquid ammonia (Scheme III).

When 111 was exposed to pinacolone enolate under illumination in liquid ammonia for 15 min, a quantitative recovery of 111 was obtained (Expts 56 and 57) (Scheme III). Attempted photostimulated and dark reactions of 104 with the carbanion of pinacolone in liquid ammonia for 15 min produced a quantitative recovery of 104 (Expts 58 and 59).

Treatment of 111 and 104 with potassioacetonitrile in liquid ammonia with or without photostimulation for 15 min produced a dark brown intractable tar (Expts 60-63).

Scheme III


H3CO
N
OCH3
104
KNH2/NH3
hν
or
dark
CH2CN
tar
OK
104


H3CO
N
Cl
111
KNH2/NH3
hν
or
dark
CH2CN
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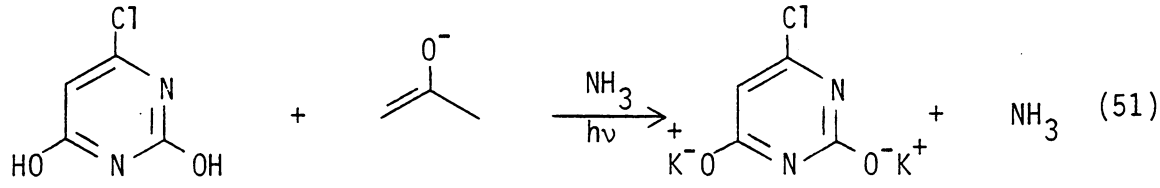
111

DISCUSSION

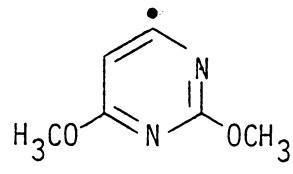
The failure of 6-chlorouracil (95) to participate in the $S_{RN}1$ reaction with potassioacetone is undoubtedly due to abstraction of the protons of 95 by potassioacetone, which produces dipotassio salt 112 (eq 51). Apparently, 112, with two negative charges, is reluctant



95 112

to accept an electron from the ketone enolate, thereby preventing initiation.

Support for the radical-chain character of the photostimulated reactions of 4-chloro-2,6-dimethoxypyrimidine (1) with potassium enolates of pinacolone and acetone are seen by the complete inhibition of this reaction with 10 mol % of DTBN. Since DTBN is a well defined radical scavenger, it is assumed that it exerts its inhibitory action by combining with pyrimidinyl radical 113. This takes such radicals out of the chain, thereby preventing the completion of the $S_{RN}1$ reaction.



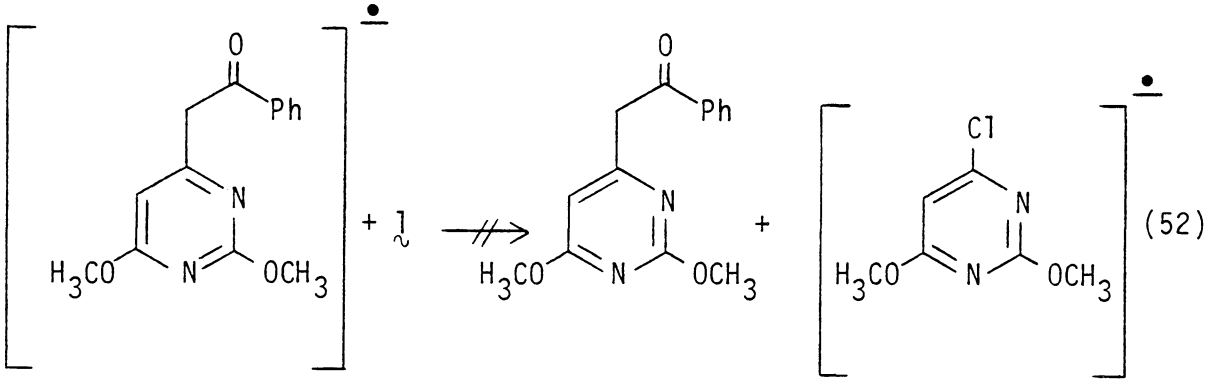
113

The failure of lithioacetone to read with 1 in THF provides further evidence that the liquid ammonia reactions proceed by a $S_{RN}1$ mechanism and not by an AE_n process since the latter mechanism should be favored by higher temperature, longer reaction times, and the polar cosolvent, HMPA, all which failed to cause formation of substitution product 98a.

In contrast to the reactions of 1 with pinacolone and acetone enolate in liquid ammonia which did not proceed in the dark, diisopropyl ketone enolate reacted with 1 in the dark to form 98b in only slightly lower yield (48%) than that (52%) with full illumination. Apparently, diisopropyl ketone enolate is a better electron donor to substrate 1 than the enolates from either acetone or pinacolone. The enolate from diisopropyl ketone has previously been found to initiate the $S_{RN}1$ process with other aromatic substrates in the dark. This enolate was found to to undergo a dark $S_{RN}1$ reaction with 2-chloroquinoline without any stimulation.[73] In a 1981 study of 2-chloropyrimidine (41) with ketone enolates from pinacolone, acetone, and diisopropyl ketone, Wolfe and co-workers found that diisopropyl ketone enolate gave the best yields of substitution product (48) when compared to other enolates (Scheme I)[2].

The failure of the attempted photoassisted reaction of potassioacetophenone with 1 to produce substitution product 98c was not totally unexpected. It had been observed in previous studies that the attempted photostimulated reactions of potassioacetophenone with iodobenzene[76], 2-chloroquinoline[77], and 2-bromopyridine[78] did not proceed efficiently.

The lack of reactivity with these systems and with 1 may be due to the failure of the radical anion of the substitution product to transfer an electron to another substrate molecule[79,80] (eq 52).



(52)

Support for the radical-chain mechanism for the reaction of 1 with ethyl phenylacetate enolate is shown by the decrease in yield of substitution product 99 (from 71% to 3%) when the reaction was conducted without photostimulation. However, unlike the cases with ketone enolates, inhibition of the photostimulated reaction with 10 mol % of DTBN only caused a decrease in the yield of 99 from 71% to 59%, while a full equivalent of DTBN (based on 1) caused the yield of 99 to decrease from 71% to 22%. The fact that the reaction of 1 with ethyl phenylacetate enolate in the presence of 10 mol % of DTBN gave a 59% yield of 99, while a full equivalent of DTBN gave only a 22% yield, demonstrates the shortness of the chain length in the reactions of 1 with the enolate of ethyl phenylacetate. Liquid ammonia appears to be a better reaction medium to support the electron transfer of 1 with the enolate of ethyl phenylacetate. Thus, the longer reaction times and higher temperatures of the photostimulated reaction of 1 with the lithium enolate of ethyl phenylacetate in THF

gave only a 50% yield of 99 (Expt 30) which is a decrease of 21% from the same reaction conducted in liquid ammonia.

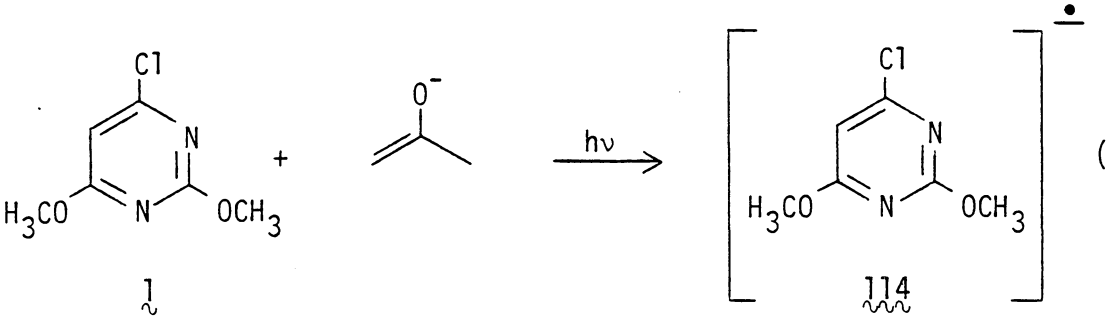
Assuming that a full equivalent of DTBN completely inhibits the $S_{RN}1$ reaction of 1 with ethyl phenylacetate enolate, formation of product 99 in 22% yield (Expt 27) indicates that ca. 49% of 99 obtained in uninhibited photoreactions is formed via the ionic S_NAR mechanism.

Reaction of 1 with the phenylacetonitrile carbanion seems to proceed mainly by an ionic mechanism, rather than via the $S_{RN}1$ mechanism. Regardless of whether the reactions of 1 with phenylacetonitrile carbanion were conducted with or without photostimulation, or in the presence of 10 mol % to one equivalent of DTBN, or in the dark with 10 mol % of DNB, good to excellent yields of substitution product 100 were obtained. Changing from potassium amide in liquid ammonia to LDA in THF gave slightly higher yields of 100, but to achieve the highest yield the reaction time had to be increased from 15 min to 4 h. The success of this reaction in THF, a poor solvent for electron transfer and a source of radical-trapping hydrogen atoms, also supports an S_N Ar mechanism.

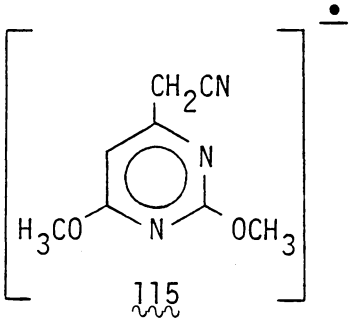
The photostimulated and dark reactions of 1 with acetonitrile carbanion in either liquid ammonia or THF produced a mixture of 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102) and 4-cyanomethyl-2,6-dimethoxypyrimidine (101) in approximately the same ratio. Regardless of the reaction conditions, 102 was always the major product. This reaction also appears to proceed mainly by an ionic mechanism.

If the reaction of 1 with acetonitrile carbanion proceeded by the

$S_{RN}1$ mechanism, then the entrainment reaction with 5 mol % of acetone enolate would be expected to give give pyrimidine 101 as the sole product, since acetone enolate should serve as an initiator for the reaction of acetonitrile carbanion with 1 to give radical-ion 114 (eq 53). In the $S_{RN}1$ process, radical-ion 114 would then expel halide ion

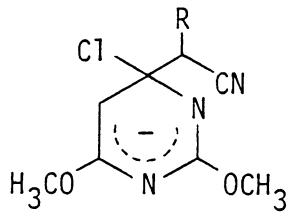


to give the appropriate pyrimidinyl radical, which would combine with acetonitrile carbanion to produce the radical-anion of the substitution product (115). Radical-anion 115 could then transfer an electron to another aromatic substrate and give substitution product 101.

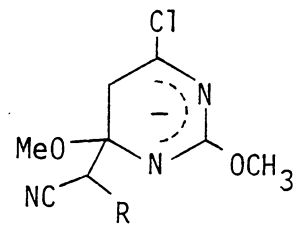


However, the entrainment reaction (Expt 51) still gives pyrimidine 102 which arises from methoxide displacement.

The dark and photostimulated reactions of 1 with propionitrile carbanion in THF produced two products, 4-(2-cyanoethyl)-2,6-dimethoxypyrimidine (108) and 4-chloro-6-(2-cyanoethyl)-2-methoxypyrimidine (109). Regardless of the reaction conditions, pyrimidine 108 resulting from chloride displacement was always the major product. The increasing tendency for ionic displacement of chloride ion from 1 may be caused by the increasing steric requirement of the nitrile carbanions in going from potassioacetonitrile to potassiopropionitrile to potassiophenylacetonitrile. Thus, the phenylacetonitrile carbanion, which is presumably the bulkiest nucleophile, tends to participate exclusively in ionic displacement of chloride because formation of the required σ-complex (116) for chloride displacement at the 4-position is less hindered by chlorine than the corresponding σ-complex (117) required for methoxide displacement formed at the carbon-6, which holds the more sterically demanding methoxy group.



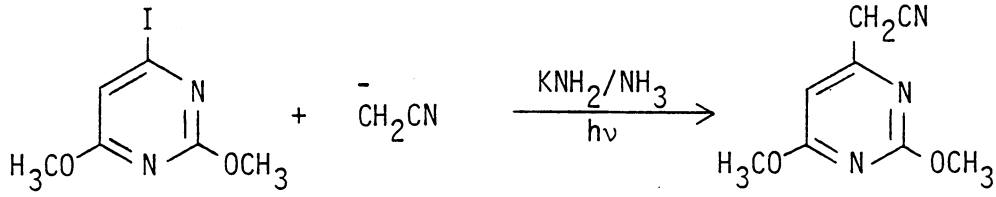
116



117

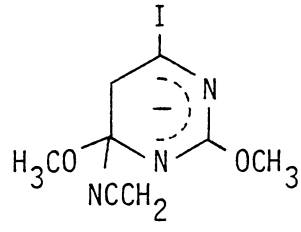
In the $S_{RN}1$ mechanism, iodine is displaced more readily than chlorine from aromatic substrates because aryl iodides are better electron acceptors than the analogous chlorides, and the carbon-iodine bond is more labile than the carbon-chlorine bond. If the reaction of 4-chloro-2,6-dimethoxypyrimidine (1) with acetonitrile carbanion occurred by

the $S_{RN}1$ mechanism, then the reaction of 4-iodopyrimidine (110) with this nucleophile might be expected to proceed even more rapidly and perhaps give rise to selective displacement of iodine to yield 101 (eq 54). However, treatment of 110 with acetonitrile carbanion, generated by means of potassium amide in liquid ammonia or with LDA in THF, under photostimulation for 15 min gave a quantitative recovery of 110. The fact that treatment of iodopyrimidine (110) with acetonitrile carbanion does not give the methoxy displaced product (102) may be



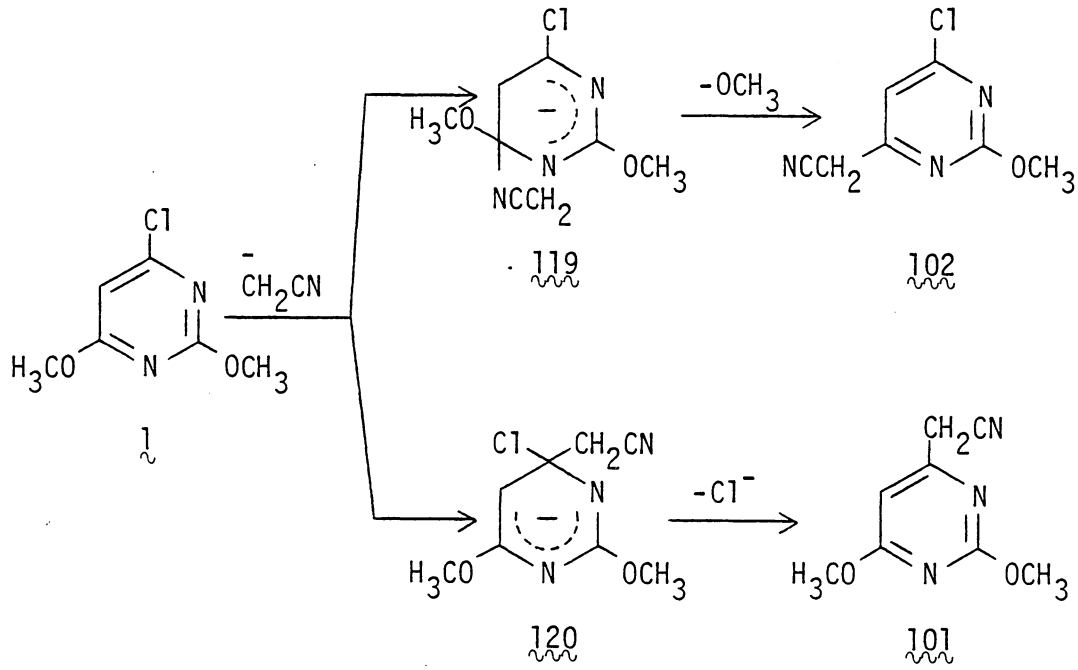
110 101 (54)

due to the fact that iodine is not as strongly electronegative, and thus does not sufficiently stabilize σ-complex (118) required for methoxide displacement. Reaction of 4-chloro-2,6-dimethoxypyrimidine (1)



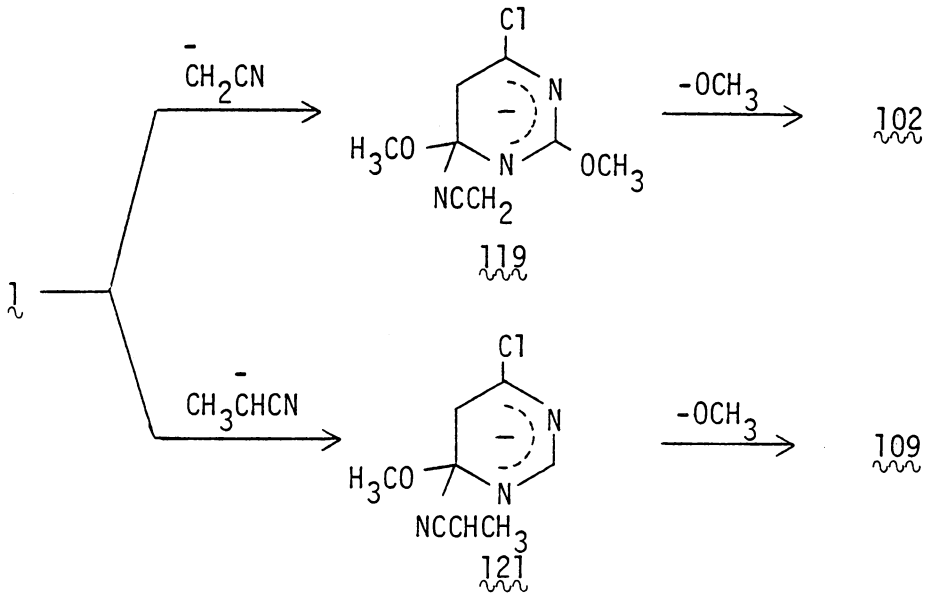
118

with acetonitrile carbanion yields 101 and 102 because chlorine can stabilize inductively the required σ-complexes 119 and 120 better than iodine (eq 55).



