The $S_{RN}1$ Mechanism in Heteroaromatic Nucleophilic Substitution. Photostimulated Reactions of Halopyridines with Ketone Enolates[1]

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Received December 15, 1976

2-Bromopyridine undergoes photostimulated $S_{RN}1$ reactions in liquid ammonia with the potassium enolates of acetone, 2,4-dimethyl-3-pentanone, cyclohexanone, and pinacolone. 2-Pyridyl radicals formed in these reactions show a preference for combination with tertiary enolates over primary enolates in competitive experiments. The reactivity of a series of haloaromatics toward potassioacetone was found to be 2-chloroquinoline > 2-bromopyridine > bromobenzene. In the 2-halopyridine series the order of reactivity with potassioacetone is 2-bromopyridine > 2-chloropyridine > 2-fluoropyridine; while the isomeric bromopyridines exhibit the order 2-bromopyridine > 3-bromopyridine > 4-bromopyridine. The reactivity of alkali salts of acetone toward 2-bromopyridine was found to be K > Na > Li. 2,6-Dibromo- and 2,6-dichloropyridine react with the potassium enolate of pinacolone to form the 2,6-disubstituted product without accumulation of a monosubstituted intermediate. The synthetic value of the present reactions is demonstrated by a large scale preparation of 2-acetonylpyridine.

Recently,[2,3] we have found that various ketone enolates react with 2-chloroquinoline in liquid ammonia under near-ultraviolet irradiation to afford α-(2-quinolyl) ketones via the radical chain process illustrated in Scheme I.

Scheme I

$$\text{Het-X} + \text{RCO}\bar{\text{C}}\text{H}_2 \xrightarrow{h\nu} \text{Het-X}^{-}\cdot + \text{RCOCH}_2\cdot \quad (1)$$

$$\text{Het-X}^{-}\cdot \longrightarrow \text{Het}\cdot + \text{X}^{-} \quad (2)$$

$$\text{Het}\cdot + \text{RCO}\bar{\text{C}}\text{H}_2 \longrightarrow \text{HetCH}_2\text{COR}^{-}\cdot \quad (3)$$

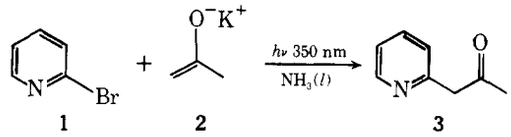
$$\text{HetCH}_2\text{COR}^{-}\cdot + \text{Het-X} \longrightarrow \text{HetCH}_2\text{COR} + \text{Het-X}^{-}\cdot \quad (4)$$

Initiation (step 1) is provided by photostimulated electron transfer, presumably from the enolate ion, to form the radical anion of the halogenated heterocycle. Expulsion of halide ion to form the heterocyclic radical (step 2), combination of the enolate with this radical (step 3), and transfer of an electron from the resulting radical anion to a substrate molecule constitute the propagating steps of the mechanism. Similar mechanisms have been verified for reactions of various nucleophiles with aliphatic[4] and carboaromatic[5] substrates containing appropriate leaving groups. These reactions have been designated by Bunnett as $S_{RN}1$ processes.[6]

In spite of the documented occurrence of $S_{RN}1$ reactions with the aforementioned classes of substrates, there are still relatively few verified examples implicating this mechanism in the area of heteroaromatic nucleophilic substitution.[2,3,7-9] Because of this, we have continued our investigations of the scope of the heteroaromatic $S_{RN}1$ mechanism by studying the reactions of halopyridines with ketone enolates. The present paper describes the results of such a study, in which it has been found that $S_{RN}1$ reactions do indeed occur under conditions of photostimulation. This is the first reported instance of participation of enolate ions in light-induced $S_{RN}1$ reactions on the pyridine nucleus.

