$S_{RN}1$ Mechanism in Heteroaromatic Nucleophilic Substitution. Reactions Involving Halogenated Pyrimidines, Pyridazines, and Pyrazines[1a]

David R. Carver,[1b] Andrew P. Komin, James S. Hubbard, and James F. Wolfe*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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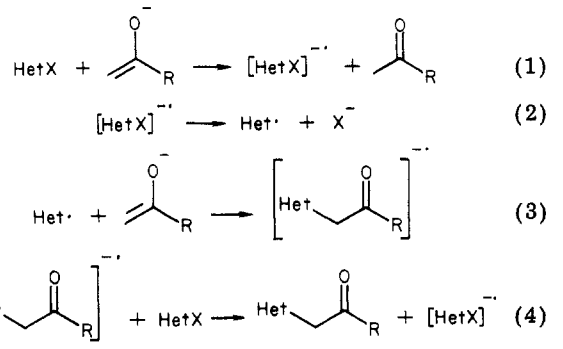
Reactions of 2-chloropyrimidine (1), 4-chloro-2,6-dimethoxypyrimidine (7), 3-chloro-6-methoxypyridazine (9), and 2-chloropyrazine (14) with a representative series of ketone enolates in liquid ammonia exhibited characteristics consistent with a radical-chain ($S_{RN}1$) mechanism for substitution. Diazines 1 and 9 showed an unexpected sensitivity to enolate ion structure, with 1 reacting best with tertiary enolates and 9 undergoing substitution most satisfactorily with primary enolates. The order of $S_{RN}1$ reactivity among the various substrates was found to be 14 > 9 > 7 ≈ 1. Thus 1 and 7 required photostimulation at 350 nm for satisfactory displacement of chloride, 9 underwent some substitution without illumination, and 14 reacted smoothly in the dark.

Previous studies in our laboratories have demonstrated that 2-chloroquinoline[2] and 2-, 3-, and 4-halopyridines[3] react with ketone enolates under photostimulation in liquid NH_3 and several other solvents[4] via the $S_{RN}1$ mechanism shown in Scheme I. The novelty of this mechanistic pathway in heteroaromatic nucleophilic substitution[4,5] prompted the present study, which was designed to further define the scope and limitations of these reactions with other heteroaromatic substrates. In this investigation the monocyclic diazines 2-chloropyrimidine (1), 4-chloro-2,6-dimethoxypyrimidine (7), 3-chloro-6-methoxypyridazine (9), and 2-chloropyrazine (14) were employed as substrates with a representative series of ketone enolates as nucleophiles. Liquid NH_3 was used as the reaction solvent, and photostimulation was supplied by 350-nm light. While this work was in progress, van der Plas and Oostveen presented evidence that certain enolate ions undergo $S_{RN}1$ reaction with 4-phenyl- and 4-*tert*-butyl-5-halopyrimidines upon stimulation with potassium metal or near-UV light.[6]

Scheme I

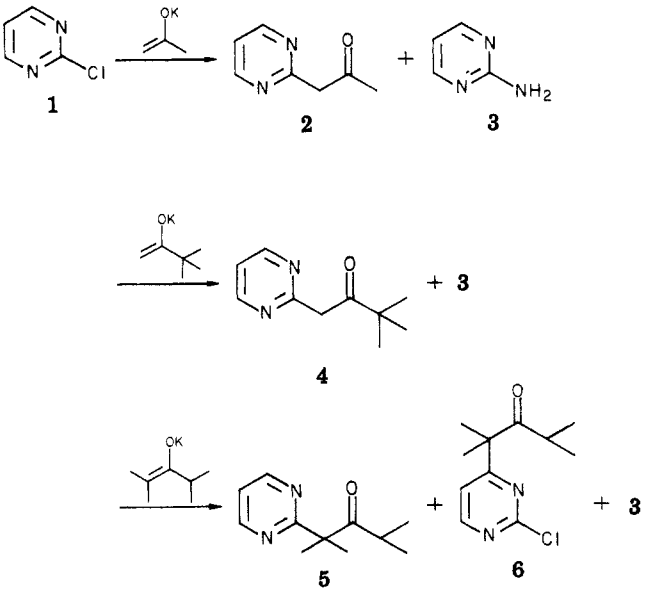


Results

Pyrimidines. Initial studies were focused on reactions of 2-chloropyrimidine (1) with the potassium enolates of acetone, pinacolone, and diisopropyl ketone. Results of these experiments are summarized in Scheme II and Table I. Photostimulated reaction of potassioacetone with 1 for 15 min afforded the expected ketone 2 in only 15% yield. The remainder of the product mixture consisted of 3 and intractable polymeric material. The photostimulated reaction of 1 with the potassium enolate of pinacolone gave 32% of 2-pyrimidinyl ketone 4, 4% of 3, and uncharacterized resinous material. However, when the potassio salt of diisopropyl ketone was used as the nucleophile, ketone 5 was obtained in 88% yield after 15 min of irradiation. The yield of 2 was increased to 61% by using THF as the solvent.[4]

When the above reactions were conducted in NH_3 without illumination, only trace amounts of the expected

Scheme II



substitution products were obtained. With acetone enolate, the major product was 3 (88%). Pinacolone enolate gave a mixture of unstable products which apparently polymerized during chromatography. Reaction of 1 with diisopropyl ketone enolate afforded 50% of recovered 1 and 17% of ketone 6, which apparently results from addition of the nucleophile to the 4-position of substrate 1 followed by rearomatization of the resulting dihydro adduct during workup.