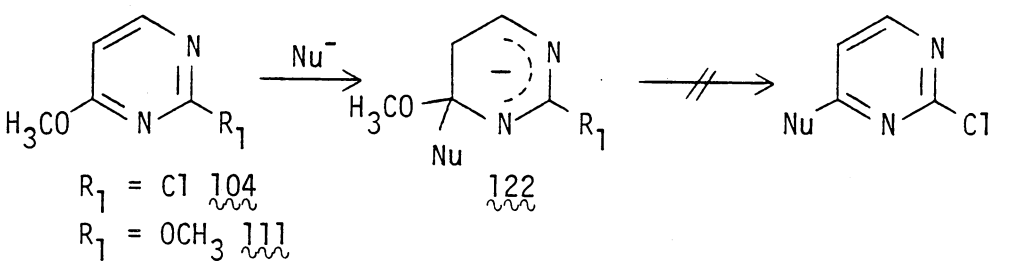
(55)

Since acetonitrile carbanion displaces $-OCH_3$ from 1 but fails to displace this same group from either 2,4-dimethoxypyrimidine (104) and 2-chloro-4-methoxypyrimidine (111), the chlorine atom must have some stabilizing effect on the reactions of 1 with acetonitrile and propionitrile carbanions. Apparently, the σ-complex intermediates (119 and 121) are stabilized by the electron-withdrawing -Cl group which allows the reactions of 1 and acetonitrile and propionitrile carbanions to occur (eq 56). In the reactions of acetonitrile carbanion and



(56)

potassium enolate of pinacolone with 111 and 104, there is no electron-withdrawing group present on C-4 in the molecule to stabilize the σ-complex (122); therefore, no ionic reaction takes place (eq 57).



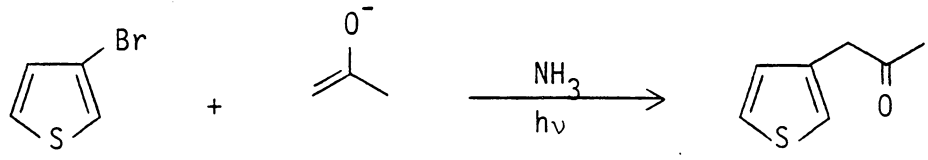
(57)

Since 2-chloro-4-methoxypyrimidine (104) contains a chlorine atom on C-2, the pyrimidine ring must need an electron-withdrawing group on both C-2 and C-6 for successful displacement of the methoxy group on C-4.

IV. Reactions of 2-Chlorothiazole (2) and Thiazole (82) with Carbanion Nucleophiles

RESULTS

In 1976, Bunnett and coworkers found that 3-bromothiophenes (123) reacted with potassioenolate of acetone, under illumination in liquid ammonia, to give good yields of substitution products 124 (eq 58).[51]



123 124 (58)

Since this is the only report of π-excessive halogenated heteroaromatics as substrates in $S_{RN}1$ reactions, we decided to investigate the reactions of 2-chlorothiazole (2) with certain carbanion nucleophiles.

Thiazole (82) and the simple alkyl or aryl derivatives of thiazole are not polarographically reducible.[81] However, substitution in the thiazole ring with electron-attracting groups such as a halogen or a carboxylic acid renders the nucleus reducible. In 1961, Lavion found that the $E_{1/2}$ values for 2-chlorothiazole varied with pH[82] (Table IX). Based on the reported $E_{1/2}$ value for substrate 2 at pH 6, we felt that 2-chlorothiazole (2) would enter into the $S_{RN}1$ reaction with carbanion nucleophiles since its reduction potential is even more positive than

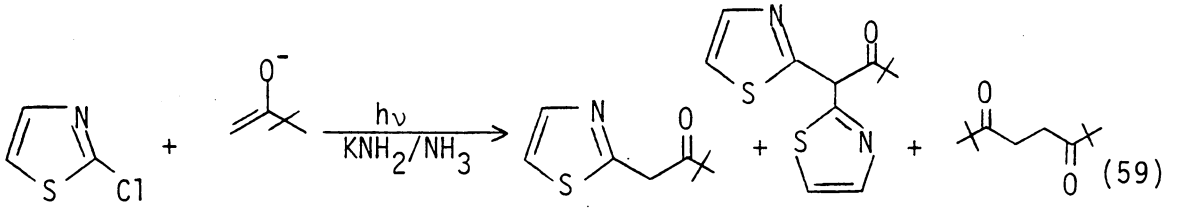
Table IX

Polarographic Reduction Potentials of 2-Chlorothiazole as a Function of pH[82]

pH	$E_{1/2}$, V
2	-1.0
4	-1.4
6	-1.6

pyrimidine and other aromatic substrates which have been shown to participate in the $S_{RN}1$ reaction.

Ketone Enolates. Photostimulated reaction of 2-chlorothiazole (2) with the potassium enolate of pincolone in liquid ammonia for 1 h gave monosubstituted product 125a (49%), disubstituted product 125b (2.4%), and 2,2,7,7-tetramethyl-3,6-octadione (126) (2.5%) when the molar ratio of 2 to pinacolone was 1:2.35 (eq 59) (Table X, Expt 64). When the molar ratio of 2 to pinacolone enolate was increased to 1:4, no pinacolone dimer (126) was produced and the yields of 125a and 125b were 53% and 13%, respectively (Expt 65).



2 125a 125b 126

Photostimulated and dark reactions of 2 with excess potassioacetone gave unstable products (Expts 66 and 67). On standing, the initial clear liquids darkened to a black liquid, which decomposed on Kugelrohr distillation. Attempted photostimulated reaction of 2 with 4 equiv of the potassium enolate of acetophenone returned 100% of 2 (Expt 68).

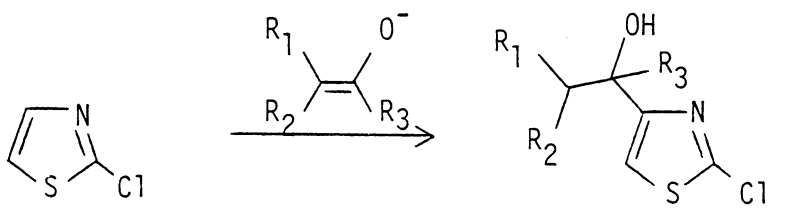
Table X

Reactions of 2-Chlorothiazole (2) with Ketone Enolates

Expt.	Enolate From	Reaction Conditions	Reaction Time (min)	Product	Product Yield, %	Recovered 2, %
64	Pinacolone	KNH_2/NH_3,hν[a]	60	126	2.5	---
				125a	49	---
				125b	1.3	---
65	Pinacolone	KNH_2/NH_3,hν	60	125a	53	---
				125a	13	---
66	Acetone	KNH_2/NH_3,hν	60	125c	unstable	---
67	Acetone	KNH_2/NH_3,dark	60	125c	unstable	---
68	Acetophenone	KNH_2/NH_3,hν	60	125d	---	100

[a]Molar ratio of 2 to pinacolone was 1:2.35

In contrast to the typical $S_{RN}1$ reaction, which requires photostimulation for displacement of the halogen, and which leads to recovery of starting materials when denied the catalytic effect of near-UV irradiation, exposure of 2 to excess pinacolone enolate in the dark gave carbinol 127a in 70% yield (eq 60) (Table XI, Expt 69).



(60)

2 127

127a: $R_1=R_2=H$; $R_3=t$-Bu

127b: $R_1=R_2=CH_3$; $R_3=CH(CH_3)_2$

The photostimulated and dark reactions of 2 with 4 equiv of excess diisopropyl ketone enolate in liquid ammonia gave similar results, in that carbinol 127b was formed in yields of 77% and 83%, respectively (eq 60) (Table XI, Expts 70 and 71). The dark reaction of 2 with the potassium enolate of diisopropyl ketone in the presence of 10 mol % of DTBN gave an 85% yield of 127b (Expt 72). A 1.5-h dark reaction employing a 1:1 molar ratio of 2 to diisopropyl ketone enolate, generated by LDA in THF, resulted in a quantitative recovery of unreacted 2 (Expt 73). Increasing the ratio of 2 to the lithium enolate of diisopropyl ketone enolate to 1:4 gave a 100% yield of 127b in THF (Expt 74).

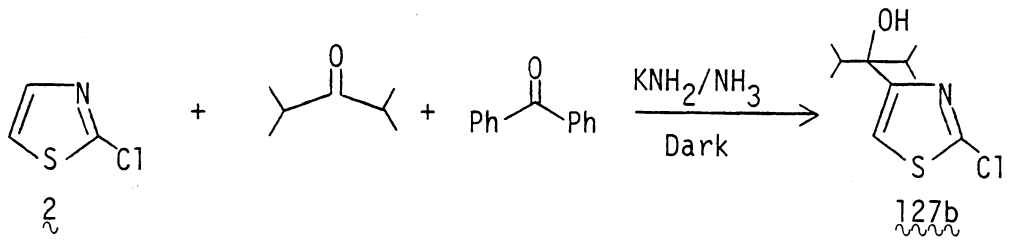
Table XI

Reactions of 2-Chlorothiazole (2) with Ketone Enolates

Expt.	Enolate From	Reaction Conditions	Reaction Time (min)	Product	Product Yield, %	Recovered 2, %
69	Pinacolone	KNH_2/NH_3,dark (4:1)[a]	60	127a	70	---
70	Diisopropyl Ketone	$KNH_2/NH_3/h\nu$ (4:1)[a]	60	127b	77	---
71	Diisopropyl Ketone	KNH_2/NH_3,dark (4:1)[a]	60	127b	83	---
72	Diisopropyl Ketone	KNH_2/NH_3,DTBN*,dark (4:1)[a]	60	127b	85	---
73	Diisopropyl Ketone	LDA/THF,dark (1:1)[a]	90	127b	---	100
74	Diisopropyl Ketone	LDA/THF,dark (4:1)[a]	90	127b	100	---

[a] Molar ratio of ketone enolate to 1

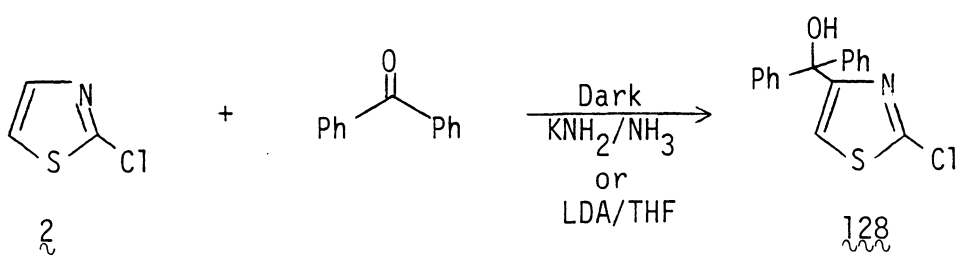
* 10 mol %



2 127b (61)

Dark reaction of 2 with diisopropyl ketone in liquid ammonia for 1 h with no potassium amide present returned a quantitative yield of 2 (Table XII, Expt 75). Treatment of 2 with 1 equiv of benzophenone and 4 equiv of diisopropyl ketone enolate, generated by potassium amide in liquid ammonia, in the dark for 1 h gave a 67% yield of 127b (Table XII, Expt 76). When the amount of benzophenone was increased to 10 equiv the 1 h dark reaction of 2 with diisopropyl ketone enolate in liquid ammonia gave a 68% yield of 127b (Expt 77).

When 2 was treated with 4 equiv of potassium amide followed by addition of benzophenone, tertiary alcohol 128 was obtained in 66% yield (eq 62) (Table XIII, Expt 78). When 4 equiv of LDA in THF was used, the dark reaction of 2 with benzophenone for 1 h gave a quantitative yield



2 128 (62)

Table XII

Dark Reactions of 2-Chlorothiazole (2) with Diisopropyl Ketone Enolate and Benzophenone in Liquid Ammonia and KNH_2

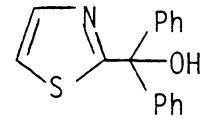
Expt.	Diisopropyl Ketone (equiv)	Benzophenone (equiv)	Reaction Time (min)	Product	% 127b	% 2
75	4.0	---	60	2	---	100
76	4.0	2.5	60	127b	67	---
77	4.0	10.0	60	127b	68	---

Table XIII

Reactions of 2-Chlorothiazole (2) with Benzophenone

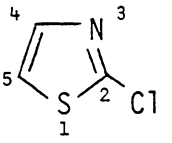
Expt.	Reaction Conditions	Rxn Time (min)	LDA (mmol)	KNH_2 (mmol)	Product	Product Yield, %	Recovered 2, %
78	KNH_2/NH_3,dark	60	---	4.0	128	66	---
79	LDA/THF,dark	60	4.0	---	128	100	---
80	LDA/THF,dark	60	1.0	---	128	100	---

of 128 (Expt 79). Also, when 1.0 equiv of benzophenone was added to a THF solution containing 1.0 equiv of 2 and 1.0 equiv of LDA, a quantitative yield of 128 was obtained (Expt 80). Addition of 1.0 equiv of benzophenone to a mixture of 1.0 equiv of 2 and 1.0 equiv of n-BuLi at -78°C yielded the tertiary alcohol 129 (Expt 81) as reported previously[54].



129

Structural assignments for thiazole condensation products 127a, 127b and 128 are based on ^{1}H NMR, mass spectral, and elemental analyses. The nmr spectra for 127a and 127b show a broad peak at approximately 2.2 δ. When D_2O is added to the nmr sample of 127b, this peak from the hydroxyl proton disappears. Evidence that incorporation of the pinacolone, diisopropyl ketone, and benzophenone units had occurred at the C-4 and not C-5 in 127a, 127b, and 128 was verified by ^{1}H NMR. The spectrum of 2 shows two sets of doublets centered at 7.3 and 7.8 δ, with the proton on C-4 being the furthest downfield, since it is adjacent to the electron-withdrawing nitrogen. The ^{1}H NMR spectra of 127a, 127b, and 128 show no doublet at 7.8 δ, and all have a singlet at 7.3 δ, thus confirming that the reaction of 2 with pinacolone, diisopropyl ketone and benzophenone had occurred with attack at C-4.