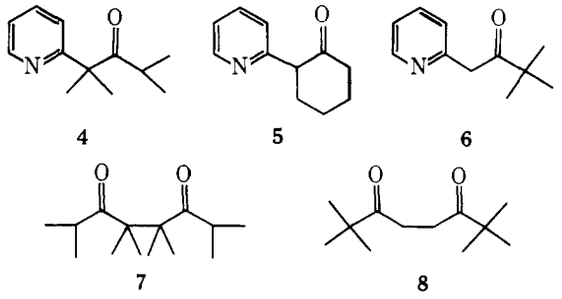
Results and Discussion

Treatment of 2-bromopyridine (1) with 3.75 molar equiv of potassioacetone (2) in liquid ammonia at −33 °C in a reaction flask protected from light resulted in nearly quantitative recovery of 1 after a reaction time of 60 min (expt 1, Table I). Photostimulation was demonstrated in a similar experiment conducted under full illumination (four 12.5-W output lamps) in a Rayonet photochemical reactor at 350 nm for 15 min. In this reaction 2-acetonylpyridine (3) was obtained in 95% yield (expt 2). Low intensity irradiation with a single lamp for 10 min or less (expt 3) led to incomplete reaction, whereas irradiation with one lamp for 15 min gave 3 in quantitative yield (expt 4). The radical-chain character of the substitution process was clearly indicated by a 15-min irradiation (one lamp) in the presence of 10 mol % of the radical scavenger, di-*tert*-butyl nitroxide.[10] Under these conditions less than 5% of 1 was consumed and no 3 was detected (expt 5). Evidently the nitroxide breaks chains involving propagating steps 2–4 (Scheme I) either by combining with 2-pyridyl radicals or by oxidizing radical anion intermediates. In connection with the inhibition studies utilizing di-*tert*-butyl nitroxide, we observed that reactions conducted under full illumination were also inhibited, but the inhibition period was usually less than 15 min with 5 mol % of inhibitor.



1 2 3

Photostimulated reactions of 1 with the potassium salts of 2,4-dimethyl-3-pentanone, cyclohexanone, and pinacolone proceeded smoothly to afford 4, 5, and 6, respectively (expt 6, 7, and 8). In addition to ketone 4, a small amount of



4 5 6

7 8

2,4,4,5,5,7-hexamethyloctane-3,6-dione (7) was produced in expt 6. Recently, Bunnett and co-workers reported that the photostimulated reaction of iodobenzene with the potassium enolate of 2,4-dimethyl-3-pentanone gave 7 and benzene in equimolar quantities along with the normal $S_{RN}1$ product.[11] The mechanism proposed[11] for formation of 7 involves electron transfer from the enolate ion to an aryl radical yielding an aryl anion, which abstracts a proton from the solvent, and a β-keto alkyl radical, which either dimerizes or combines with another enolate ion with subsequent electron transfer. The present results, along with those of an earlier study,[2] demonstrate that 2-pyridyl and 2-quinolyl radicals are less susceptible to reduction by the enolate of 2,4-dimethyl-3-pentanone than are phenyl radicals. This might be attributed to

Table I. Photostimulated $S_{RN}1$ Reactions of Ketone Enolates with Halopyridines[a]

Expt. no.	Substrate	Enolate derived from	Irradiation time, min	Product distribution[b] Pyridyl no.	Ketone yield, %	Unreacted substrate, %
1	2-BrPy	Acetone	*c*	3	0	98
2	2-BrPy	Acetone	15	3	95	0
3	2-BrPy	Acetone	10[d]	3	85	10
4	2-BrPy	Acetone	15[d]	3	100	0
5	2-BrPy	Acetone	15[d,e]	3	0	95
6	2-BrPy	2,4-Dimethyl-3-pentanone	60	4	97	0[f]
7	2-BrPy	Cyclohexanone	60	5	47	Present
8	2-BrPy	Pinacolone	90	6	94[g]	0
9	2-BrPy	Acetone	15	3	21	0[f]
		2,4-Dimethyl-3-pentanone		4	77	
10	2-BrPy	2,4-Dimethyl-3-pentanone	15	4	61	36
11	2-BrPy	Acetone[h]	15	3	74	0
12	2-BrPy	Acetone[i]	15	3	6	58
13	2-ClPy	Acetone	60	3	85	0
14	2-FPy	Acetone	120	3	40	20
15	3-BrPy	Acetone	15	14	65	0
16	3-BrPy	Acetone	15[c,e]	14	0	Mostly
17	4-BrPy	Acetone	15	15	28	Present