Support for the radical-chain character of the photostimulated reactions involving 1 was obtained by the complete inhibition of the photostimulation reactions with

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(3) Komin, A. P.; Wolfe, J. F. *J. Org. Chem.* **1977**, *42*, 2481.

(4) Moon, M. P.; Wolfe, J. F. *J. Org. Chem.* **1979**, *44*, 4081.

(5) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Wolfe, J. F.; Caver, D. R. *Org. Prep. Proced. Int.* **1978**, *10*, 224.

(6) Oostveen, E. A.; van der Plas, H. C. *Recl. Trav. Chim. Pay-Bas*, **1979**, *98*, 441.

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Table I. Reactions of Pyrimidines 1 and 7 with Ketone Enolates

expt	substr	enolate from	conditions[a,b]	products	yield, %
1	1	acetone	$h\nu$	2	(61)[e]
				3	4
2	1	acetone	dark	2	0
				3	88
3	1	acetone	$h\nu$, inhibited[c]	2	0
				3	5
4	1	pinacolone	$h\nu$	4	32
				3	4
5	1	diisopropyl ketone	$h\nu$	5	88
				3	4
6	1	diisopropyl ketone	dark	5	0
				1	50
				3	7
				6	16
7	1	diisopropyl ketone	$h\nu$, inhibited[d]	5	0
				1	58
				3	7
				6	15
8	7	pinacolone	$h\nu$	7	<1
				8	98
9	7	pinacolone	dark	7	80
				8	0
10	7	pinacolone	$h\nu$, inhibited[d]	7	65
				8	6

[a] Reaction time 15 min. [b] Ratio of enolate to substrate of 3.75:1. [c] 10 mol % of DTBN was used as an inhibitor. [d] 20 mol % of DTBN was used as an inhibitor. [e] THF, 0 °C, 15-min irradiation.

Table II. Reactions of 3-Chloro-6-methoxypyridazine (9) with Ketone Enolates

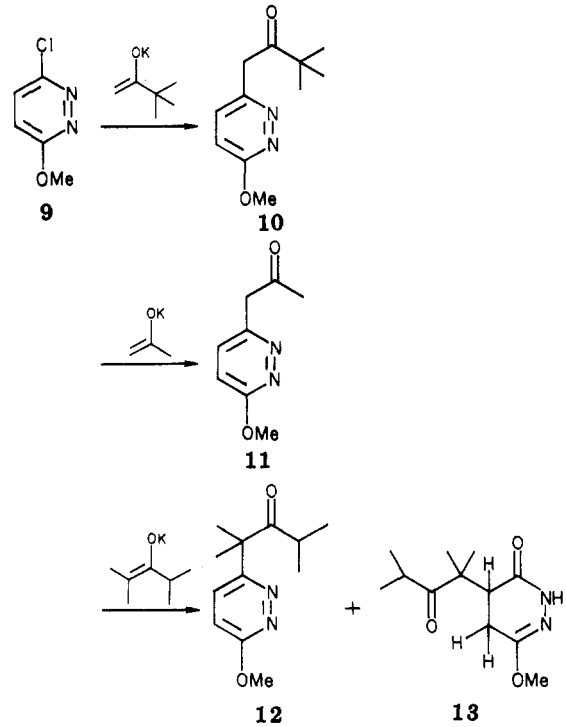
expt	enolate from	conditions[a,b]	products	yield, %
11	pinacolone	dark	9	24
			10	38
12	pinacolone	$h\nu$	9	5
			10	72
13	pinacolone	dark, inhibited[c]	9	70
			10	0
14	acetone	dark	11	60
15	diisopropyl ketone	$h\nu$	9	50
			12	13
16	diisopropyl ketone	$h\nu$[d]	9	15
			12	20
17	diisopropyl ketone	dark	9	90
			12	trace
18	diisopropyl ketone	dark[d,e]	12	50
			13	8
19	diisopropyl ketone and acetone	dark[b,f]	11	5
			12	31

[a] Reaction time 15 min. [b] Ratio of enolate to substrate of 3.75:1. [c] 10 mol % of DTBN used as inhibitor. [d] Reaction time 1 h. [e] Reaction mixture treated with wet silica gel for 48 h. [f] Ratio diisopropyl ketone to acetone of 9:1.

di-*tert*-butyl nitroxide (DTBN), a known radical scavenger.[7] In the reaction of acetone enolate, addition of 10 mol % of DTBN to the photostimulated reaction resulted in no detectable amount of substitution product **2**; the only products in this reaction were **3** (5%) and red tar. The photostimulated reaction of **1** and diisopropyl ketone enolate was inhibited by 20 mol % of DTBN. This reaction gave 68% of **1**, 7% of **3**, 15% of the addition product **6**, but no detectable amount of substitution product **5**.

By use of the readily available 2,6-dimethoxy-4-chloropyrimidine (**7**) as a model for substitutions at the 4-position of pyrimidine, excellent success was achieved with pinacolone enolate. Under photostimulation for 15 min a nearly quantitative yield of the substitution product **8** was obtained. Treatment of **7** with pinacolone enolate in the dark returned 80% of starting material. Inhibition of the 15-min photoinduced reaction with 20 mol % of DTBN gave ketone **8** in only 6% yield; 65% of **7** was recovered.

Scheme III



(7) (a) Hoffman, A. K.; Feldman, A. M.; Geblum, E., Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639. (b) Nelson, S. F.; Bartlett, P. D. *Ibid.* **1966**, *88*, 143.