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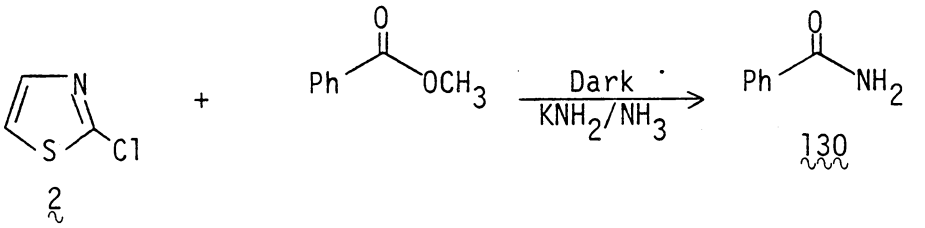
The dark reaction of 2 with methyl benzoate in the presence of 4 equiv of potassium amide in liquid ammonia for 1 h gave benzamide (130) (eq 63) (Expt 82). When this reaction was repeated in the presence of



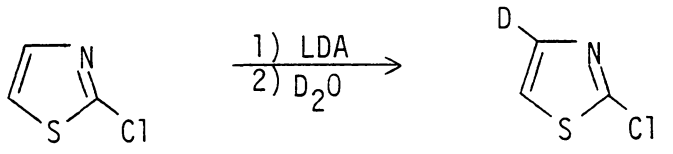
(63)

2

130

4 equiv of LDA in THF, the reaction mixture contained at least eight compounds (tlc analysis) (Expt 83).

Exposure of 2 to 4 equiv of LDA in THF followed by quenching the reaction mixture with D_2O afforded 2 containing 70% of a deuterium atom at position-4 as shown by mass spectral and ^1H NMR analysis (eq 64) (Expt 84). Exposure of 2 to excess LDA in THF followed by quenching the



(64)

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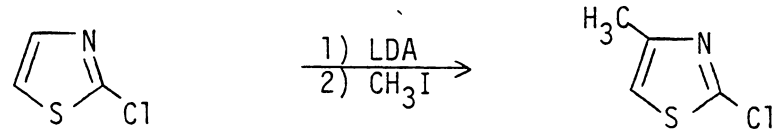
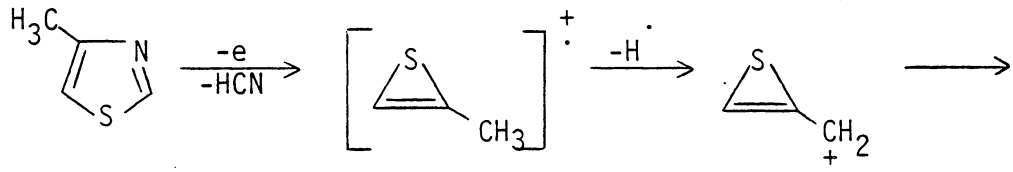
131

reaction mixture with iodomethane gave a 52% yield of 2-chloro-4-methylthiazole (132) (eq 65) as shown by mass spectral and ^{1}H NMR analysis (Expt 85). The mass spectrum of 132 correlates well with the mass spectrum for 4-methylthiazole as reported by Budzikiewicz.[83]

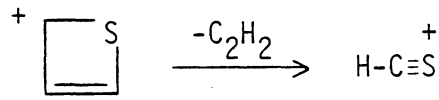


2 132 (65)

Structure assignments for 131 and 132 were based on interpretation of their mass spectra. The mass spectra of thiazole and methylthiazoles are dominated by the molecular ions fragments and by fragments formed by cleavage of the 1,2 and 3,4 bonds.[83] The driving force for those fragmentations probably results from the stability of the neutral hydrogen cyanide which can be generated by 1,2 and 3,4-cleavage.[83] This is illustrated in eq 66 for the fragmentation of 4-methylthiazole.



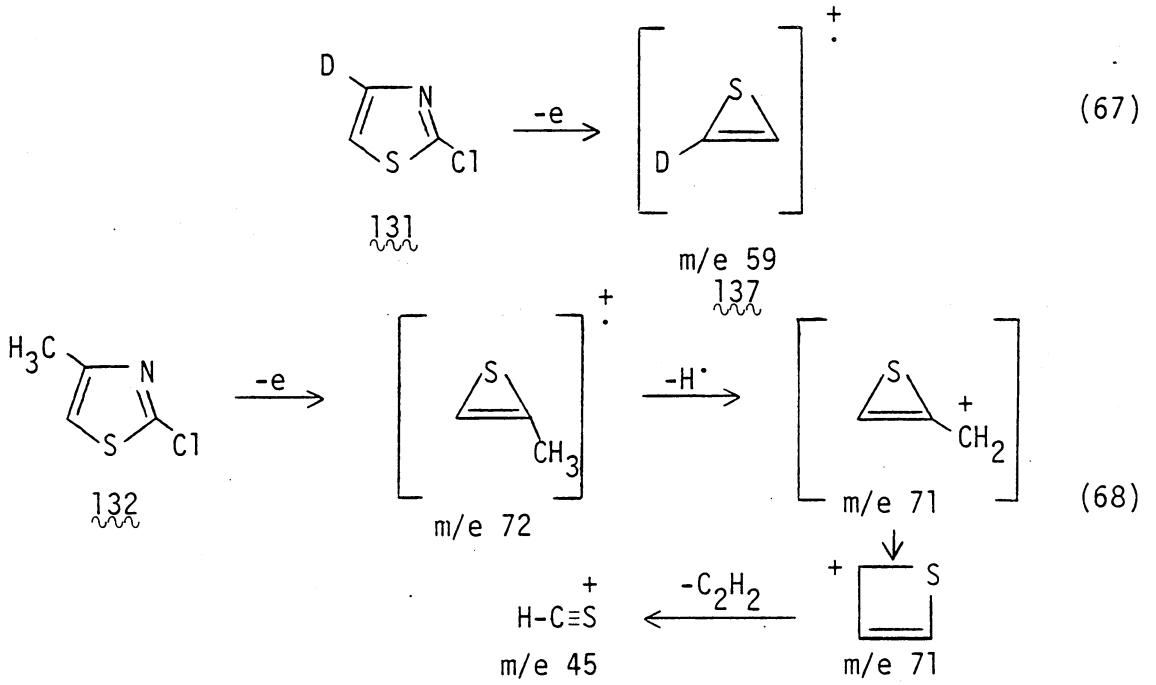
m/e 72 m/e 71 (66)
133 134



m/e 71 m/e 45
135 136

The M-HCN ion may be formulated as the methylthirene ion-radical (133), which then loses a hydrogen radical to give an ion of mass 71 (134). Cation 128 can then ring expand to thietenyl cation (135), which ultimately eliminates C_2H_2 to form ion 136.

The mass spectra for 131 and 132 can be explained by the same type fragmentation patterns as illustrated for the fragmentation of 4-methylthiazole (eq 67 and 68). Examining the mass spectra for 131 and

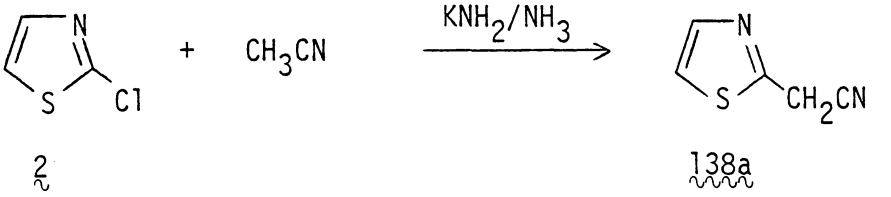


132 indeed shows peaks for the appropriate molecular ions and fragments 133, 134, and 137.

N,N-Dimethylacetamide Enolate. Attempted photostimulated and dark reactions of 2 with N,N-dimethylacetamide enolate in liquid ammonia for 1 h produced a black intractable tar (Expts 86 and 87).

Nitrile Carbanions. Photostimulated reaction of 2 with potassioacetonitrile carbanion for 1 h in liquid ammonia gave a 79% yield

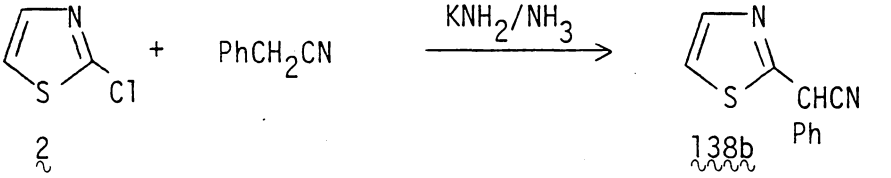
of 138a, while a dark reaction gave a 96% yield of 138a (eq 69) (Table XIV, Expts 88 and 89). When the dark reaction was conducted in the



2 138a (69)

presence of 10 mol % of DTBN, a 96% yield of 138a was obtained (Expt 90).

The photostimulated reaction of 2 with phenylacetonitrile carbanion in liquid ammonia for 1 h gave a 48% yield of 138b, while the dark reaction gave a 56% yield of 138b (eq 70) (Expts 91 and 92). When a dark



2 138b (70)

reaction of these two reactants was conducted in the presence of 10 mol % of p-dinitrobenzene (p-DNB), 138b was produced in 42% yield (Expt 93). Increasing the reaction time from 1 h to 4 h gave a 39% yield of 138b (Expt 94).

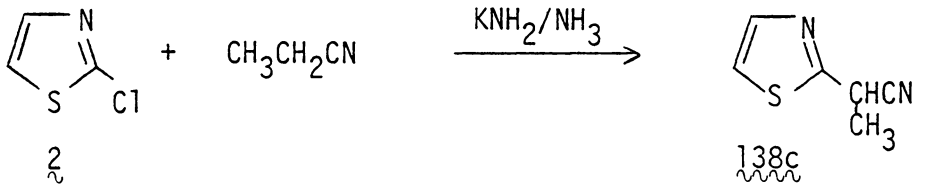
Photostimulated reaction of 2 with propionitrile carbanion for 1 h in liquid ammonia gave a 62% yield of 138c, while the dark reaction gave an 83% yield of 138c (eq 71) (Expts 95 and 96).

Table XIV

Reactions of 2-Chlorothiazole (2) with Nitrile Carbanions

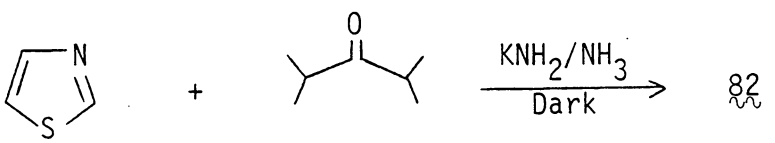
Expt.	Carbanion From	Reaction Conditions[a]	Reaction Time (min)	Product	Product Yield, %
88	Acetonitrile	KNH_2/NH_3,hν	60	138a	79
89	Acetonitrile	KNH_2/NH_3,dark	60	138a	96
90	Acetonitrile	KNH_2/NH_3,dark,DTBN	60	138a	96
91	Phenylacetonitrile	KNH_2/NH_3,hν	60	138b	48
92	Phenylacetonitrile	KNH_2/NH_3,dark	60	138b	56
93	Phenylacetonitrile	KNH_2/NH_3,dark,p-DNB	60	138b	42
94	Phenylacetonitrile	KNH_2/NH_3/hν	240	138b	39
95	Propionitrile	KNH_2/NH_3,hν	60	138c	62
96	Propionitrile	KNH_2/NH_3,dark	60	138c	83

[a] Molar ratio of carbanion to 2 was 4:1



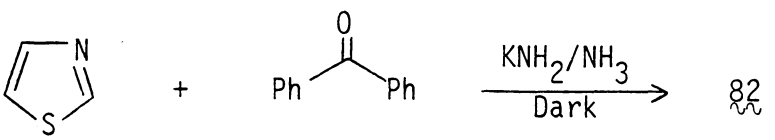
2 138c (71)

Attempted Reactions of Thiazole (82) with Diisopropyl Ketone Enolate and Benzophenone. From the results of our work with the reactions of 2 with diisopropyl ketone and benzophenone, we decided to extend our study of the parent thiazole ring system. We wondered if thiazole (82) would react in an aldol-type condensation with diisopropyl ketone and benzophenone as did 2-chlorothiazole (2). Treatment of 82 with 4 equiv of diisopropyl ketone enolate, generated by means of potassium amide in liquid ammonia, for 1 h and for 5 h gave a quantitative recovery of 82 (eq 72) (Table XV, Expts 98 and 99). An attempted 5-h reaction of



82 (72)

82 with benzophenone in the presence of 4 equiv of potassium amide in liquid ammonia gave a quantitative recovery of 82 (eq 73) (Table XV, Expt 100).



82 (73)

Table XV

Attempted Reactions of Thiazole (82) with Diisopropyl Ketone Enolate and Benzophenone

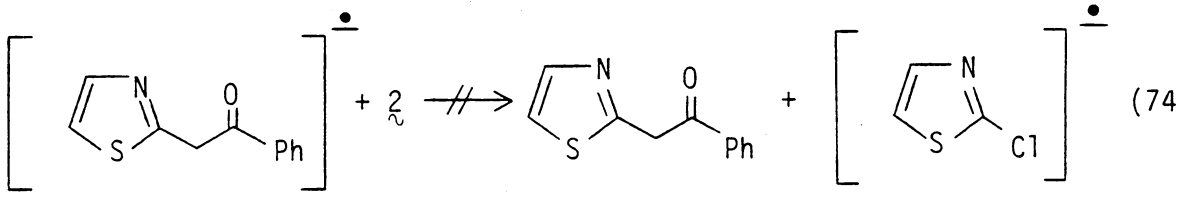
Expt.	Ketone	Reaction Conditions	Reaction Time (min)	Product	Product Yield %
98	Diisopropyl Ketone	KNH_2/NH_3,dark	60	82	100
99	Diisopropyl Ketone	KNH_2/NH_3,dark	300	82	100
100	Benzophenone	KNH_2/NH_3,dark	300	82	100

DISCUSSION

Formation of ketone 125a in the photostimulated reaction of 2 with the potassium enolate of pinacolone provides good evidence that chloride displacement proceeds via the $S_{RN}1$ mechanism as shown in Scheme IV. This sequence is typical of aromatic $S_{RN}1$ reactions (Scheme IV)[26]. Disubstitution product 125b probably arises by a similar mechanistic pathway involving the enolate derived from monosubstitution product 125a (Scheme V).

Reasons for the failure of the photostimulated and dark reactions of 2 with potassioacetone are not clear at the present. From ^1H NMR analysis, the expected substitution product (125c) appeared to have been formed, but decomposed during attempted purification.