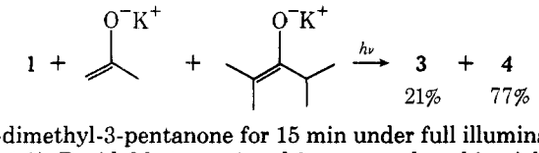
[a] In expt 8 the ratio of 2-BrPy to enolate was 1:2.5 and in expt 9, the ratio of 2-BrPy to the two enolates was 1:1.9:1.9. In all other cases the ratio of halopyridine to enolate was 1:3.75. [b] In all reactions employing acetone, appreciable quantities of 4-hydroxy-4-methyl-2-pentanone were formed along with small amounts of 2,6-dihydroxy-2,6-dimethyl-4-heptanone. [c] This experiment was conducted in the dark (foil-wrapped vessel). [d] This reaction was irradiated with single 12.5-W output 350-nm lamp. [e] Di-*tert*-butyl nitroxide (10 mol % based on **1**) was present. [f] Dimer **7** was produced in 5% yield in expt 6 and 2% yield in expt 9. [g] Isolated yield. [h] The sodium enolate was used. [i] The lithium enolate was used.

the greater electrophilicity of the heterocyclic radicals, which favors their combination with the enolate ion, while the less electrophilic phenyl radicals suffer appreciable reduction via electron transfer from the enolate.[8]

Another 1,4-diketone, **8**, was found in prolonged irradiations of pinacolone enolate with halopyridines. In these cases, however, the diketone arises from a photostimulated reaction independent of the $S_{RN}1$ reaction, since **8** accumulated only slowly, even though the $S_{RN}1$ reactions were rapid. Irradiation of pinacolone potassium enolate alone in liquid ammonia for 120 min gave **8**, but a similar experiment conducted in the dark did not produce **8**.

2-Bromopyridine failed to react under irradiation with the monoanion of benzoylacetone (120 min) or the potassium enolates of acetophenone and propiophenone (both 60 min). Previous attempts to react β-dicarbonyl monoenolates with 2-chloroquinoline[2] or halobenzenes[11] have all met with failure. Potassioacetophenone is totally unreactive toward bromo- and iodobenzene under photostimulation,[11] whereas with 2-chloroquinoline, a very slow substitution occurs.[2]

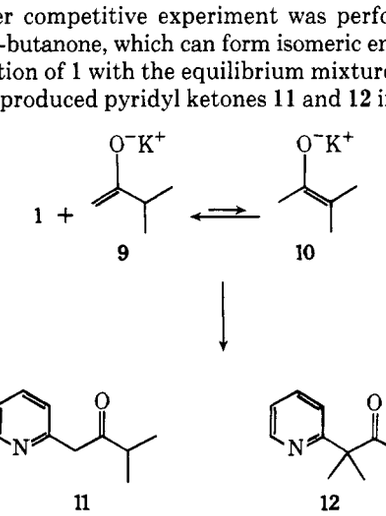
Competitive Reactions. In an earlier study, we observed that 2-quinolyl radicals, generated during photostimulated $S_{RN}1$ reactions, exhibited a significant degree of selectivity in competitive reactions involving mixtures of primary and tertiary potassium enolates. In order to ascertain if 2-pyridyl radicals might show similar selectivity, **1** was allowed to react with an equimolar mixture of the potassio salts of acetone and



2,4-dimethyl-3-pentanone for 15 min under full illumination (expt 9). Pyridyl ketones **4** and **3** were produced in yields of 77 and 21%, respectively. This product ratio (3.7:1) is nearly the same as that (3.2:1) observed when an identical mixture of enolates was allowed to react with 2-chloroquinoline under the same reaction conditions.[2] The present results indicate that 2-pyridyl radicals exhibit a degree of selectivity similar to 2-quinolyl radicals in reactions with enolates.

A comparison of expt 1, 9, and 10 revealed an additional feature of this competitive reaction. When 2,4-dimethyl-3-pentanone enolate was irradiated with **1** for 15 min, **4** was obtained in only 61% yield (expt 10), while acetone enolate gave **3** in 95% yield (expt 1) after the same irradiation time. The 77% yield of **4** obtained in expt 9 demonstrates entrainment[2,4] of 2,4-dimethyl-3-pentanone enolate by acetone enolate. In the entrainment process, acetone enolate functions as the better electron-donating species (step 1, Scheme I) thus initiating more chains than 2,4-dimethyl-3-pentanone enolate, while 2,4-dimethyl-3-pentanone enolate is the better nucleophile for combination with the pyridyl radicals (step 3, Scheme I).