Table III. Reactions of 2-Chloropyrazine (14) with Carbanions

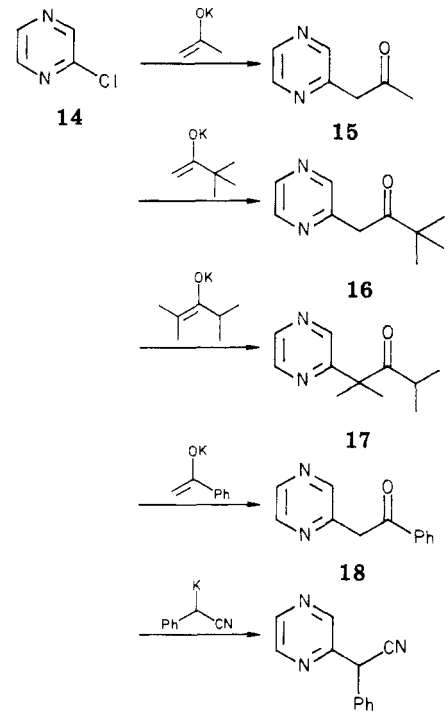
expt	carbanion from	conditions[a,b]	products	yield, %
20	acetone	dark	15	98
21	acetone	dark, inhibited[c]	14	91
			15	0
22	pinacolone	dark	16	95
23	diisopropyl ketone	dark	17	85
24	acetophenone	dark	18	82
25	acetophenone	dark, inhibited[d]	14	90
			18	0
26	phenylaceto-nitrile	dark	19	78
27	phenylaceto-nitrile	dark[e]	19	44
28	phenylaceto-nitrile	dark, inhibited[f]	19	38
29	phenylaceto-nitrile	dark, inhibited[e,f]	19	11
30	phenylaceto-nitrile	dark, inhibited[c]	19	77

[a] Reaction time 15 min. [b] Ratio of carbanion to substrate of 3.75:1. [c] 10 mol % of DTBN used as inhibitor. [d] 15 mol % of DTBN used as inhibitor. [e] Reaction time 3 min. [f] 20 mol % of DTBN used as inhibitor.

Pyridazine. Commercially available 3-chloro-6-methoxypyridazine (9) was using for probing the $S_{RN}1$ reactivity of ketone enolates toward a halogenated pyridazine. Results of reactions with pinacolone, acetone, and diisopropyl ketone potassium enolates are summarized in Scheme III and Table II. Reaction of 9 with pinacolone enolate afforded 38% of ketone 10 after 15 min in the dark. The yield of 10 was increased to 72% by 15 min of illumination. Formation of 10 in the dark reaction was completely inhibited by 10 mol % of DTBN, which indicated that substitution under these conditions occurred mainly by a thermally induced $S_{RN}1$ reaction. Potassioacetone exhibited even greater reactivity than pinacolone enolate, affording 60% of ketone 11 after 15 min in the dark. Inhibition by DTBN again provided evidence for a thermal radical-chain mechanism. Although the potassio salt of diisopropyl ketone reacted smoothly with pyrimidine 1, it afforded only 13% of the expected product 12 upon treatment with pyridazine 9 and by using a 15-min irradiation period; 50% of 9 was recovered. Extending the irradiation period to 1 h gave 20% of 12, while recovery of 9 dropped to 15%. Both reactions were accompanied by formation of considerable amounts of unstable material, which rapidly became intractable upon exposure to the atmosphere or attempted chromatography on silica gel. A 15-min dark reaction of diisopropyl ketone enolate with 9 resulted mainly in recovery of 9 (90%). A similar experiment for 1 h also failed to generate ketone 12. Instead, 50% of 9 was recovered, intractable tar was formed, and 8% of a compound with ^1H NMR characteristics and elemental analysis consistent with structure 13 was isolated (see Experimental Section).

Pyrazine. In this series of experiments, 2-chloropyrazine (14) was allowed to react with the potassio salts of acetone, pinacolone, diisopropyl ketone, acetophenone, and phenylacetonitrile (Scheme IV and Table III). All of these nucleophiles reacted with 14 in the dark to give excellent yields of substitution products 15–19. Inhibition (DTBN) of the reactions with potassioacetone, potassioacetophenone, and potassiophenylacetonitrile provided evidence that these reactions, and presumably those with pinacolone and diisopropyl ketone enolates, were mainly thermal $S_{RN}1$ substitutions. The somewhat lower efficacy

Scheme IV



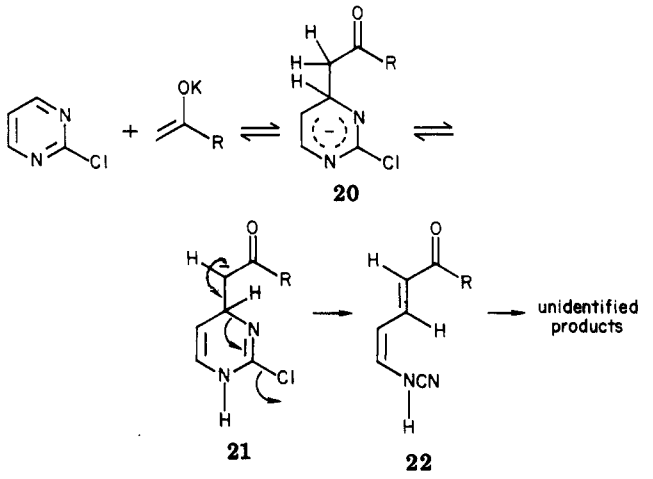
of DTBN toward inhibition of the reaction of 14 with potassiophenylacetonitrile indicates that formation of 19 occurs by a dual mechanistic pathway involving both radical-chain and AE reactions.