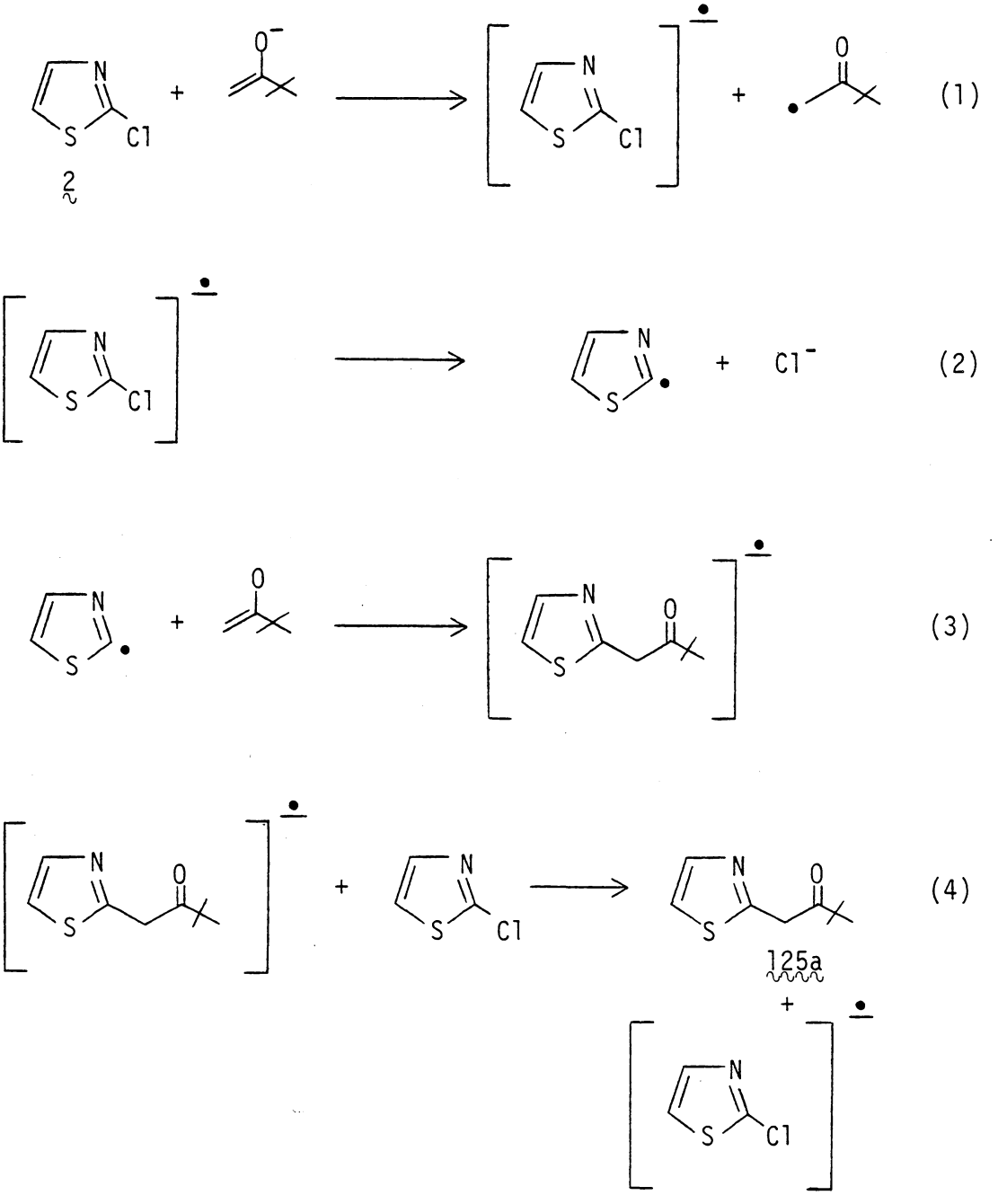
The absence of a photostimulated reaction of 2 with potassioacetophenone enolate may be due to the reluctance of the radical anion of the substitution product to transfer an electron to another substrate molecule (eq 74).



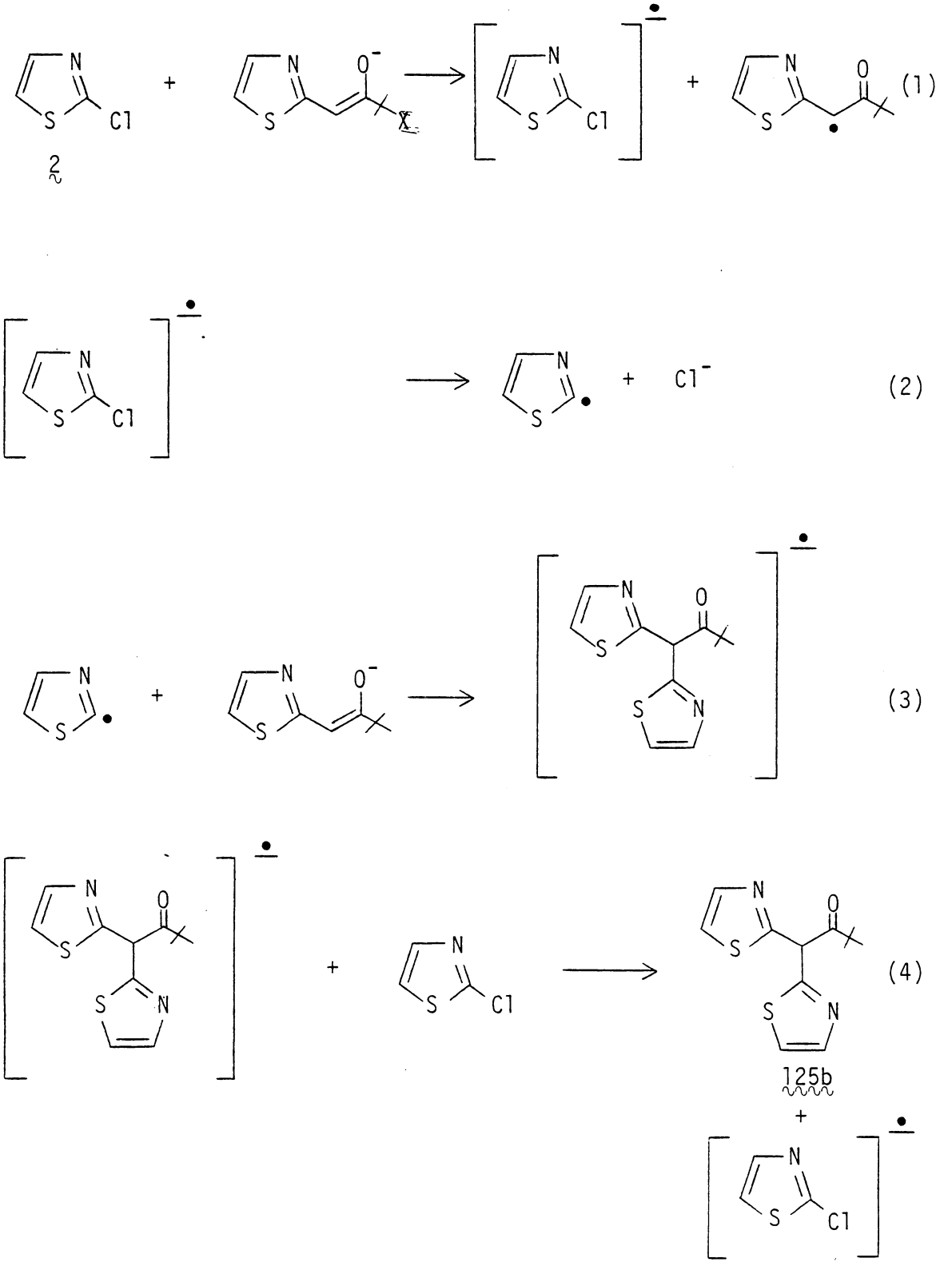
(74)

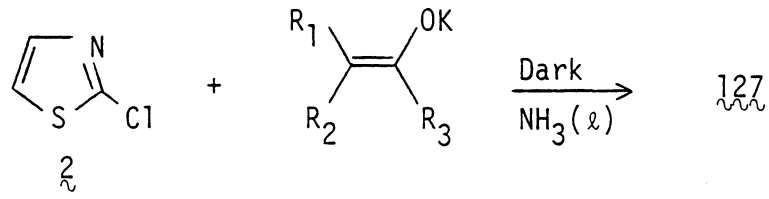
When 2-chlorothiazole (2) was allowed to react with the potassium enolate of pinacolone in the absence of illumination, a completely unexpected product (127a) was formed (eq 75).

Scheme IV



Scheme V



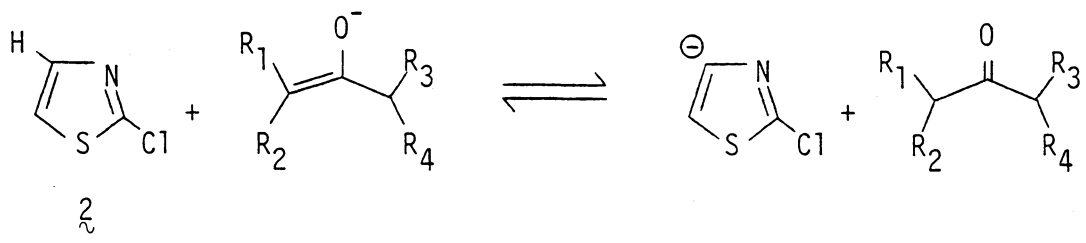


(75)

127a: R1=R2=H; R3=t-Bu

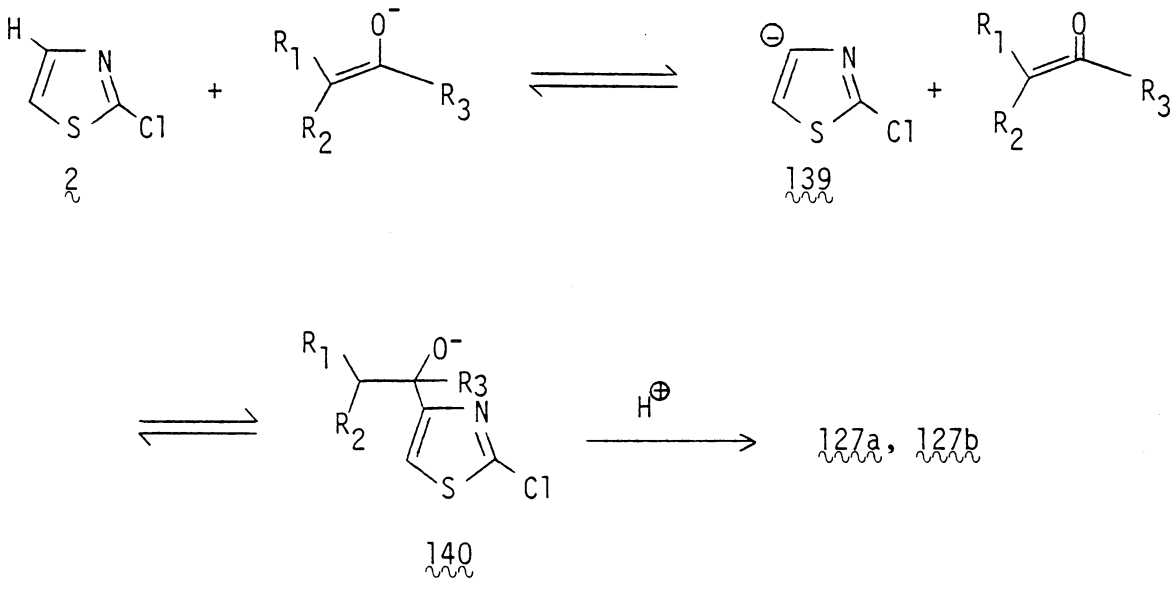
127b: R1=R2=CH3; R3=i-PrO

It appears that formation of carbinols 127a and 127b from reactions of 2 with the potassium enolates of pinacolone and diisopropyl ketone in liquid ammonia is best explained by the "Aldol-type" reaction illustrated in Scheme VI. In this sequence of reactions, the appropriate ketone enolate reacts with 2 to abstract a proton from position-4 to form anion 139 and neutral ketone. Condensation of these reactants then yields alkoxide ion 140, which gives the observed alcohols upon acidification of the reaction mixture. Formation of 140 presumably overcomes the unfavorable equilibrium associated with generation of 139. The dark reactions of 2 with diisopropyl ketone enolate generated by LDA in THF demonstrate that the amount of LDA and ketone to 2 must be greater than 1:1 for successful condensation. This can be explained by eq 76. When the ratio of 2



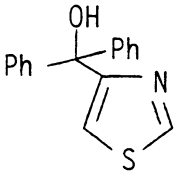
(76)

Scheme VI


H
N
S
Cl
2
+
R1
O⁻
R2
R3
⊖
N
S
Cl
139
+
R1
O
R2
R3
R1
O⁻
R3
R2
N
S
Cl
140
H⊕
127a, 127b

to ketone enolate is 1:1, the equilibrium in eq 76 lies to the left, but with an excess of ketone enolate present the equilibrium is shifted to the right, thus producing carbinol 127b. To see if base is needed for the formation of 127a and 127b, 2 was reacted with diisopropyl ketone in a 1:4 ratio in liquid ammonia for 1 h (Table XII, Expt 75). With these reaction conditions, a quantitative recovery of 2 was produced, thus showing the requirement for a strong base such as diisopropyl ketone enolate.

If the formation of 127a and 127b proceeded by the aldol-type condensation as shown in Scheme VI, conducting a series of trapping experiments as illustrated in Table XIII would confirm this. If an anion was being generated at C-4 on 2 as shown in Scheme VI, then benzophenone could trap the anion, thus giving rise to product 128. This was shown to be the case by Experiments 78, 79, and 80 (Table XIII) when

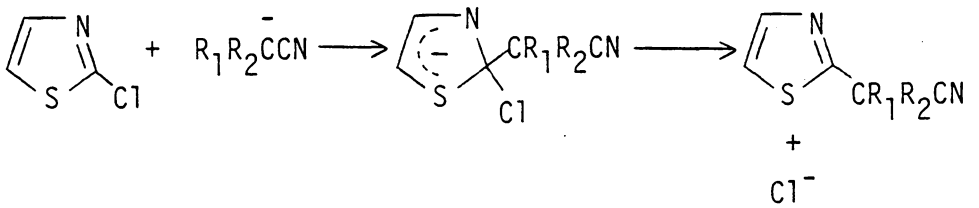


128

128 was formed in yields of 66%, 100%, and 100%, respectively from the dark reaction of 2 with 4.0 equiv of benzophenone using 4.0 equiv of potassium amide in liquid ammonia, 4.0 equiv or 1.0 equiv of LDA in THF.

That deprotonation of 2 as shown in Scheme VI is, indeed, a viable mechanism for such aldol-type condensations is also supported by the results of D_2O and iodomethane quenching following treatment of 2 with either LDA or KNH_2 (Expts 84 and 85).

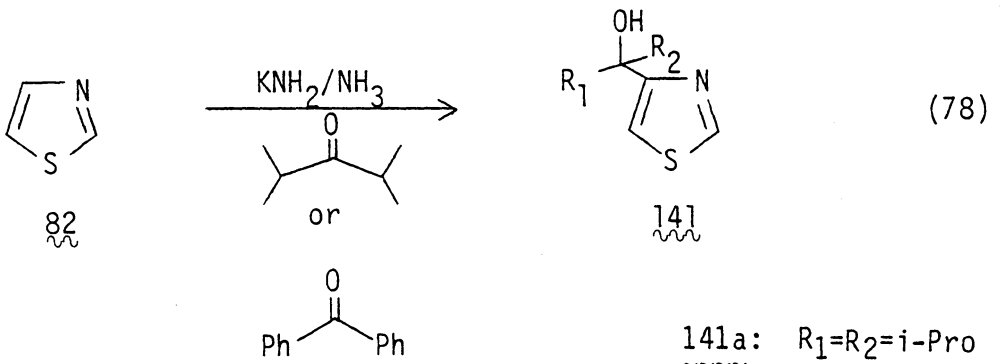
From the results in Table XIV, reactions of 2 with the carbanions of acetonitrile, phenylacetonitrile, and propionitrile do not appear to proceed by the $S_{RN}1$ mechanism, but by the S_nAr mechanism (eq 77) since



(77)

the yields of substitution products 138a, 138b, and 138c were not decreased when the reactions were conducted in the dark or in the presence of 10 mol % of DTBN.

Apparently, the reactions of diisopropyl ketone enolate and benzophenone with 82 in potassium amide do not generate an anion at C-4 since products 141a and 141b were not produced (eq 78). To the best of our knowledge this represents the first example of direct metalation at position C-4 of a thiazole derivative. As discussed earlier in this dissertation, metalation occurs at the position-2 of thiazole[68]. Our results open a new aspect of thiazole chemistry.