A further competitive experiment was performed using 3-methyl-2-butanone, which can form isomeric enolates **9** and **10**. Irradiation of **1** with the equilibrium mixture of **9** and **10** for 15 min produced pyridyl ketones **11** and **12** in a 7:1 ratio.



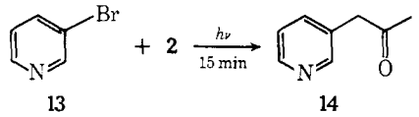
Comparison of these results with those from a previous study[12] concerning photostimulated phenylation of enolates **9** and **10** indicates that the ratio of pyridyl ketones **11** and **12** is determined mainly by the equilibrium composition of this enolate mixture in liquid ammonia.

In order to determine the relative $S_{RN}1$ reactivity of **1** compared to other haloaromatic compounds, two competitive reactions were conducted employing bromobenzene and 2-chloroquinoline. Irradiation of an equimolar mixture of **1** and bromobenzene in the presence of acetone enolate for 7 min (one lamp) resulted in complete consumption of **1** and production of phenylacetone and **3** in a ratio of 0.27:1.00. Thus **1** is seen to be more reactive than bromobenzene toward $S_{RN}1$ substitution. Irradiation of an equimolar mixture of **1** and 2-chloroquinoline with acetone enolate for 1.5 min (one lamp) returned **1** unchanged and converted 66% of the 2-chloroquinoline to 2-acetonylquinoline. Presumably, 2-bromoquinoline would show even greater reactivity than 2-chloroquinoline in a competitive reaction with **1**. Previously,[2] we had determined that 2-chloroquinoline was more reactive than iodobenzene toward $S_{RN}1$ substitution by acetone enolate. This comparison may now be expanded to give the following reactivity sequence: 2-haloquinoline > 2-halopyridine > halobenzene, provided similar halogen substituents are compared. This selectivity may be linked to the ease with which the haloaromatic substrate is reduced to its radical anion as in steps 1 and 4 of Scheme I.

Metallic Cation Effects. In order to assess the influence of the gegenion, a series of experiments using **1** with the sodio and lithio salts of acetone were conducted under illumination for 15 min. As may be seen from Table I (expt 11 and 12), potassioacetone (**2**) was superior to either the sodium or lithium enolate, although for preparative scale reactions, sodioacetone may be a satisfactory substitute for the potassio analogue.

Influence of Halogen. Whereas potassioacetone reacted with **1** to form **3** in quantitative yield after 15 min of illumination, the reaction of 2-chloropyridine with potassioacetone was somewhat slower, affording 85% of **3** after 60 min of irradiation (expt 13). A further decrease in reactivity was observed when 2-fluoropyridine was irradiated for 120 min with potassioacetone. In this experiment, 20% of 2-fluoropyridine was recovered and **3** was formed in only 40% yield (expt 14). It has been shown that 2-fluoropyridine forms a relatively stable radical anion upon reduction with sodium in liquid ammonia, whereas the radical anions of 2-bromo- and 2-chloropyridine quickly expel their respective halide ions.[13] In view of this, it appears that the comparatively low reactivity of 2-fluoropyridine may be traced to step 2 of Scheme I, where expulsion of halide ion is necessary for maintenance of the propagating sequence.