Discussion

Our initial objective in this study was to determine if halogenated pyrimidines, pyridazines, and pyrazines would participate in $S_{RN}1$ substitutions. If this proved to be the case, we wished to establish a qualitative ranking of reactivity of these substrates. It seemed possible that the $S_{RN}1$ reactivity order might follow the ease with which an electron can be added to the LUMO of the respective heterocycle. On the basis of the premises that the relative energies of the LUMO of the heterocyclic substrates are reflected in the polarographic half-wave potentials of the parent diazine systems[8,9] and that the rate of electron transfer to a substrate with more positive reduction potential (less negative $E_{1/2}$ value) will be faster than reduction of a molecule with a more negative $E_{1/2}$,[10] one might anticipate a reactivity order of 14 > 9 > 7 ≃ 1. Indeed, pyrazine 14 is the most reactive substrate, undergoing rapid $S_{RN}1$ substitution without photostimulation. The relative reactivities of 9, 7, and 1 were somewhat less precisely determined because of competing ionic additions, which prevent valid comparison of each substrate with a common nucleophile. However, the proposed reactivity sequence appears to be reasonably valid, in that pyridazine 9 afforded 38% and 60% $S_{RN}1$ substitution in the dark with pinacolone and acetone enolates, respectively, while pyrimidines 1 and 7 gave no detectable substitution without illumination. The observation that acetophenone enolate undergoes facile $S_{RN}1$ substitution with pyrazine 14 in the dark but reacts poorly or not at all under photostimulation with iodobenzene,[11] 2-chloroquinoline,[2] and

(8) Wilberg, K. B.; Lewis, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 7154.
(9) Amatore, C.; Chaussard, J.; Pinson, J.; Saveant, J.-M.; Thiebault, A. *J. Am. Chem. Soc.* **1979**, *101*, 6012.
(10) Dorfman, L. M. *Acc. Chem. Res.* **1970**, *3*, 224.

Scheme V



2-bromopyridine[3] may also be linked to the relatively low reduction potential of **14**. The lack of reactivity of potassioacetophenone toward previous systems has been attributed to failure of the radical anion of the substitution product (Scheme I, eq 3) to transfer an electron to another substrate molecule.[9,12] It appears that **14** is easier to reduce than ketone **18**, thus the radical anion of **18** readily donates an electron to **14**.

The marked sensitivity of $S_{RN}1$ reactions of pyrimidine **1** to the nature of the ketone enolate is unusual in that heteroaromatic $S_{RN}1$ reactions have not previously shown much sensitivity to enolate structure.[3] Isolation of 2-chloro-4-pyrimidinyl ketone **6** from the inhibited reaction of **1** with diisopropyl ketone enolate indicates that ionic addition to the 4-position of **1** can compete with $S_{RN}1$ displacement of halogen. In fact, similar adducts have been obtained from DTBN-inhibited reactions of pinacolone enolate with 5-halo-4-phenylpyrimidines.[6] It is also well-known that amide ion adds to the 6-position of 2-halo-4-phenylpyrimidines to initiate a S_N(ANRORC) mechanism[13] involving cleavage of the N_1–C_6 bond and subsequent ring closure to form 2-amino-4-phenylpyrimidine. It is conceivable that degradation of **1** by enolate nucleophiles may originate in the ring-opening sequence proposed in Scheme V. Initial attack of the appropriate enolate (R = Me or *t*-Bu) at the 4-position of **1** could produce σ complex **20**. Formation of exocyclic carbanion **21** could lead to fragmentation of the ring to give **22**. There is ample precedent[13,14] for ring opening of the type shown in Scheme V with amide ion as the nucleophile. Evidence for the presence of intermediate **22** (R = *t*-Bu) was obtained from the IR and ^{1}H NMR spectra of the crude product mixture prior to aqueous workup. A strong nitrile band was observed at 2230 cm^{-1} along with conjugated carbonyl absorption at 1615 cm^{-1}. Vinyl proton signals appeared at δ 5.6, 6.3, and 7.0, while the characteristic peaks at δ 7.4–8.6 for pyrimidine hydrogens were not present. With the enolate of diisopropyl ketone, an intermediate such as **20** may form, but carbanion **21** cannot be produced, and ring opening may be prevented. Formation of ketone **6** is consistent with this hypothesis. That exocyclic carbanions such as **21** are sometimes necessary for pyrimidine ring opening has been demonstrated recently in reactions of 1,3-dimethyluracil derivatives with α-substituted acetamides to give 2,6-dihydroxypyridines.[15,16]

The mechanism by which **1** undergoes extensive amination to form **3** in the dark reaction with potassioacetone is not obvious at this time. In attempts to define the course of this reaction, it was found that **1** is not converted to **3** in liquid NH_3, either in the dark or under photostimulation. Reaction of **1** with 20 mol % of KNH_2 afforded only ca. 20% of **3**; this eliminated the possibility that formation of **3** is caused by catalytic amounts of amide ion. Small amounts (5 and 10 mol %) of potassium metal also failed to give significant amounts of **3**.