82 141 (78)

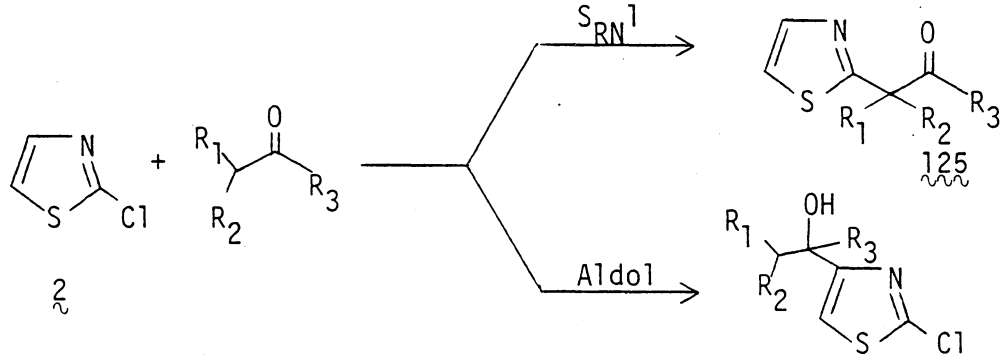
141a: $R_1=R_2=$i-Pro

141b: $R_1=R_2=$Ph

IV. SUMMARY

This study has extended the knowledge of the $S_{RN}1$ reaction to include the photostimulated reactions of 4-chloro-2,6-dimethoxypyrimidine (1) and 2-chlorothiazole (2) with selected carbanion nucleophiles. The reactions of 1 with the enolates of acetone, diisopropyl ketone, pinacolone, and ethyl phenylacetate have been shown to be a viable method for the synthesis of precursors to 6-substituted uracils via the $S_{RN}1$ reaction. Although the reactions of 1 with acetonitrile and propionitrile have been shown to give both 101 and 108 resulting from displacement of chloride and 102 and 109 arising from displacement of methoxide, all four products could in theory be hydrolyzed to give the desired substituted uracils.

Reactions of 2 with ketone enolates have been shown to proceed by two competitive reaction pathways (eq 79). With relatively unhindered ketones such as pinacolone, the photostimulated reaction proceeds



2

125

127

(79)

125a: $R_1=R_2=H$; $R_3=t$-Bu

125b: $R_1=H$; $R_2=$; $R_3=t$-Bu

127a: $R_1=R_2=H$; $R_3=t$-Bu

127b: $R_1=R_2=CH_3$; $R_3=CH(CH_3)_2$

by the $S_{RN}1$ mechanism to give two chlorine displaced products (125a,125b), while the dark reaction proceeds by an aldol-type condensation to give carbinol (127a). Dark or photostimulated reactions of 2 with hindered ketones such as diisopropyl ketone give only carbinol (127b). Reactions of 2 with carbanions of nitriles such as acetonitrile, propionitrile, and phenylacetonitrile proceed by the S_nAr mechanism to give chlorine displaced products (138a, 138b, and 138c).

Evidence for the formation of carbinols 127a and 127b via an aldol-type condensation (Scheme VI) is supported by the KNH_2 and LDA promoted reactions of 2 with benzophenone, and by the results of D_2O and iodomethane quenching following treatment of 2 with LDA.

Finally, thiazole itself does not enter into the aldol-type reactions with diisopropyl ketone or benzophenone as was observed for 2. Apparently, the reactions of thiazole (82) with the potassium enolate of diisopropyl ketone and with benzophenone in liquid ammonia require the electron-withdrawing effect of the chlorine atom at carbon-2.

IV. EXPERIMENTAL

Photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor equipped with four 12.5 W lamps emitting maximally at 350 nm.[84] Commercial anhydrous liquid ammonia (Matheson) was used directly from the tank. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl under nitrogen. Solvents such as hexane, ethyl acetate, methylene chloride, and chloroform, which were used for flash chromatography, were distilled before use. All other solvents were used without further purification. The heteroaromatic substrates and the carbanion precursors were purified by either distillation or recrystallization.

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were obtained on Varian EM-390 and Bruker WP-200 spectrometers, respectively. Chemical shifts are reported based on the center of the peak in parts per million (δ) with respect to the internal standard, tetramethylsilane (TMS). The abbreviations for the reported splitting patterns are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Infrared spectra were determined on a Perkin-Elmer 710B or a Beckman IR-20A-X infrared spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Mass spectra were determined by Kim Harich on a Varian MAT-112 mass spectrometer in the Department of Biochemistry and Nutrition at Virginia Tech. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. Gas chromatographic analyses were performed on a Varian Aerograph 90-P instrument, using a 5' x 1/4"

aluminum column packed with 5% Carbowax 20 M on Chromosorb W. Helium was used as the carrier gas at a flow rate of 60-70 mL/minute. HPLC analyses were done on a Waters Associates 6000 HPLC instrument, using a 10 mm x 250 mm reverse phase (HP-8) MICROSORB column. Analytical thin layer chromatography (TLC) was conducted on Eastman 13181 silica gel with fluorescent indicator on plastic backing. Flash chromatography[85] was conducted with E. M. Merck silica gel (230-400 mesh) under compressed air. Kugelrohr distillation was conducted with an Aldrich Kugelrohr distillation apparatus at 50-70°C (0.1 mm).

Procedure A - Photostimulated Reactions Using KNH_2 in Liquid Ammonia

Approximately 150-175 mL of anhydrous ammonia was introduced directly into a cylindrical Dewar flask (unsilvered) equipped with a two-armed adapter, a Dry-Ice condenser, and a metal stirring bar under an atmosphere of nitrogen (Fig. 1). Using positive nitrogen pressure, 0.44 g (11.25 mg atm) of potassium metal was dropped into the ammonia, which immediately produced a dark blue color. A few crystals of ferric nitrate ($Fe(NO_3)_3 \cdot 9H_2O$) were added and vigorous gas evolution was observed. The blue color disappeared within 60-75 min, and the formation of potassium amide was assumed to be complete. An anhydrous ethereal solution of the purified precursor of the carbanion nucleophile (11.25 mmol) was added dropwise via syringe. The reaction solution was stirred for about 20 min to allow for anion formation. The lights of the photochemical reactor were turned on, and 3 mmol of the appropriate substrate in 10 mL of anhydrous ether was added dropwise via syringe. After irradiation for 15 min, the reaction mixture was quenched by pouring the liquid ammonia

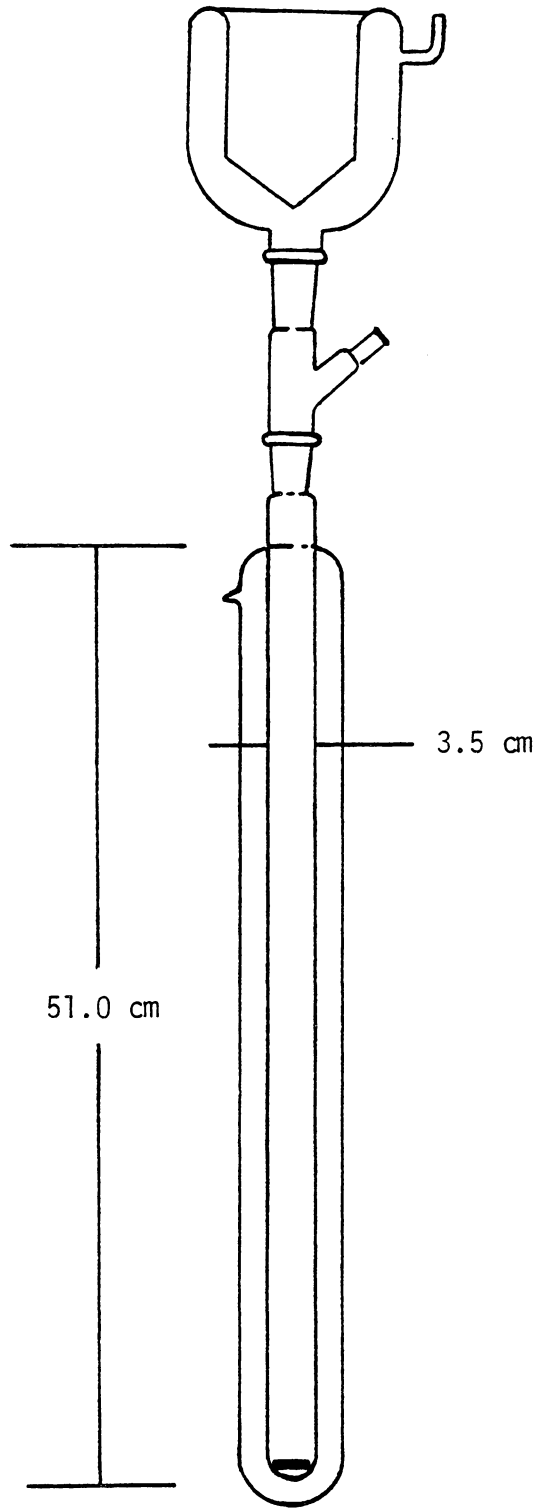


Figure 1: Unsilvered Cylindrical Dewar Flask

solution directly onto solid ammonium chloride (3.5 g) in a 2-L beaker. The reaction vessel was then rinsed with 2 x 100 mL of ether, and the rinses were added to the original ammonia solution. Evaporation of the ammonia was accomplished by using a warm hot plate (ammonia was evaporated within 30 min). The remaining ethereal solution was filtered and the solid residue triturated with 4 x 50 mL of ether to extract organic materials. The remaining solid residue was neutralized to pH 5-6 with 10% HCl solution, then extracted once again with 4 x 50 mL of ether. The ethereal washings were combined and dried over $MgSO_4$. Evaporation of the ether by means of a rotorary evaporator yielded the crude products.

Procedure B - Photostimulated Reactions Using LDA in THF

Into a 250 mL 3-neck round-bottomed flask equipped with a thermometer, glass adapter, glass stopper, and teflon coated stirring bar was added 30 mL of THF and 1.6 mL (8.23 mmol) of N,N-diisopropylamine via syringe under an atmosphere of nitrogen. The flask was then immersed in an acetone-Dry Ice bath and allowed to cool to -78°C. To this was added dropwise via syringe 7.5 mmol of n-BuLi over a period of 5-10 min. After the addition was complete, the reaction mixture was allowed to stir at -78°C for about 30 min to assure formation of lithium diisopropylamide (LDA). After LDA formation was completed, 7.5 mmol of the purified carbanion precursor was added dropwise via syringe. The reaction was stirred for about 20 min to assure anion formation, then the Dry Ice-acetone bath was removed to allow the reaction mixture to warm to room temperature. After the solution reached room temperature, 3 mmol of the aromatic substrate was added via syringe, then the entire contents of the

flask were transferred to an air-jacketed, water-cooled photoreaction vessel via a double-ended needle (Fig. 2). The original 3-necked reaction flask was rinsed with 50-75 mL of THF, which was also added to the photoreaction flask as before. The lamps of the photoreactor were turned on, and the reaction mixture was irradiated for 4 h. The reaction mixture was then quenched by pouring the THF solution directly over a mixture of ice and 100 mL of 2N HCl solution. The acidified solution was extracted with 4 x 50 mL portions of ether. The ethereal washings were combined, then dried over $MgSO_4$. The THF/ether mixture was removed by rotorary evaporation to yield the crude products.

Procedure C - Dark Reactions Using KNH_2 in Liquid Ammonia

These reactions were conducted in the same manner as described in Procedure A, with the exception that the photoreaction vessel was carefully wrapped with several layers of black cloth and the surrounding lights extinguished prior to addition of the aromatic substrate.

Procedure D - Dark Reactions Using LDA in THF

These reactions were conducted in the same manner as described in Procedure B, with the exception that the air-jacketed, water-cooled photoreaction vessel was carefully wrapped with several layers of black cloth and the surrounding lights extinguished prior to addition of the aromatic substrate.

Procedure E - Inhibited Photostimulated Reactions

These reactions were conducted in the same manner as described in Procedure A, with the exception that 0.04 g (10 mol %) of di-t-butyl

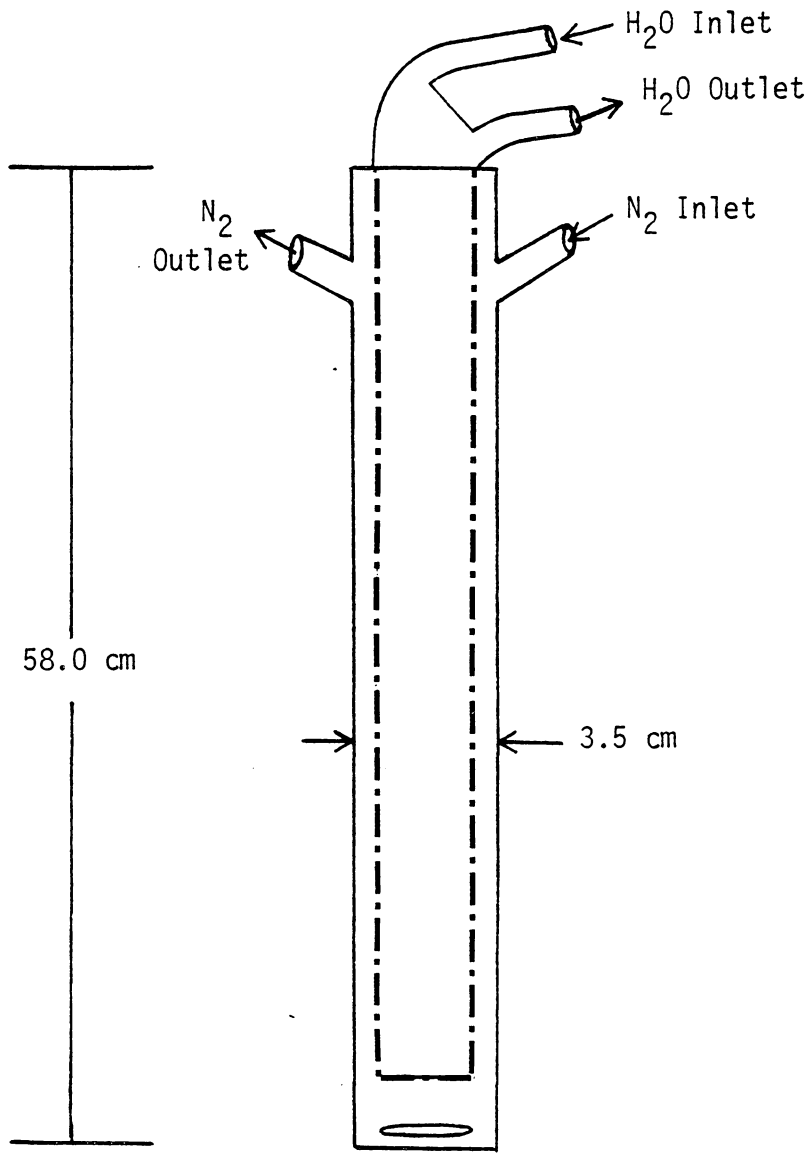


Figure 2: Air-Jacketed, Water-Cooled Photoreaction Vessel

nitroxide (DTBN)[21] was introduced prior to addition of the substrate.

Procedure F - Inhibited Dark Reactions

These reactions were conducted in the same manner as described in Procedure E, except that the reaction was conducted in the dark.

Procedure G - Inhibited Dark Reactions

These reactions were conducted in the same manner as described in Procedure F with the exception that 0.05 g (10m %) of p-dinitrobenzene was introduced prior to addition of the substrate.

Procedure H - Modification of Photostimulated Reactions With 2-Chlorothiazole (2) as Substrate

Reactions involving 2 were conducted in the same manner as in Procedure A with the following exceptions. First, the amounts of each reactant used were as follows: 0.66 g (17 mg atm) of potassium metal in 200 mL of liquid ammonia, 17 mmol of the carbanion precursor, and 0.5 g (4 mmol) of 2. Secondly, the irradiation period was 1 h.

Procedure I - Modification of Dark Reactions With 2 as Substrate

These reactions were conducted in the same manner as Procedure H with the exception that the glassware was wrapped in a black cloth, and the surrounding lights extinguished prior to addition of 2.

Experiment 1. Preparation of 2,4,6-Trichloropyrimidine[86]

Into a 1-L, 3-neck round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel was added 150 mL of phosphorus oxychloride ($POCl_3$) and 89 mL of N,N-dimethylaniline. To this

was added 52 g (0.41 mol) of barbituric acid, which had been dried for 2 days at approximately 90°C. The reaction mixture was then refluxed for 2 h in a hot water bath, after which the excess $POCl_3$ was removed by vacuum distillation, bp 34°C (4 mm). The syrupy residue that remained was poured over ice. The resulting aqueous suspension was extracted with 6 x 50 mL of ether. The ethereal extracts were combined and dried over $MgSO_4$. The ether was removed by rotorary evaporation, and the remaining yellow residue distilled under vacuum, bp 110-112°C (4 mm) (Lit.[86] bp 95°C (11 mm)), to yield 49.0 g (66%) of 2,4,6-trichloropyrimidine as white crystals, mp 20°C. (Lit.[86] mp 21°C): ^1H NMR ($CDCl_3$) δ 7.4 (s,1H,H_5 pyr).