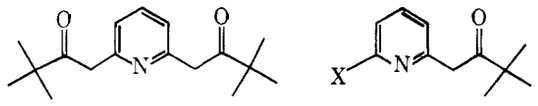
Effect of Halogen Position. To date, photostimulated $S_{RN}1$ reactions of enolates with haloquinolines and halopyridines have involved displacement of halide exclusively from the 2 position of the heterocycle. We have now found that 3-bromopyridine (**13**) readily participates in the reaction with potassioacetone (**2**). Thus, exposure of **13** to 3.75 molar equiv of the enolate with illumination for 15 min afforded ketone



13 14

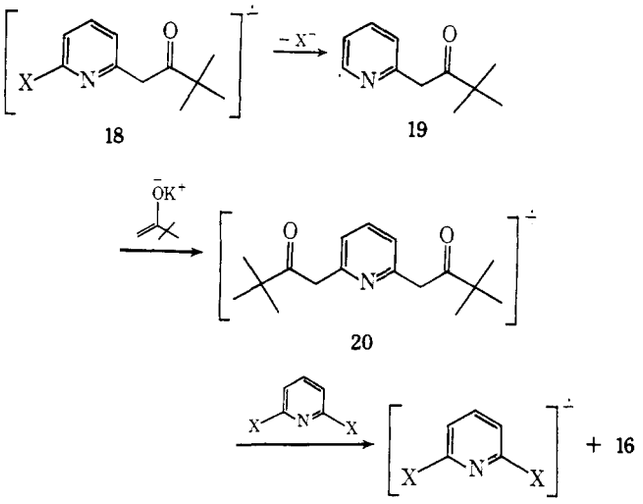
14 in 65% yield. The $S_{RN}1$ character of this reaction was confirmed by an experiment in which a mixture of **13**, **2**, and 10 mol % of di-*tert*-butyl nitroxide was maintained in the dark for 15 min (expt 16). No starting material was consumed. Substitution at the 4 position of 4-bromopyridine by **2** proceeded poorly. Irradiation of the reaction mixture for 15 min gave only 28% of 4-acetonylpyridine (**15**) along with an appreciable amount of recovered 4-bromopyridine (expt 17).

2,6-Dihalopyridines. Photostimulated reaction of the potassium enolate of pinacolone with 2,6-dibromopyridine gave 89% of the 2,6-disubstituted derivative **16**, along with a trace of **6** after 60 min of irradiation. 2,6-Dichloropyridine reacted similarly to give a 86% yield of **16**. Formation of disubstituted product **16** appears to arise directly from 2,6-dichloropyridine without buildup of the monosubstituted



16 17

compound **17**. Evidence for direct formation of **16** was obtained from an experiment in which a reaction of 2,6-dichloropyridine and pinacolone enolate was irradiated for only 45 s. Under these conditions, none of the monosubstituted pyridine **17** (X = Cl) was detected, but rather starting material and **16** were found in a ratio of 1:3. Similar results have been observed recently in the $S_{RN}1$ reactions of dihalobenzenes with thiophenoxide in liquid ammonia.[14] By analogy with these studies, disubstitution without accumulation of monosubstituted product is attributed to preferential expulsion of halide from an intermediate radical anion such as **18** to form



18 19 20

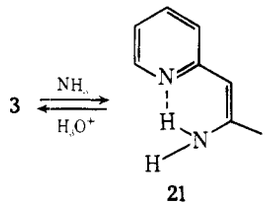
radical **19** rather than electron transfer from **18** to 2,6-dihalopyridine as in step 4 of Scheme I. Combination of radical **19** with pinacolone enolate yields radical anion **20**, which then initiates a new cycle by transferring an electron to another molecule of 2,6-dihalopyridine. In our experiments, the small amount of **6** formed may result from either reduction of radical **19** or reduction of the initial 6-chloro-2-pyridyl radical followed by $S_{RN}1$ reaction of the resulting 2-chloropyridine with pinacolone enolate.

Metal-Promoted Reaction. Solvated electrons, furnished by alkali metals, have been shown to promote $S_{RN}1$ reactions between enolate nucleophiles and halobenzenes in liquid ammonia.[15] The solvated electrons initiate the chain sequence by a one-electron reduction of the substrate to its radical anion.