The sluggish reaction of pyridazine **9** with diisopropyl ketone enolate contrasts with the observation that substrates **1** and **14** react smoothly with this enolate. Entrainment of the dark reaction of **9** with diisopropyl ketone enolate with 10 mol % of potassioacetone (expt 19, Table II) increased the yield of **12** from trace amounts to 31%. This implies that inefficient initiation of the $S_{RN}1$ reaction of **9** by diisopropyl ketone enolate is a major factor in causing these reactions to proceed poorly. The high peripheral electron density of **9** coupled with the hindered nature of this enolate may be responsible for the rather poor initiation. Formation of adduct **13** in the 1-h dark reaction of **9** with diisopropyl ketone enolate suggests that addition of this nucleophile to the C_4–C_5 bond can form unstable 3-chloro-4,5-dihydro adducts, which may decompose during the reaction or upon workup.

In previous studies we have found that nucleophilic substitution reactions involving halogenated quinolines and pyridines proceed slowly without illumination to initiate the $S_{RN}1$ process. In most of these instances the substrate is returned. However, with pyrimidines having a nucleofugal group at the 2-position the substrate is extremely susceptible to damaging ring transformations. Therefore, photoinduced $S_{RN}1$ reactions are the *only* way to effect satisfactory substitution, at least with the nucleophiles employed in this investigation.

Experimental Section

General Methods. All reactions were conducted under an atmosphere of nitrogen; quenching and processing of reaction mixtures were performed under atmospheric conditions unless otherwise noted. All photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor equipped with four 12.5-W bulbs emitting maximally at 350 nm. Gas chromatographic (GLC) analyses and separations were accomplished on Varian Associates 90-P or 1200 instruments using columns of 2% Carbowax 20M on Chromosorb supports at 153–235 °C. Determinations of GLC yields were accomplished with benzoate and phthlate esters as internal standards. ^{1}H NMR spectra were determined on a JEOL JMN-PS-100 or a Varian EM-390 spectrometer at 100 or 90 MHz, respectively, with tetramethylsilane as an internal reference. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Infrared spectra were produced on a Beckman IR-20A-X spectrophotometer. Elemental microanalyses were performed by Galbraith Laboratories. Melting points were observed with a Thomas-Hoover apparatus and are uncorrected.

All solvents were of commercial quality except for those purified as noted. Liquid ammonia was commercial anhydrous grade and was used without further purification.

Chromatographic separations were performed on silica gel and by preparative GLC. Preparative TLC plates were made from

(11) Bunnett, J. F.; Sundberg, J. E. *J. Org. Chem.* **1976**, *41*, 1702.
(12) Wolfe, J. F.; Moon, M. P.; Sleevi, M. C.; Bunnett, J. F.; Bard, R. R. *J. Org. Chem.* **1978**, *43*, 1019.
(13) van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462 and references therein.
(14) Kos, N. J.; van der Plas, H. C. *J. Org. Chem.* **1980**, *45*, 2942.
(15) It is possible that **21** may be a dianion and that removal of an exocyclic α-hydrogen while the heterocyclic ring bears a negative charge is a prerequisite for ring opening.
(16) Hirota, K.; Kitade, Y.; Senda, S.; Halet, M. J.; Watanabe, K. A.; Fox, J. *J. Am. Chem. Soc.* **1979**, *101*, 4423.

E. M. Merck PF-254 type-60 silica gel. Analytical TLC separations were carried out on Eastman 13181 silica gel plates with a fluorescent indicator (no. 6060) with polymer backing. Other less active separations were carried out on Merck HF-254 (type 60) silica gel (catalogue no. 7739) mechanically spread on glass microscope slides. Column chromatography was accomplished by using a low-pressure column and reservoir under 10–25 lb of nitrogen pressure with Woelm 126 silica gel (<0.063 mm).

Reactions of the various heteroaromatic compounds were carried out by one of the following procedures. Exceptions to these general methods are noted for individual reactions.

Procedure A. Photostimulated Reactions. For the photostimulated reactions, 150–175 mL of anhydrous ammonia was introduced directly into a cylindrical Dewar flask (unsilvered) that measured 51.0 × 3.5 cm (i.d.) topped with a single 35/40 ⧩ ground-glass joint. This joint was fitted, prior to ammonia introduction, with an adapter containing three 24/40 male ground-glass joints. These joints were equipped with stoppers, addition funnels, or dry ice condensers as needed. Short reaction times (<30 min) did not reqire the condenser, since loss of ammonia in the insulated flask was negligible. Under positive nitrogen pressure, 11.25 mmol of potassium metal was dropped into the ammonia. Addition of a few milligrams of ferric nitrate hydrate catalyzed amide formation. After amide formation was complete, an anhydrous ethereal solution of the ketone (11.25 mmol) was added dropwise. After mixing of the solution was complete (magnetic stirring with a bare metal magnet), the lamps in the reactor were turned on. Addition of the aromatic substrate (3.00 mmol) in 10 mL of ether was accomplished in 1.5 min. After irradiation for 15 min (total), the reaction mixture was quenched by pouring the liquid ammonia solution directly onto solid ammonium chloride (3.5 g in a 2-L beaker). The reaction vessel was washed twice with 100 mL of ether, and the washes were combined with the ammonia solution. Evaporation of the ammonia was accomplished by using a warm hot plate wet with ethanol (to help transfer heat and prevent ice formation). Brief boiling of the remaining ether removed residual ammonia; the ethereal solution was then filtered from the solid salts. Crushing the salts with a spatula and four triturations with ether (50 mL) gave good extraction in most cases. Drying ($MgSO_4$) and evaporation of the ether afforded crude products.