Experiment 2. Preparation of 4-Chloro-2,6-Dimethoxypyrimidine[87] (1)

Into a 1-L erlenmeyer flask equipped with a teflon-coated stirring bar was added 47 g (0.26 mol) of 2,4,6-trichloropyrimidine (142) and 677 mL of spectranalyzed grade methanol. To this was added portionwise a solution of sodium methoxide prepared from 12 g (0.52 mol) of freshly cut sodium metal in 152 mL of spectra grade methanol. After addition of the sodium methoxide solution was complete the reaction mixture was allowed to stir at room temperature overnight. The reaction solution was then decanted from the precipitated NaCl and cooled in ice, which produced white crystals. The crystals were filtered and washed with water, dried in vacuo, and then recrystallized from petroleum ether to afford 48 g (98%) of 1, mp 74°C (Lit.[87] mp 76-77°C): ^1H NMR ($CDCl_3$) δ 3.9 (d,6H, $(OCH_3)_2$), 7.4 (s,1H,H_5 pyr); ^{13}C NMR ($CDCl_3$) δ 172.168 (s,1C,C-2), 164.831 (s,1C,C-4), 161.181 (s,1C,C-6), 100.768 (s,1C,C-5), 55.247 (s,1C,OCH_3), 54.342 (s,1C,OCH_3).

Experiment 3. Preparation of 2-Methoxypyrimidine[88] (105)

Into a 1-neck, 100 mL round-bottomed flask was added 25 mL of methanol and 0.5 g (0.02 mol) of sodium metal. To this solution was added 2 g (0.017 mol) of 2-chloropyrimidine, then the flask was fitted with a reflux condenser and the reaction mixture refluxed for 30 min. The reaction flask was cooled, then carbon dioxide was passed into the flask until the solvent was saturated. The methanol was removed by rotorary evaporation, then the solid residue was extracted with 3 x 20 mL portion of ether. The ether washings were combined and dried over $MgSO_4$. The ether was removed by rotorary evaporation, and the remaining liquid distilled to yield 0.70 g (80%) of 105 as a clear liquid, bp 77°C (25 mm) (Lit.[89] 70-71°C (15 mm)): ^{13}C NMR ($CDCl_3$) δ 164.947 (s,1C,C-2), 158.640 (s,1C,C-6), 114.316 (s,1C,C-5), 54.108 (s,1C,OCH_3).

Experiment 4. Preparation of 2,4-Dimethoxypyrimidine[88] (104)

Into a 1-neck, 250 mL round-bottomed flask was added 100 mL of methanol and 1.66 g (72 mmol) of sodium metal. To this solution was added 4 g (27 mmol) of 2,4-dichloropyrimidine, then the flask was fitted with a reflux condenser and the mixture refluxed for 4 h. After the reflux period, the flask was cooled, then carbon dioxide was passed into the flask until saturation occurred. The methanol was removed by rotorary evaporation, then the solid residue was extracted with 3 x 20 mL portions of ether. The ether washings were combined, then dried over $MgSO_4$. the ether was removed by rotary evaporation and the remaining liquid was vacuum distilled to yield 2.65 g (clear liquid 70%) of 104 as a clear liquid, bp 97°C (15 mm) (Lit.[88] 110°C (20 mm)).

Experiment 5. Preparation of 4-Iodo-2,6-Dimethoxypyrimidine[89] (110)

Into a 1-neck, 100 mL round-bottomed flask was added 3 g (0.0173 mol) of 4-chloro-2,6-dimethoxypyrimidine, 12.1 g of NaI, and 30 mL of DMF. The flask was fitted with a reflux condenser equipped with a nitrogen inlet, then the reaction mixture was refluxed for 1 h. After the reaction period, the flask was cooled to room temperature, then the DMF was removed by vacuum distillation. The remaining solid was washed with water, and recrystallized twice from ethanol to give 2 g (44%) of 110 as white crystals, mp 174-175°C (Lit.[89] mp 175-176°C).

Experiment 6. Preparation of 2-Chloro-4-Methoxypyrimidine[90] (111)

Into a 1-neck, 250 mL flask was added 5.5 g (0.034 mol) of 2,4-dichloropyrimidine, 60 mL of methanol, and 50 ml of sodium methoxide solution prepared from 0.85 g of sodium metal. The flask was fitted with a reflux condenser, and the reaction mixture was refluxed for 35 min. The methanol was removed by rotary evaporation, the residue was diluted with water and extracted with 4 x 40 mL portions of $CHCl_3$. The $CHCl_3$ washings were combined, dried over $MgSO_4$, and concentrated. The solid residue was extracted once with hexane to yield 3.7 g (69%) of 111 as white crystals, mp 50-52°C (Lit.[90] mp 55°C).

Experiment 7. Preparation of 6-Chloro-2,4-Dihydroxypyrimidine (95)[89]

Into a 1-neck, 250 mL round-bottomed flask was added 0.3 g (0.0017 mol) of 4-chloro-2,6-dimethoxypyrimidine, 26 mL of glacial acetic acid, and 3.3 mL of 2N HCl. The flask was then fitted with a reflux condenser and refluxed for 1 h. The mixed acids were then removed under reduced

pressure, and the resulting yellow solid recrystallized twice from H_2O to yield 0.14 g (55%) of 95 as white crystals, mp 296-297°C (Lit.[89] 299-300°C).

Experiment 8. Preparation of t-butylpropionate[91]

The method[91] of Hauser et al. was followed to yield 101.5 g (68%) of t-butylpropionate, bp 117°C (Lit.[91] bp 118°C).

Experiment 9. Preparation of 2,2,7,7-tetramethyl-3,6-octadione (126)[92,93]

The method of Ito[92,93] was followed to yield 1.5 g (38%) of 2,2,7,7-tetramethyl-3,6-octadione, bp 97-99°C (7 mm).

Experiment 10. Preparation of 2-Chlorothiazole (2)[94]

Into a 4-L erlenmeyer flask was added 60 g (0.599 mol) of 2-aminothiazole and 240 mL of 85% H_3PO_4. The flask was cooled to 5°C, then 120 mL of concentrated HNO_3 was added in portions so that the temperature did not exceed 5°C. To the resulting solution was added dropwise from a funnel a solution of 48 g of $NaNO_2$ in 125 mL of H_2O. After the addition was complete, the solution was stirred for 15 min, then a solution of 100 g of $CuSO_4 \cdot 5H_2O$ and 100 g of NaCl in 400 mL of H_2O was added over a 45 min period. The solution was stirred for an additional 30 min, then partially neutralized to pH5 with 50% NaOH solution. The solution was then steam distilled to give 31 g of crude 2-chlorothiazole. The crude product was then taken up in ether, washed with dilute NaOH solution and H_2O, then dried over $MgSO_4$. The ether was removed by rotorary evaporation, and the remaining liquid was distilled

to yield 30 g (46%) of 2 as a clear liquid, bp 55-57°C (25 mm) (Lit.[94] bp 44-45°C (5 mm)): ^{1}H NMR ($CDCl_3$) δ 7.3 (d,1H,H_5), 7.6 (d,1H,H_4); ^{13}C NMR ($CDCl_3$) 151.904 (s,1C,C-2), 141.618 (s,1C,C-4), 121.456 (s,1C,C-5), mass spectrum, m/e (relative intensity) 43(10), 57(12), 58(100), 119(60), 121(21).

Experiment 11. Photostimulated Reaction of Acetone Enolate with 4-Chloro-2,6-Dihydroxypyrimidine (94)

Procedure A was followed, with the exception that an irradiation period of 2 h was employed to yield starting 94 and 4-hydroxy-4-methyl-2-pentanone 133: ^{1}H NMR ($CDCl_3$) δ 1.3 (s,9H,$(CH_3)_3$), 2.6 (s,2H,CH_2), 3.5 (s,1H,OH). Anal. Calcd for $C_6H_{12}O_2$: C, 62.07; H, 10.34; O, 27.59. Found: C, 62.22; H, 10.36.

Experiment 12. Photostimulated Reaction of Pinacolone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a yellow oil which was purified by flash chromatography[85] (80:20 hexane-ethylacetate). Kugelrohr distillation then yielded 0.03 g (6%) of recovered 1 and 0.49 g (69%) of 1-(2,6-dimethoxypyrimidin-4-yl)-3,3-dimethyl-2-butanone (50) as a light yellow oil: IR (neat) 3020 w(CH), 1705 s(C=O), 1635 s, 1595 s, 1560 s, 1540 s, 1385 s, 1095 s, 1057 s cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19(s,9H,t-Bu), 3.88 (s,2H,CH_2), 3.94 (s,6H,$(OCH_3)_2$), 6.28 (s,1H,H_5 pyr). Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.50; H, 7.56; N, 11.76; O, 20.16. Found C, 60.31; H, 7.74; N, 11.75; mass spectrum, m/e (relative intensity) 153(27), 154(50), 181(100), 238(M^+9).

Experiment 13. Dark Reaction of Pinacolone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give only recovered 1 and pinacolone.

Experiment 14. Photostimulated Reaction of Acetone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a yellow oil, which was purified by flash chromatography (80:20 hexene-ethyl acetate) and then Kugelrohr distillation to give 0.04 g (8%) of recovered 1 and 0.44 g (75%) of 1-(2,6-dimethoxypyrimidin-4-yl)-2-propanone (98a) as a colorless oil: IR (neat) 2980 w(CH), 1720 s(C=O), 1590 s(pyr), 1490 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (s,3H,CH_3), 3.7 (s,2H,CH_2), 3.9 (s,6H,$(OCH_3)_2$), 6.3 (s,1H,H_5 pyr). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.10; N, 6.10; N, 14.40. Found: C, 54.88; H, 6.08; N, 14.28; mass spectrum, m/e (relative intensity) 153(5), 154(100), 181(20), 196(M^+27).

Experiment 15. Dark Reaction of Acetone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give a light yellow crystalline material which was shown to contain two compounds, 4-chloro-2,6-dimethoxypyrimidine (1) and 1-(2,6-dimethoxypyrimidin-4-yl)-2-propanone (98a) by tlc (80:20 hexane-ethyl acetate). The compounds were separated by flash chromatography (80:20 hexane-ethyl acetate), and found to be 0.47 g (90%) of 1 and 0.05 g (9%) of 98a by tlc (80:20 hexane-ethyl acetate) comparison to authenic samples of 1 and 98a.

Experiment 16. Inhibited Photostimulated Reaction of Acetone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure E was followed to give .52 g (100%) of recovered 1.

Experiment 17. Photostimulated Reaction of Acetone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure B was followed with the exception that the reaction time was extended from 15 min to 6 h. This procedure resulted in quantitative recovery of 1.

Experiment 18. Photostimulated Reaction of Acetone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure B was followed with the following two exceptions to yield a quantitative recovery of 1. First, the reaction time was 6 h, and, secondly, 30 mmol of hexamethylphosphromide (HMPA) was added to the reaction prior to illumination.

Experiment 19. Photostimulated Reaction of Diisopropyl Ketone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a light yellow liquid which was purified by flash chromatography (80:20 hexane-ethyl acetate) and then Kugelrohr distillation to give 0.05 g (5%) of recovered 1 and 0.39 g (52%) of 2-(2,6-dimethoxypyrimidin-4-yl)-2,4-dimethyl-3-pentanone (98b) as a colorless oil: IR (neat) 2990 w(CH), 1720 s(C=O), 1590 s, 1470 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (d,6H,$(CH_3)_2$), 1.4 (d,6H,$(CH_3)_2$), 2.7 (septet,1H,CH), 3.9 (s,12H,$(OCH_3)_4$), 5.6 (s,1H,vinylic), 6.3

(s,2H,H_5 pyr). Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.90; H, 7.94; N, 11.11. Found: C, 61.67; H, 8.04; N, 11.40; mass spectrum, m/e (relative intensity) 167(35), 181(26), 182(100), 183(13), 252(2).

Experiment 20. Dark Reaction of Diisopropyl Ketone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give a bronze oil which was purified by flash chromatography (90:10 hexane-ethyl acetate) to give 0.22 g (42%) of 4-chloro-2,6-dimethoxypyrimidine (1) and 0.36 g (48%) of 2-(2,6-dimethoxypyrimidin-4-yl)-2,4-dimethyl-3-pentanone (98b) (tlc comparison to authenic samples of 1 and 98b).

Experiment 21. Inhibited Photostimulated Reaction of Diisopropyl Ketone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure E was followed to give 0.52 g (100%) of recovered 1.

Experiment 22. Inhibited Dark Reaction of Diisopropyl Ketone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure G was followed to give 0.52 g (100%) of recovered 1.

Experiment 23. Photostimulated Reaction of Acetophenone Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give only starting compounds 1 and acetophenone.

Experiment 24. Photostimulated Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a light orange oil which was

purified by flash chromatography (80:20 hexane-ethyl acetate) to yield white crystals (99). Recrystallization from hexane yielded 0.13 g (25%) of recovered 1 and 0.64 g (71%) of 4-(2-carbethoxybenzyl)-2,6-dimethoxypyrimidine (99), mp 63-64°: IR (CH_2Cl_2) 2990 w (C-H), 1720 s (C=O), 1580 s, 1560 s, 1460 s, 1450 s, 1340 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t,3H,CH_3), 3.9 (d,6H,$(OCH_3)_2$), 4.2 (q,2H,CH_2), 4.9 (s,1H,CH), 6.3 (s,1H,H_5 pyr), 7.3 (m,5H,a). Anal. Calcd in $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.53; H, 5.94; N, 9.17; mass spectrum, m/e (relative intensity) 157(16), 158(41), 230(100), 231(33), 301(88), 302(71).

Experiment 25. Dark Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give a yellow oil which was found by tlc (95:5 hexane-ethyl acetate) to be a mixture of two compounds. Flash chromatographic separation (95:5 hexane-ethyl acetate) yielded 0.31 g (60%) of recovered 4-chloro-2,6-dimethoxypyrimidine (1) and .03 g (8%) of 4-(2-carbethoxybenzyl)-2,6-dimethoxypyrimidine 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 26. Inhibited Photostimulated Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure E was followed to give a dark bronze oil, which was shown by tlc (80:20 hexane-ethyl acetate) to be a mixture of two components. Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.14 g (27%) of recovered 1 and 0.53 g (59%) of 99 (tlc comparison to

authenic samples of 1 and 99).

Experiment 27. Inhibited Photostimulated Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure E was followed with the exception that a full equivalent of DTBN was used. The resulting dark bronze oil consisted of two components as shown by tlc (80:20 hexane-ethyl acetate). Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.34 g (65%) of recovered 1 and 0.20 g (22%) of 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 28. Photostimulated Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed with the exception that the irradiation period was reduced from 15 min to 5 min. This procedure gave a bronze oil which contained two components as shown by tlc (80:20 hexane-ethyl acetate). Flash chromatographic separation yielded 0.11 g (21%) of recovered 1 and 0.54 g (60%) of 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 29. Inhibited Photostimulated Reaction of Ethyl Phenylacetate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure E was followed with the exception that the reaction time was 5 min rather than 15 min. This procedure gave a dark yellow oil which consisted of two components by tlc (80:20 hexane-ethyl acetate). Flash chromatographic separation yielded 0.11 g (21%) of recovered 1 and 0.42 (46%) of 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 30. Dark Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure D was followed to give a dark yellow oil which was shown to consist of two compounds by tlc (80:20 hexane-ethyl acetate). Flash chromatographic separation (80:20 hexane-ethyl acetate) produced 0.32 g (62%) of recovered 1 and 0.29 g (30%) of 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 31. Photostimulated Reaction of Ethyl Phenylacetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure B was followed to give a dark yellow oil which was found to consist of two compounds by tlc (80:20 hexane-ethyl acetate). Flash chromatographic separation yielded 0.23 g (44%) of recovered 1 and 0.45 g (50%) of 99 (tlc comparison to authenic samples of 1 and 99).