Addition of 1 molar equiv of potassium metal to a liquid ammonia solution of **1** and **2**, maintained in a flask protected from light, failed to effect significant catalysis of the substitution reaction. Instead, 38% of **1** was recovered, an appreciable quantity of pyridine was generated, and ketone **3** was produced in only 4% yield. Formation of pyridine indicates that reduction of 2-pyridyl radicals to 2-pyridyl anions by solvated electrons and subsequent protonation by ammonia competes strongly with the desired combination of 2-pyridyl radicals with enolate **2**. To date, metal-promoted $S_{RN}1$ reac-

tions of heteroaromatics have been found to be less satisfactory than those involving carboaromatic substrates.[2,3]

Preparative Scale Reactions. The synthetic utility of the present photostimulated reactions was verified by a preparative scale reaction involving 0.4 mol of **1** and 1.2 mol of **2**, which afforded **3** in 84% isolated yield after 90 min of irradiation. It should be noted that reactions which produce **3** may be accompanied by formation of enamine **21** if evaporation



21

of the ammonia subsequent to quenching is not carried out rapidly. However, this minor inconvenience can be circumvented easily by hydrolyzing **21** with dilute hydrochloric acid (see Experimental Section). A reaction similar to the preceding one, conducted in a 5-L flask illuminated from 15 cm by a 150-W flood light, required 9 h to achieve completion. For more economical use of the ketone, the ketone enolate to halopyridine ratio may be reduced to a small excess over the theoretical ratio of 2:1.[16] A ratio of 2.5:1 of pinacolone enolate to **1** gave **6** in 94% isolated yield after 90 min of irradiation (expt 8).

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen. The photostimulated reactions were carried out using a Rayonet RPR-204 photochemical reactor equipped with four 12.5-W output 350-nm lamps. Photolysis vessels were of cylindrical Pyrex 4.4 cm i.d. or 10.6 cm i.d. for preparative runs and were occasionally rinsed with ethanol to remove the frost buildup. Product yields were determined by vapor phase chromatography (VPC) on Varian Associates 90-P or 1200 instruments using columns of 10% SE-30 or 1.5% SE-52 on Chromosorb W AW/DMCS or 5% Carbowax 20M on Chromosorb G employing methyl benzoate, dimethyl phthalate, or benzyl benzoate as internal standard. ^{1}H NMR spectra were obtained on a JEOL JMN-PS-100 instrument with internal tetramethylsilane as reference. Mass spectra (70 eV) were recorded on Varian MAT CH-7 or 112 instruments. Microanalyses were performed in this laboratory by C. D. Anderson employing a Perkin-Elmer 240 elemental analyzer or by Galbraith Laboratories, Knoxville, Tenn. Unless otherwise noted, analytical samples were obtained by preparative VPC using the columns described above.

Liquid ammonia (Matheson) was used directly from the tank since essentially no difference was observed in product composition and yield compared to ammonia distilled from benzophenone potassium ketyl. 2-Bromopyridine (**1**) and acetone were dried and fractionated, 2,6-dichloropyridine was vacuum sublimed; other reagents were used as received. Anhydrous magnesium sulfate was routinely used as a drying agent. Di-*tert*-butyl nitroxide[17] was prepared from 2-methyl-2-nitropropane.[18] Inhibited reactions were carried out by mixing the di-*tert*-butyl nitroxide (10 mol %, based on halopyridine) with the halopyridine before it was added to the enolate solution. Dark reactions were run in a darkened room using a foil-wrapped 500-mL three-necked flask equipped with a mechanical stirrer, air-cooled condenser, addition funnel, and nitrogen inlet. The molar ratio of halopyridine to ketone enolate was 1:3.75 unless otherwise indicated. Starting material was often consumed before the end of the irradiation period given in Table I.

Reaction Workup. After an appropriate period (Table I), reaction mixtures were poured onto excess solid ammonium chloride contained in a 1.5-L beaker. Ether (300 mL) was added to the resulting suspension while the ammonia was evaporated with the aid of a warm water bath. The ether was then allowed to boil briefly to ensure removal of the residual ammonia. At this point either workup procedure A or B was followed.

Procedure A. Water (150 mL) was added, followed by enough dilute hydrochloric acid to make the aqueous layer distinctly acidic (pH <1). Sodium bicarbonate was then added to neutralize the acid, and the ethereal layer was separated. The aqueous layer was extracted twice with chloroform (75 mL). The combined organic extracts were dried, concentrated, mixed with an internal standard, and analyzed by VPC.

Procedure B. The ethereal suspension remaining after evaporation of the ammonia was decanted through a filter and the residual salts were triturated with warm ether (4 × 75 mL). The combined ethereal extracts were concentrated, mixed with an internal standard, and analyzed by VPC.