Procedure B. Dark Reactions. To a 250-mL, three-necked, 24/40 ⧩ flask fitted with two nitrogen bubblers and an addition funnel was added 150–175 mL of anhydrous liquid ammonia run in directly from the tank via a Tygon tube. Potassium amide (11.25 mmol) was generated as described in procedure A, and then addition of the ketone (11.25 mmol) in 7–10 mL of ether was carried out. Before the substrate (3.00 mmol in 10 mL of ether) was added, the flask was wrapped with several layers of black cloth, and the room lights were extinguished. Subsequent workup was identical with that described in procedure A. The following experiments detail isolation of specific reaction products. Inhibited reactions were conducted by adding an ethereal solution of the appropriate heteroaromatic and DTBN to the enolate solution.

Photostimulated Reaction of Acetone Enolate with 2-Chloropyrimidine (1). Procedure A was used to produce a bright red solution at the end of the irradiation period. This solution was quenched to give a bright orange solution that changed to dark red upon evaporation of the ammonia. Kugelrohr distillation of the crude product at 100 °C (0.1 torr) gave a red oil which was >90% 1-(2-pyrimidinyl)-2-propanone (**2**). GLC analysis of a crude reaction mixture with 2-aminopyrimidine (**3**) as internal standard indicated a 15% yield of **2** and 4.4% of **3**. The remainder of the crude product was an intractable tar, soluble in polar solvents. Attempted purification of this material by preparative TLC gave a yellow oil still contaminated by two minor impurities.

An analytically pure sample of **2** was prepared using THF as the solvent. Potassioacetone (27.2 mmol) was prepared in 150 mL of THF using excess KH according to Brown's procedures.[17] A 12.5-W lamp emitting at 350 nm was used to irradiate the 250-mL flask. 2-Chloropyrimidine (0.83 g, 6.0 mmol) was added cautiously as a solid at 0 °C. After 15 min, the THF was removed (rotary evaporator); ether and ice were added. Dilute HCl (3 N) was added until the pH reached 6.0. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried and filtered; the solvents were removed by using a rotary evaporator. The ^1H NMR of this crude material indicated that it was >90% **2**. Chromatography on 40 g of silica gel using a short column and 20:80 ethyl acetate–hexane elution gave 0.25 g (61%) of **2** as a yellow oil. Alternatively, the crude reaction mixture could be distilled as described above but the distillate contained small amounts of diacetone alcohol: IR (neat) 3040 (w, CH), 1715 (s, C=O), 1640 (m), 1560 (s), 1430 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 0.6 H, enol CH_3), 2.28 (s, 2.4 H, keto CH_3), 4.13 (s, 1.6 H, keto CH_2), 5.45 (s, 0.2 H , enol CH), 6.90 (5, 0.2 H, H_5 pyr),[13] 7.20 (t, 0.8H, H_5 pyr), 8.50 (d, 0.4 H, $H_{4(6)}$ pyr), 8.68 (d, 1.6 H, $H_{4(6)}$ pyr), 13.40 (br s, 0.2 H, enol OH).

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.76; H, 6.21; N, 20.18.

Dark Reaction of Acetone Enolate with 1. Procedure B gave a dark red solution which afforded a red oil upon removal of the ammonia. A minimal amount of water (10–20 mL) was added; the pH was adjusted to 6.5. This aqueous solution was extracted with ether (2 × 75 mL), chloroform (3 × 75 mL), and ethyl acetate (3 × 75 mL). The organic extracts were combined, dried, and filtered, and the solvents were removed using a rotary evaporator. The sticky solid obtained was rinsed with warm ether, affording 88% of **3**. Recrystallization from ethanol gave a sample of **3** which was identical by TLC, ^1H NMR, and melting point [123–126 °C (lit.[18] mp 126 °C)] with an authentic sample of **3**.

Photostimulated Reaction of Pinacolone Enolate with 1. Procedure A gave a red solution that produced, after Kugelrohr distillation (90 °C, 0.07 torr), 32% of 1-(2-pyrimidinyl)-3,3-dimethyl-2-butanone (**4**) and ~4% of 2-aminopyrimidine (**3**). An analytical sample of **4** was obtained as a pale yellow oil by preparative GLC: IR (neat) 3040 (w, CH), 1705 (s, C=O), 1625 (s), 1575 (s), 1560 (s), 1540 (s), 1430 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H, *t*-Bu), 4.17 (s, 1.3 H, CH_2), 5.66 (s, 0.35 H, enol CH), 6.87 (t, J = 5 Hz, 0.35 H, H_5 pyr), 7.12 (t, J = 5 Hz, 0.65 H, H_5 pyr), 8.46 (d, J = 5 Hz, 0.7 H, $H_{4(6)}$ pyr), 8.63 (d, J = 5 Hz, 1.3 H, $H_{4(6)}$ pyr), 13.80 (br s, 0.35 H, enol OH).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.22; H, 7.72; N, 15.46.

The remainder of the reaction mixture was an intractable red tar that was similar to the tar formed with potassioacetone.