Experiment 32. Photostimulated Reaction of t-Butyl Acetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure B was followed to give a quantitative recovery of 1.

Experiment 33. Dark Reaction of t-Butyl Acetate Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure D was followed to give a quantitative recovery of 1.

Experiment 34. Photostimulated Reaction of N,N-Dimethylacetamide Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give an uncharacterizeable, intractable black tar.

Experiment 35. Dark Reaction of N,N-Dimethylacetamide Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give an uncharacterizeable, intractable black tar.

Experiment 36. Dark Reaction of N,N-Dimethylacetamide Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure D was followed to yield a dark red, intractable tar.

Experiment 37. Photostimulated Reaction of N,N-Dimethylacetamide Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure B was followed to give a dark red, intractable tar.

Experiment 38. Photostimulated Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a light brown oil which was purified by flash chromatography (80:20 hexane-ethyl acetate) to give an off-white crystalline compound. Recrystallization from hexane yielded 0.15 g (29%) of recovered 1 and 0.52 g (68%) of white crystalline 4-(α-cyanobenzyl)-2,6-dimethoxypyrimidine (100), mp 69-71°C: IR (CH_2Cl_2) 2990 w (CH), 2220 s (C≡N), 1590 s, 1480 s, 1460 s, 1380 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (d,6H,$(OCH_3)_2$), 5.0 (s,1H,CH), 6.4 (s,1H,H_5 pyr), 7.3 (m,5H,a). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.88; H, 5.09; N, 16.47. Found: C, 65.60; H, 5.21; N, 16.25; mass spectrum, m/e (relative intensity) 155(13), 183(12), 255(98), 256(100).

Experiment 39. Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give light yellow crystals which were recrystallized from hexane to yield 0.48 g (63%) of 4-(α-cyanobenzyl)-2,6-dimethoxypyrimidine (100) (tlc comparison to an authenic sample of 100).

Experiment 40. Inhibited Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure F was followed to give a dark yellow oil consisting of two components. Flash chromatographic separation (90:10 hexane-ethyl acetate) yielded 0.18 g (35%) of recovered 1 and 0.41 g (54%) of 100 (tlc comparison to authenic samples of 1 and 100).

Experiment 41. Inhibited Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure G was followed to give a black oil which was shown by tlc to consist of two components. Flash chromatographic separation (80:20 hexane-ethyl acetate) produced 0.05 g (3%) of recovered 1 and 0.60 g (79%) of 100 (tlc comparison to authenic samples of 1 and 100).

Experiment 42. Inhibited Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure F was followed with the exception that a full equivalent rather than 10 mol % of di-t-butyl nitroxide (DTBN) was used to give a black oil. Flash chromatographic separation (80:20 hexane-ethyl acetate) of the reaction mixture yielded 0.04 g (8%) of recovered 1, 0.59 g (51%)

of 100 (tlc comparison to authenic samples of 1 and 100), and 0.31 g of black tar.

Experiment 43. Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed with the exception that the reaction time was reduced from 15 min to 5 min. This procedure afforded a light yellow crystalline material that was recrystallized from hexane to yield 0.45 g (59%) of 100 (tlc comparison to an authenic sample of 100).

Experiment 44. Dark Inhibited Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure F was followed with the exception that the reaction time was reduced from 15 min to 5 min. This procedure gave 0.54 g (71%) of white crystalline 100 (tlc comparison to an authenic sample of 100).

Experiment 45. Photostimulated Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure B was followed to give a dark bronze oil which by tlc (80:20 hexane-ethyl acetate) was shown to consist of two compounds. Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.09 g (17%) of recovered 1 and 0.57 g (75%) of 100 (tlc comparison to authenic samples of 1 and 100).

Experiment 46. Dark Reaction of Phenylacetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure D was followed to yield a dark bronze oil which by tlc (80:20 hexane-ethyl acetate) was shown to contain two components. Flash

chromatographic separation (80:20 hexane-ethyl acetate) produced 0.07 g (13%) of recovered 1 and 0.38 g (50%) of 100 (tlc comparison to authenic samples of 1 and 100).

Experiment 47. Photostimulated Reaction of Acetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure A was followed to give a light green oil which was shown to contain two compounds, 4-cyanomethyl-2,6-dimethoxypyrimidine (101) and 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102) by tlc (80:20 hexane-ethyl acetate). The two compounds were separated by flash chromatography (80:20 hexane-ethyl acetate) and purified by recrystallization from hexane to yield 0.25 g (45%) of 102 and 0.04 g (7%) of 101. Compound 102 exhibited the following spectral data: IR (CH_2Cl_2) 3040 w (CH), 2260 s (C≡N), 1410 s, 1260 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s,2H,CH_2), 3.9 (s,3H,OCH_3), 6.6 (s,1H,H_5 pyr).

Anal. Calcd for $C_7H_6ClN_3O$: C, 45.90; H, 3.27; N, 22.95. Found: C, 45.86; H, 3.37; N, 22.77; mass spectrum, m/e (relative intensity) 154(67), 157(73), 183(100), 184(84), 185(28).

Compound 101 provided the following spectral characteristics: IR (CH_2Cl_2) 3040 w (CH), 2240 s (C≡N), 1480 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7 (s,2H,CH_2), 3.9 (d,6H,$(OCH_3)_2$), 6.4 (s,1H,H_5 pyr). Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.02; N, 23.46. Found: C, 53.36; H, 5.08; N, 22.58; mass spectrum, m/e (relative intensity) 149(83), 153(100), 155(33), 179(60).

Experiment 48. Dark Reaction of Acetonitrile Carbanion Enolate with 4-Chloro-2,6-Dimethoxypyrimidine (1)

Procedure C was followed to give a light yellow oil which was found to contain two compounds by tlc (80:20 hexane-ethyl acetate). The mixture of compounds was separated by flash chromatography (80:20 hexane-ethyl acetate) and recrystallized from hexane to give 0.32 g (58%) of 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102), 0.14 g (26%) of 4-cyanomethyl-2,6-dimethoxypyrimidine (101) and 0.02 g (4%) of 4-chloro-2,6-dimethoxypyrimidine (1) (tlc comparison to authenic samples of 100, 101 and 1).

Experiment 49. Dark Reaction of Acetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using n-Butyllithium in THF

Procedure D was followed with the exception that the reaction time was extended from 15 min to 6 h and the reaction temperature was maintained at -78°C. This procedure yielded a dark yellow oil which was purified by flash chromatography to give 0.18 g (35%) of recovered 1, 0.25 g (45%) of 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102) and 0.06 g (12%) of 4-cyanomethyl-2,6-dimethoxypyrimidine (101) (tlc comparison to authenic samples of 101 and 102).

Experiment 50. Photostimulated Reaction of Acetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA

Procedure B was followed with the exceptions listed in Experiment 49. This procedure yielded a dark yellow oil whose components were separated by flash chromatography (80:20 hexane-ethyl acetate). This

separation yielded 0.38 g (69%) of 102 and 0.09 g (18%) of 101 (tlc comparison to authenic samples of 101 and 102).

Experiment 51. Photostimulated Reaction of Acetonitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1) with Acetone Enolate as an Entraining Agent

Procedure A was followed with the exception that 5 mol % of acetone was added along with the acetonitrile to yield a dark yellow oil. Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.30 g (55%) of 4-chloro-6-cyanomethyl-2-methoxypyrimidine (102) and 0.16 g (30%) of 4-cyanomethyl-2,6-dimethoxypyrimidine (101).

Experiment 52. Photostimulated Reaction of Propionitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA

Procedure B was used with the following exceptions: 1) the reaction temperature was maintained at -78°C, 2) the reaction time was 5 h instead of 15 min, and 3) the base was n-BuLi. This procedure produced a light orange oil that was found by tlc (80:20 hexane-ethyl acetate) to consist of three compounds. Flash chromatographic separation yielded 0.02 g (4%) of recovered 1, 0.16 g (27%) of 6-(α-cyanoethyl)-4-chloro-2-methoxypyrimidine (109), and 0.34 g (58%) of 4-(α-cyanoethyl)-2,6-dimethoxypyrimidine (108). Compound 108 exhibited the following spectral characteristics: IR (neat) 2980 w (C-H), 2245 s (C≡N), 1580 s, 1460 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7 (d,3H,CH_3), 4.0 (s,7H,$(OCH_3)_2$),CH), 6.5 (s,1H,H_5 pyr). Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.96; H, 5.70; N, 21.76. Found: C, 55.71; H, 5.83; N, 21.58.

Compound 109 exhibited the following spectral characteristics: IR (neat) 2990 w (C-H), 2240 s (C≡N), 1570 s, 1460 s, 1360 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7 (d,3H,CH_3), 4.0 (s,4H,OCH_3,CH), 6.6 (s,^1H,H_5 pyr). Anal. Calcd for $C_8H_8ClN_3O$: C, 48.73; H, 4.06; N, 21.31. Found: C, 48.88; H, 4.28; N, 21.02.

Experiment 53. Dark Reaction of Propionitrile Carbanion with 4-Chloro-2,6-Dimethoxypyrimidine (1) Using LDA in THF

Procedure D was followed with the exceptions listed in Experiment 52. Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.18 g (35%) of recovered 1, 0.11 g (19%) of 6-(α-cyanoethyl)-4-chloro-2-methoxypyrimidine (109), and 0.26 g (45%) of 4-(α-cyanoethyl)-2,6-dimethoxypyrimidine (108) (tlc comparison to authenic samples of 108 and 109).

Experiment 54. Photostimulated Reaction of Acetonitrile Carbanion with 4-Iodo-2,6-Dimethoxypyrimidine (110)

Procedure A was followed to give a dark brown intractable tar.

Experiment 55. Photostimulated Reaction of Acetonitrile Carbanion with 4-Iodo-2,6-Dimethoxypyrimidine (110)

Procedure B was followed, with the exception that n-BuLi was used as the base, to yield 100% of recovered starting 110.

Experiment 56. Photostimulated Reaction of Pinacolone Enolate with 2-Chloro-4-Methoxypyrimidine (111)

Procedure A was followed to yield 100% of recovered 103.

Experiment 57. Dark Reaction of Pinacolone Enolate with 2-Chloro-4-Methoxypyrimidine (111)

Procedure C was followed to yield 100% of recovered 103.

Experiment 58. Photostimulated Reaction of Pinacolone Enolate and 2,4-Dimethoxypyrimidine (104)

Procedure A was followed to yield 100% of recovered 104.

Experiment 59. Dark Reaction of Pinacolone Enolate with 2,4-Dimethoxypyrimidine (104)

Procedure C was followed to yield 100% of recovered 104.

Experiment 60. Photostimulated Reaction of Acetonitrile Carbanion with 2-Chloro-4-Methoxypyrimidine (111)

Procedure A was followed to yield an intractable red-yellow tar.

Experiment 61. Dark Reaction of Acetonitrile Carbanion with 2-Chloro-4-Methoxypyrimidine (111)

Procedure C was followed to yield an intractable red-yellow tar.

Experiment 62. Photostimulated Reaction of Acetonitrile Carbanion with 2,4-Dimethoxypyrimidine (104)

Procedure A was followed to yield a dark brown intractable tar.

Experiment 63. Dark Reaction of Acetonitrile Carbanion with 2,4-Dimethoxypyrimidine (104)

Procedure C was followed to yield a dark brown intractable tar.

Experiment 64. Photostimulated Reaction of Pinacolone Enolate with 2-Chlorothiazole (2)

Approximately 150 mL of anhydrous ammonia was introduced directly into a cylindrical Dewar flask (unsilvered) equipped with a two-armed adapter, a Dry-Ice condenser, and a metal stirring bar under an atmosphere of nitrogen (Fig. 1). Using positive nitrogen pressure, 1.56 g (40 mmol) of potassium metal was dropped into the ammonia, which immediately produced a dark blue color. A few crystals of ferric nitrate ($Fe(NO_3)_3 \cdot 9H_2O$) were added and vigorous gas evolution was observed. An anhydrous ethereal solution of 4.01 g (40 mmol) of pinacolone was added dropwise via syringe. The lights of the photochemical reactor were turned on, and 2.02 g (17 mmol) of 2-chlorothiazole (2) in 10 mL of anhydrous ether was added dropwise via syringe. After irradiation for 1 h, the work-up for the reaction mixture was the same as described in Procedure A. Flash chromatographic separation (80:20 hexane-ethyl acetate) yielded 0.82 g of pinacolone dimer (126), 0.02 g (1.3%) of 1,1-bis(thiazol-2-yl)-3,3-dimethyl-2-butanone (125b) and 1.51 g (49%) of 1-(thiazol-2-yl)-3,3-dimethyl-2-butanone (125a). Compound 126 exhibited the following spectral data: IR (neat) 3380 w (OH), 2900 w (CH), 1700 s (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (s,1H,(t-Bu)$_2$), 2.7 (s,4H,$(CH_2)_2$).

Compound 125a exhibited the following spectral data: IR (neat) 2950 w (CH), 1700 s (C=O), 1605 s, 1460 s, 1340 s, 1110 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (s,9H,t-Bu), 4.3 (s,2H,CH_2), 7.2 (d,1H,H_5), 7.7 (d,H,H_4). Anal. Calcd for $C_9H_{13}NOS$: C, 59.02; H, 7.10; N, 7.66; S, 17.49. Found: C, 58.91; H, 7.20; N, 7.72; S, 17.31.

Compound 125b exhibited the following spectral data: IR (neat) 2950 w (CH), 1700 s (C=O), 1490 s, 1120 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s,9H,t-Bu), 6.5 (s,1H,CH), 7.2 (d,1H,H_5), 7.7 (d,1H,H_4). Anal. Calcd for $C_{12}H_{14}N_2OS_2$: C, 54.14; H, 5.26; N, 10.52; S, 24.06. Found: C, 54.31; H, 5.47; N, 10.75.

Experiment 65. Photostimulated Reaction of Pinacolone Enolate with 2-Chlorothiazole (2)

Procedure H was followed to give a dark green liquid. Flash chromatographic separation (80:20 hexane-ethyl acetate) of the crude reaction mixture yielded 0.41 g (53%) of 1-(thiazol-2-yl)-3,3-dimethyl-2-butanone (125a) and 0.14 g (13%) of 1,1-bis(thiazol-2-yl)-3,3-dimethyl-2-butanone (125b).

Experiment 66. Photostimulated Reaction of Acetone Enolate with 2-Chlorothiazole (2)

Procedure H was followed to give a dark green liquid which decomposed to a black liquid on standing. Kugelrohr distillation yielded only a black tarry residue.

Experiment 67. Dark Reaction of Acetone Enolate with 2-Chlorothiazole (2)

Procedure I was followed to give a dark green liquid. Kugelrohr distillation yielded a clear liquid that decomposed to a black liquid on standing, which in turn produced a black tar upon attempted Kugelrohr distilling.

Experiment 68. Photostimulated Reaction of Acetophenone Enolate with 2-Chlorothiazole (2)

Procedure H was followed to yield only recovered 2 and acetophenone.

Experiment 69. Dark Reaction of Pinacolone Enolate with 2-Chlorothiazole (2)

Procedure I was followed to give a yellow liquid which consisted of one component (tlc 80:20 hexane-ethyl acetate). Kugelrohr distillation yielded 2.6 g (70%) of 2-(2-chlorothiazol-4-yl)-3,3-dimethyl-2-hydroxybutane (127a) as a clear liquid: IR (neat) 3580 s (-OH), 3350 s (N=C), 2980 w (C-H), 1460 s, 1400 s, 1380 s, 1200 s, 1080 s cm^{-1}; ^1H NMR ($CDCl_3$) 1.0 (s,9H,$(CH_3)_3$), 1.6 (s,3H,CH_3), 2.3 (s,1H,OH), 7.3 (s,1H,H_5). Anal. Calcd for $C_9H_{14}ClNOS$: C, 49.32; H, 6.39; N, 6.39; S, 14.61. Found: C, 49.65; H, 6.69; N, 6.67; S, 14.49.

Experiment 70. Photostimulated Reaction of Diisopropyl Ketone Enolate with 2-Chlorothiazole (2)

Procedure H was followed to give a homogeneous dark yellow liquid (tlc 80:20 hexane-ethyl acetate). Kugelrohr distillation yielded a white crystalline material that was recrystallized from hexane-ethyl acetate to give 0.75 g (77%) of 3-(2-chlorothiazol-2-yl)-2,4-dimethyl-3-hydroxypentane (127b), mp 99-100°C: IR ($CHCl_3$) 3580 s (OH), 3350 w (N=C), 2950 w (C-H), 1460 s, 1400 s, 1380 s, 1200 s, 1080 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d,6H,$(CH_3)_2$), 0.90 (d,6H,$(CH_3)_2$), 2.0 (s,3H,$(CH)_2$,OH), 7.3 (s,1H,H_5). Anal. Calcd for $C_{10}H_{16}ClNOS$: C, 51.50; H, 6.87; N, 6.00; S, 13.73. Found: C, 51.30; H, 6.89; N, 5.84; S, 13.90; mass spectrum,

m/e (relative intensity) 148(100), 150(36), 190(90), 192(33), 233(4), 235(2).

Experiment 71. Dark Reaction of Diisopropyl Ketone Enolate with 2-Chlorothiazole (2)

Procedure I was followed to give white crystalline 3-(2-chlorothiazol-4-yl)-2,4-dimethyl-3-hydroxypentane (127b) (tlc comparison to an authenic sample of 127b): IR ($CHCl_3$) 3580 s (OH), 3350 w (N=C), 2950 w (CH), 1460 s, 1400 s, 1380 s, 1200 s, 1080 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d,6H,$(CH_3)_2$), 0.90 (d,6H,$(CH_3)_2$), 2.0 (s,3H,$(CH)_2$,OH), 7.3 (s,1H,H_5).

Experiment 72. Dark Inhibited Reaction of Diisopropyl Ketone with 2-Chlorothiazole (2)

Procedure I was followed with the exception that 10 mol % of DTBN was added to the reaction flask before addition of 2-chlorothiazole. This procedure yielded 0.70 g (85%) of crystalline 127b.

Experiment 73. Dark Reaction of Diisopropyl Ketone Enolate with 2-Chlorothiazole (2)

Procedure I was followed with the following exceptions. The reaction time was 1.5 h, the temperature of the reaction mixture was kept at -65°C and the base was LDA (4.2 mmol). This procedure yielded only starting 2-chlorothiazole (2).

Experiment 74. Dark Reaction of Diisopropyl Ketone Enolate with 2-Chlorothiazole (2)

The procedure from Experiment 70 was followed with the exception that 17 mmol of LDA was used. This procedure gave a quantitative yield

of 127b (tlc comparison to authentic 127b).

Experiment 75. Dark Reaction of Diisopropyl Ketone Enolate with 2-Chlorothiazole (2)

Procedure I was followed with the exception that the reaction is conducted in liquid ammonia with no base present. This procedure yielded a quantitative recovery of 2-chlorothiazole (2).

Experiment 76. Dark Reaction of Diisopropyl Ketone Enolate and Benzophenone with 2-Chlorothiazole (2)

Procedure I was followed with the exception that a mixture of diisopropyl ketone and benzophenone was used. Flash chromatographic separation (80:20 hexane-ethyl acetate) of the crude product yielded 0.44 g of benzophenone and 0.48 g (59%) of diisopropyl ketone condensation product (127b).

Experiment 77. Dark Reaction of Diisopropyl Ketone Enolate and Benzophenone with 2-Chlorothiazole (2)

Procedure I was followed with the exception that a mixture of diisopropyl ketone and 42 mmol of benzophenone was used. Kugelrohr distillation of the crude product yielded 0.56 g (68%) of diisopropyl ketone condensation product (127b).

Experiment 78. Dark Reaction of Benzophenone with 2-Chlorothiazole (2)

Procedure I was followed to give a bronze oil. Flash chromatographic (80:20 hexane-ethyl acetate) purification and Kugelrohr distillation yielded 0.83 g (66%) of 2-chloro-4-(diphenylhydroxymethyl)-

thiazole (128) as a bronze oil. IR (neat) 3540 s (OH), 3300 w (C=N), 1485 s, 1420 s, 1395 s, 1195 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5 (s,1H,OH), 7.0(s,1H,H_5), 7.3 (m,10,a). Anal. Calcd for $C_{16}H_{12}ClNOS$: C, 63.79; H, 3.99; N, 4.65; S, 10.63. Found: C, 63.50; H, 4.23; N, 4.38; S, 10.36; mass spectrum, m/e (relative intensity) 146(56), 148(21), 196(100), 198(36), 224(49), 226(19), 301(15), 303(7).

Experiment 79. Dark Reaction of Benzophenone with 2-Chlorothiazole (2)

The procedure from Experiment 73 was followed with the exception that 17 mmol of LDA was used. This procedure gave a bronze oil which was purified by flash chromatography to give a quantitative yield of 128 as a colorless oil (tlc comparison to an authenic sample of 128).

Experiment 80. Dark Reaction of Benzophenone with 2-Chlorothiazole (2)

The procedure from Experiment 79 was followed with the exception that 4.2 mmol of LDA was used. This procedure gave a quantitative yield of 128.

Experiment 81. Dark Reaction of Benzophenone with 2-Chlorothiazole (2)

The procedure from Experiment 73 was used with the exception that 4.2 mmol of n-BuLi was used. This procedure yielded a quantitative yield of 129, mp 114°-115°C (Lit[54] 116°-117°C).

Experiment 82. Dark Reaction of Methyl Benzoate with 2-Chlorothiazole (2)

Procedure I was followed to yield an off-white crystalline material that was recrystallized from ethyl acetate to give 0.58 g of benzamide (130), mp 129-131°C (Lit 132.5-133.5°C): ^1H NMR ($CDCl_3$) δ 7.4 (m,a), 7.8(m,a).

Experiment 83. Dark Reaction of Methyl Benzoate with 2-Chlorothiazole (2)

The procedure from Experiment 79 was used to give a dark purple liquid which contained eight components (tlc 80:20 hexane-ethyl acetate).

Experiment 84. D_2O Quench Reaction of 2-Chlorothiazole (2)

This reaction was conducted in the same manner as in Procedure A with the following exceptions. First, 0.5 g (4 mmol) of 2-chlorothiazole (2) was added to a 17 mmol LDA/THF solution. Secondly, a 100% excess of D_2O was added to this solution, and the reaction time was extended from 1 h to 1.5 h. This procedure yielded compound 131: ^1H NMR ($CDCl_3$) δ 7.6 (s,1H, H_4), 7.2 (d,1H,H_5); mass spectrum, m/e (relative intensity) 57(10), 58(46), 59(100), 60(7), 61(6), 119(22), 120(65), 121(11), 122(24).

Experiment 85. Dark Reaction of Iodomethane with 2-Chlorothiazole (2)

This reaction was conducted in the same manner as in Procedure A with the following exceptions. First, 0.5 g (4 mmol) of 2-chlorothiazole (2) was added to a 17 mmol LDA/THF solution. Secondly, 17 mmol of iodomethane was added to this solution, and the reaction time was extended from 1 h to 1.5 h. This procedure yielded 0.30 g (52%) of 2-chloro-4-methylthiazole (132): ^1H NMR ($CDCl_3$) δ 2.4 (s,3H,CH_3), 7.3 (s,1H,H_5); mass spectrum, m/e (relative intensity) 71(42), 72(39), 98(30), 133(36), 135(17).

Experiment 86. Photostimulated Reaction of N,N-Dimethylacetamide Enolate with 2-Chlorothiazole (2)

Procedure H was followed to give a dark black intractable tar.

Experiment 87. Dark Reaction of N,N-Dimethylacetamide Enolate with 2-Chlorothiazole (2)

Procedure I was followed to give a black intractable tar.

Experiment 88. Photostimulated Reaction of Acetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure H was followed to give a homogeneous dark green liquid (tlc 80:20, hexane-ethyl acetate). Kugelrohr distillation yielded 0.41 g (79%) of 2-(cyanomethyl)thiazole (139a) as a clear liquid: IR (neat) 3400 w (N=C), 2900 s (C-H), 2230 s (C≡N), 1495 s, 1400 s, 1200 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2 (s,2H,CH_2), 7.3 (d,1H,H_5), 7.7 (d,1H,H_4). Anal. Calcd for $C_5H_4N_2S$: C, 48.39; H, 3.23; N, 22.58; S, 25.81. Found: C, 47.79; H, 3.20; N, 22.15; S, 25.08; mass spectrum, m/e (relative intensity) 57(13), 58(100), 59(8), 97(9), 124(83).

Experiment 89. Dark Reaction of Acetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure I was followed to give a dark yellow liquid which was found to be 138a by tlc (80:20 hexane-ethyl acetate). Kugelrohr distillation yielded 0.50 g (96%) of 138a as a clear liquid: IR (neat) 3400 w (N=C), 2900 s (C-H), 2230 s (C≡N), 1495 s, 1400 s, 1200 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2 (s,2H,CH_2), 7.3 (d,1H,H_5), 7.7 (d,1H,H_4).

Experiment 90. Dark Inhibited Reaction of Acetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure I was followed with the exception that 10 mol % of DTBN

was added to the reaction flask before addition of 2-chlorothiazole. This procedure yielded 0.50 g (96%) of 138a.

Experiment 91. Photostimulated Reaction of Phenylacetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure H was followed to give a dark brown liquid which was shown by tlc (80:20 hexane-ethyl acetate) to consist of two compounds. Flash chromatography (80:20 hexane-ethyl acetate) yielded phenylacetonitrile, 0.48 g of crude 2-(α-cyanobenzyl)thiazole (138b), and 0.32 g of intractable tar. Kugelrohr distillation of crude 124b gave 0.40 g (48%) of 124b as a clear liquid: IR (neat) 3400 w (N=C), 3000 s (C-H), 2350 s (C≡N), 1610 s, 1200 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.6 (s,1H,CH), 7.3 (m,6H,a,H_5), 7.7 (d,1H,H_4). Anal. Calcd for $C_{11}H_8N_2S$: C, 66.00; H, 4.00; N, 14.00. Found: C, 65.70; H, 4.21; N, 13.73.

Experiment 92. Dark Reaction of Phenylacetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure I was followed to give a dark red liquid which was shown to consist of two components by tlc (80:20 hexane-ethyl acetate). Flash chromatography (80:20 hexane-ethyl acetate) yielded 0.47 g (56%) of 2-(α-cyanobenzyl)thiazole (138b), 0.04 g of phenylacetonitrile, and 0.04 g of black tar.

Experiment 93. Dark Inhibited Reaction of Phenylacetonitrile Carbanion with 2-Chlorothiazole (2)

Procedure I was followed with the exception that 10 mol % of p-dinitrobenzene was added to the reaction flask before addition of

2-chlorothiazole. This procedure yielded 0.35 g (42%) of 138b.

Experiment 94. Photostimulated Reaction of Phenylacetonitrile Carbanion and 2-Chlorothiazole (2)

Procedure H was followed with the exception that the reaction time was extended from 1 h to 4 h. Flash chromatography of the crude product yielded phenylacetonitrile and 0.33 g (39%) of 138b (tlc comparison to authenic 138b.

Experiment 95. Photostimulated Reaction of Propionitrile Carbanion with 2-Chlorothiazole (2)

Procedure H was followed to give a dark yellow liquid that was composed of two components (tlc 80:20 hexane-ethyl acetate). Flash chromatography (80:20 hexane-ethyl acetate) yielded crude 2-(α-cyano-ethyl)thiazole (138c) and 0.20 g of a propionitrile self-condensation product. Kugelrohr distillation of 138c yielded 0.36 g (62%) of 138c as a clear yellow liquid: IR (neat) 3400 w (N=C), 2900 w (C-H), 2220 s (C≡N), 1495 s, 1440 s, 1200 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9 (d,3H,CH_3), 4.4 (q,1H,CH), 7.3 (d,1H,H_5), 7.7 (d,1H,H_4). Anal. Calcd for $C_6H_6N_2S$: C, 52.17; H, 4.35; N, 20.29; S, 23.19. Found: C, 52.26; H, 4.67; N, 20.08; mass spectrum, m/e (relative intensity) 57(21), 58(100), 111(82), 137(70), 138(88).

Experiment 96. Dark Reaction of Propionitrile Carbanion with 2-Chlorothiazole (2)

Procedure I was followed to give a dark yellow liquid which was subjected to Kugelrohr distillation to yield 0.48 g (83%) of

2-(α-cyanoethyl)thiazole (138c) as a yellow liquid (tlc 80:20 hexane-ethyl acetate).

Experiment 97. Photostimulated Reaction of Propionitrile Carbanion with 2-(Cyanoethyl)thiazole (138c)

Procedure H was followed with the exception that compound 138c was used as the aromatic substrate. This procedure yielded an uncharacterizable propionitrile self-condensation product.

Experiment 98. Dark Reaction of Diisopropyl Ketone Enolate with Thiazole (82).

Procedure I was followed with the exception that the aromatic substrate was thiazole (82). This procedure yielded a quantitative recovery of thiazole (82).

Experiment 99. Dark Reaction of Diisopropyl Ketone Enolate with Thiazole (82)

Procedure I was followed with the exception that the aromatic substrate was thiazole (82) and the reaction time was extended from 1 h to 5 h. This procedure yielded a quantitative recovery of thiazole (82).

Experiment 100. Dark Reaction of Benzophenone with Thiazole (82) Using KNH_2

Procedure I was followed to give a quantitative yield of thiazole (82) and benzophenone.

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REACTIONS OF 4-CHLORO-2,6-DIMETHOXYPYRIMIDINE AND 2-CHLOROTHIAZOLE WITH CARBANION NUCLEOPHILES

by

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(ABSTRACT)

Reactions of 4-chloro-2,6-dimethoxypyrimidine (1) with enolates of acetone, pinacolone, diisopropyl ketone, and ethyl phenylacetate generated by means of potassium amide in liquid ammonia were found to proceed by the $S_{RN}1$ mechanism upon photostimulation with near-UV light to give good yields of substitution products resulting from displacement of chloride ion.

Both photostimulated and dark reactions of 4-chloro-2,6-dimethoxypyrimidine (1) with the carbanions of acetonitrile and propionitrile proceed exclusively by an ionic mechanism in liquid ammonia or THF to give a mixture of monosubstitution products resulting from displacement of chloride or the 6-methoxy substituent. With the acetonitrile carbanion the product resulting from displacement of methoxide was the major substitution product, while reaction of 1 with propionitrile carbanion afforded a preponderance of the product resulting from chloride displacement.

Photostimulated reaction of 2-chlorothiazole (2) with the potassium enolate of pinacolone proceeds by a radical-chain mechanism to give the substitution product resulting from chloride displacement. However, when 2 is allowed to react with pinacolone enolate in the dark a completely unexpected product is formed. Under these conditions, the tertiary

alcohol, 2-(2-chlorothiazol-4-yl)-3,3-dimethyl-2-hydroxybutane, was formed in which the pinacolone unit had been incorporated in an aldol fashion at the 4-position of 2. Both photostimulated and dark reactions of 2 with the enolate of diisopropyl ketone produced a similar carbinol, 3-(2-chlorothiazol-4-yl)-2,4-dimethyl-3-hydroxypentane, in good yields. Treatment of 2 with potassium amide in liquid ammonia or LDA in THF followed by addition of benzophenone afforded 2-chloro-4-(diphenyl-hydroxymethyl) thiazole in excellent yield. Trapping experiments with deuterium oxide and iodomethane provide evidence that such aldol-type reactions take place via initial metalation of 2 at position-4, followed by reaction of the resulting carbanion with the appropriate electrophile. This is the first example of direct metalation occurring at the 4-position of a thiazole derivative.