Dark Reaction of Pinacolone Enolate with 1. Procedure B gave a red tar devoid of **1**. Nonaqueous workup (NH_4Cl, ether extraction of the salts) gave an unstable product with the following characteristics: IR (KBr) 1010, 1080, 1280, 1555, 1615 (C=O), 2140, 2230 (CN), 2960 cm^{-1}; ^1H NMR ($CDCl_3$) 1.35 (s, 9 H), 5.6 (t, 1 H), 6.3 (t, 1 H), 7.0 (br d, 1 H), 7.1–7.7 (br m, 2 H). This material rapidly decomposed and could not be fully characterized. Chromatography over silica gel gave a yellow solid: mp 191–193 °C; IR (KBr) 1010, 1080, 1170, 1280, 1340, 1550, 1660, 2960, 3300, 3440 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.15 (s, 9 H), 5.8 (t, J = 14 Hz, 1 H), 6.3 (d, J = 15 Hz, 1 H), 7.05 (dd, J = 10, 15 Hz, 1 H), 7.35 (dd, J = 10, 14 Hz, 1 H); mass spectrum, m/e (relative intensity), 45 (25), 137 (100), 148 (5), 232 (50), 245 (1), 289 (5).

Photostimulated Reaction of Diisopropyl Ketone Enolate with 1. Procedure A was followed to give a slightly yellow ethereal solution. Evaporation of the solvent and Kugelrohr distillation gave (GLC analysis) 88% of 2-(2-pyrimidinyl)-2,4-dimethyl-3-pentanone (**5**) as an oil and 4% of **3**: IR (neat) 3030 (w, CH), 1710 (s, C=O), 1670 (s), 1660 (s), 1415 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 6 H, isopropyl CH_3), 1.58 (s, 6 H, CH_3), 2.63 (septet, J = 7 Hz, 1 H, isopropyl CH), 7.17 (t, J = 5 Hz, 1 H, H_5 pyr), 8.68 (d, J = 5 Hz, 2 H, $H_{4(6)}$ pyr).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.40; N, 14.57. Found: C, 68.92; H, 8.70; N, 14.47.

Dark Reaction of Diisopropyl Ketone Enolate with 1. Procedure B gave an almost colorless oil that by GLC indicated a 50% recovery of **1**, 7% of **3**, and no detectable trace of the substitution product **5**. 2-(2-Chloropyrimidin-4-yl)-2,4-di-

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methyl-2-pentanone (6) was isolated by preparative GLC: mp 54–58 °C; IR (solid) 3080 (w, CH), 1705 (s, C=O), 1575 (s), 1538 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 7 Hz, 6 H, isopropyl CH_3), 1.56 (s, 6 H, CH_3), 2.74 (septet, J = 7 Hz, 1 H, isopropyl CH), 7.21 (d, J = 5 Hz, 1 H, H_5 pyr), 8.62 (d, J = 5 Hz, 1 H, H_6 pyr).

Anal. Calcd for $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; N, 12.36; Cl, 15.64. Found: C, 58.50; H, 7.01; N, 12.09.

Procedure A with 0.07 g of di-*tert*-butyl nitroxide added to the reaction flask gave, by GLC analysis, a 58% recovery of 1, 7% of 3, and 15% of 6.

Photostimulated Reaction of Pinacolone Enolate with 4-Chloro-2,6-dimethoxypyrimidine (7). Procedure A gave a crude product mixture which was shown by GLC with benzyl benzoate as an internal standard to be >98% 1-(2,6-dimethoxypyrimidin-4-yl)-3,3-dimethyl-2-butanone (8). A sample of 8 was collected by preparative GLC as a light yellow oil: IR (neat) 3020 (w, CH), 1705 (s, C=O), 1635 (s), 1595 (s), 1560 (s), 1540 (s), 1385 (s), 1350 (s), 1095 (s, CO), 1057 (s, CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9 H, *t*-Bu), 3.88 (s, 2 H, CH_2), 3.94 (s, 6 H, OCH_3), 6.28 (s, 1 H, H_5 pyr).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.39; H, 7.85; N, 11.68.

Photostimulated Reaction of Pinacolone Enolate and 3-Chloro-6-methoxypyridazine (9). Procedure A gave, after chromatography (ether–hexane, 1:3), 72% of 1-(6-methoxypyridazin-3-yl)-3,3-dimethylbutan-2-one (10) as an orange solid: mp 46–49 °C; IR (KBr) 3035 (w, CH), 1707 (s, C=O), 1595 (m), 1555 (m), 1470 (s), 1420 (s), 1305 (s), 1060 (s), 1015 (CO); ^1H NMR ($CDCl_3$) δ 1.21 (s, 9 H, *t*-Bu), 4.06 (s, 3 H, OCH_3), 4.08 (s, 2 H, CH_2), 6.86 (d, J = 9 Hz, 1 H, ring H), 7.27 (d, J = 9 Hz, 1 H, ring H).

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.07; H, 7.81; N, 13.52.

Dark Reaction of Acetone Enolate with 9. Procedure B gave a 60% yield of 1-(6-methoxypyridazin-3-yl)-2-propanone (11) isolated as a light yellow oil by preparative GLC: IR (neat) 3080 (w, CH), 1705 (s, C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H, CH_3), 4.03 (s, 2 H, CH_3), 4.13 (s, 3 H, OCH_3), 6.93 (d, 15 Hz, 1 H, ring H), 7.29 (d, 15 Hz, 1 H, ring H).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.60; H, 6.28; N, 16.75.

Dark Reactions of Diisopropyl Ketone Enolate with 9. Procedure B yielded a colorless solution that gave slightly impure starting material on evaporation of the ether. Longer reaction times (1 h) gave an ethereal solution, which after being stirred with wet silica gel for 48 h afforded 8% of 2-(4,5-dihydro-6-methoxy-3-oxopyridazin-4-yl)-2,4-dimethyl-3-pentanone (13). Purification of 13 was accomplished by developing the crude mixture on a preparative layer chromatography plate (PLC; silica gel, 50:50 ether–hexane): IR (solid) 3520 (br m, NH), 1705 (s, C=O), 1660 (s, C=O), 1475 (m), 1345 (s), 1005 (s, CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, J = 7 Hz, 6 H, isopropyl CH_3), 1.20 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 3.08 (septet, 1 H, J = 7 Hz, isopropyl CH), 2.45 and 2.52 (ABX, J_{AB} = 17 Hz, 2 H, CH_2), 3.32 (ABX, $J_{AX} = J_{BX}$ = 8 Hz, 1 H, pyrid H_4), 3.65 (s, 3 H, OCH_3), 8.50 (br s, 1 H, NH).

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.95; H, 8.41; N, 11.63.

The remainder of the reaction material was recovered 9.

Dark Reaction of Acetone Enolate and Diisopropyl Ketone Enolate with 9. Procedure B was modified so that the total enolate concentration was the same as that in the previous experiments, but the acetone/diisopropyl ketone enolate molar ratio was 1:9. GLC analysis using dimethyl phthalate as an internal standard indicated a 5% yield of 11 and a 31% yield of 12.

Dark Reactions of 2-Chloropyrazine (14) with Ketone Enolates. (A) Acetone Enolate. Procedure B, modified by shortening the reaction time to 5 min, gave 98% of 1-(2-pyrazinyl)-2-propanone (15) as a nearly colorless oil. A sample was collected for analysis by preparative GLC: IR (neat) 3040 (CH), 1710 (s, C=O), 1520 (w), 1035 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 0.18 H, enol CH_3), 2.12 (s, 2.82 H, keto CH_3), 2.91 (s, 1.8 H, CH_2), 5.38 (s, 0.12 H, enol CH), 8.40 (m, 3 H, ring H).

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.81; H, 6.08; N, 20.54.

(B) Pinacolone Enolate. Procedure B for 10 min produced 95% of 16 as a light yellow oil, which was collected by preparative GLC: IR (neat) 3035 (CH), 1705 (s, C=O) 1510, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H, *t*-Bu), 2.89 (s, 2 H, CH_2), 8.36 (m, 3 H, ring H).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.45; H, 7.88; N, 15.49.

(C) Diisopropyl Ketone Enolate. Procedure B gave an almost colorless solution. A 75% yield of 2-pyrazinyl-2,4-dimethyl-3-pentanone (17) was isolated by Kugelrohr distillation: IR (neat) 3065 (w), 3040 (CH), 1710 (s, C=O), 1570 (w), 1035 (s), 1015 (s), 1000 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 6 H, isopropyl CH_3), 1.60 (s, 6 H, CH_3), 2.72 (septet, J = 7 Hz, 1 H, isopropyl CH), 8.55 (m, 3 H, pyrazine).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.40; N, 14.57. Found: C, 68.61; H, 8.26; N, 14.63.

Dark Reaction of Acetophenone Enolate with 14. Procedure B gave a green solution from which α-pyrazinylacetophenone (18) was isolated in 60% yield by recrystallization from benzene–hexane: mp 95–96 °C; IR (neat, crushed solid) 3050 (w, CH), 1705 (s, C=O), 1650 (s), 1605 (m), 1475 (s), 760 (s), 740 (s), 680 (s) cm^{-1} ^1H NMR ($CDCl_3$) δ 4.47 (s, 1.2 H, CH_2), 6.18 (s, 0.4 H, enol CH), 7.34 (m, 3 H, aromatic), 7.75 (m, 1 H, aromatic), 7.95 (m, 1 H, aromatic), 8.15 (s, 1 H, ring H), 8.40 (m, 2 H, ring H), 13.77 (br s, 0.4 H, enol OH).

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.92; H, 5.10; N, 13.94.

Dark Reaction of the Potassium Salt of Phenylacetonitrile with 14. Procedure B was followed to give a red solution in ammonia which faded to a colorless solution when in ether. The crude product was recrystallized once from 2 mL of benzene diluted to 6 mL with hexane. A 78% yield of α-pyrazinylphenylacetonitrile (19) was obtained: mp 132–133.5 °C (lit.[18] mp 132–133 °C); IR (solid) 3080 (w), 3060 (w), 3040 (w) (CH), 2250 (m, CN), 1600 (w), 1520 (w, phenyl), 1490 (m), 1470 (m), 1450 (m), 1400 (s), 1035 (m), 1000 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (s, 1 H, CH), 7.37 (m, 5 H, phenyl), 8.55 (s, 2 H, pyrazine), 8.67 (s, 1 H, pyrazine).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.96; H, 4.46; N, 21.53.

Decreasing the reaction time to 3 min resulted in a 44% isolated yield of 19.

Registry No. 1, 1722-12-9; 2, 75782-22-8; 3, 109-12-6; 4, 75782-23-9; 5, 75782-24-0; 6, 75782-25-1; 7, 6320-15-6; 8, 75782-26-2; 9, 1722-10-7; 10, 75782-27-3; 11, 75782-28-4; 12, 75782-29-5; 13, 75782-30-8; 14, 14508-49-7; 15, 6784-62-9; 16, 40911-30-6; 17, 75782-31-9; 18, 40061-45-8; 19, 1080-87-1; potassioacetone, 25088-58-8; potassiopinacolone, 62415-77-4; potassiodiisopropyl ketone, 55887-17-7; potassioacetophenone, 59175-43-8; potassiophenylacetonitrile, 75782-32-0.