2-Acetonylpyridine (3). Potassium metal (2.93 g, 75 mg-atoms) was added to 300 mL of liquid ammonia along with a small amount of powdered ferric nitrate nonahydrate. After the potassium amide had formed, acetone (4.36 g, 75 mmol) was added dropwise and rinsed into the vessel with a small amount of anhydrous ether. Irradiation was begun after the enolate had been stirred for 10 min, and 2-bromopyridine (**1**, 3.16 g, 20 mmol) was added along with 50 mL of anhydrous ether. After 15 min of illumination, the reaction was processed according to procedure A. Analytical and spectral properties of **3** are given in the description of the large scale preparation of **3** (vide infra).

Enamine 21. Enamine **21** was isolated as a light yellow oil by preparative VPC of the crude product mixture obtained by employing workup procedure B in an experiment otherwise identical with the one described above. Highly air sensitive **21** showed ^{1}H NMR (CCl_4) δ 1.91 (s, 3 H, CH_3), 4.86 (s, 1 H, CH), 6.46 (broad s, 2 H, disappeared on shaking with D_2O, NH_2) 6.62–6.82 (m, 2 H, PyH-3,5), 7.26–7.47 (m, 1 H, PyH-4), and 8.29–8.39 (m, 1 H, PyH-6); mass spectrum *m/e* (rel intensity) 134 (40), 133 (100), 117 (13), 93 (61), 92 (43), 90 (19), 79 (11), 78 (16), 66 (19), 65 (31), 63 (10), 52 (10), 43 (17), 42 (13), 41 (11), and 39 (23).

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.94; H, 7.26; N, 20.94.

2,4-Dimethyl-2-(2-pyridyl)-3-pentanone (4). 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added to an enolate solution prepared from 8.56 g (75 mmol) of 2,4-dimethyl-3-pentanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 60 min, it was processed by procedure B. This reaction afforded 5% of **7** and 97% of **4**, the latter of which was isolated as a colorless oil by preparative VPC and showed ^{1}H NMR (CCl_4) δ 0.85 (d, J = 6.6 Hz, 6 H, isopropyl methyls), 1.45 [s, 6 H, $C(CH_3)_2$], 2.61 (septet, J = 6.6 Hz, 1 H, CH), 6.97–7.22 (m, 2 H, PyH-3,5), 7.44–7.64 (m, 1 H, PyH-4), and 8.38–8.48 (m, 1 H, PyH-6) (no enol).[19]

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.47; H, 9.08; N, 7.39.

A similar reaction mixture irradiated for 15 min gave unchanged **1** (36%) and 61% of **4**.

Diketone **7**, obtained as a colorless oil by preparative VPC, was spectroscopically identical with an authentic sample of **7** prepared by irradiation of iodobenzene with the potassium enolate of 2,4-dimethyl-3-pentanone in liquid ammonia according to the procedure of Bunnett and Sundberg.[11]

2-(2-Pyridyl)cyclohexanone (5). 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added to the white enolate suspension (all other potassium enolates were soluble) prepared from 7.36 g (75 mmol) of cyclohexanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 90 min, it was worked up by procedure B. VPC analysis showed unreacted **1** along with 47% of **5**. A sample of **5** was collected for analysis. This light yellow oil had ^{1}H NMR (CCl_4) δ 1.5–2.4 (m, cyclohexyl protons), 6.82–7.10 (m, 2 H, PyH-3,5), 7.45–7.65 (m, 1 H, PyH-4), 8.21–8.31 (m, PyH-6 of enol), 8.35–8.45 (m, PyH-6 of keto), and 14.62 (broadened s, enol OH) (enol content ca. 84%).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.58; H, 7.44.

3,3-Dimethyl-1-(2-pyridyl)-2-butanone (6). 2-Bromopyridine (**1**, 15.8 g, 100 mmol) was added to the enolate solution prepared from 25.0 g (250 mmol) of pinacolone and potassium amide [prepared from 9.78 g (250 mg-atoms) of potassium in 1500 mL of liquid ammonia]. After the mixture had been irradiated for 90 min, it was poured onto excess ammonium chloride and the ammonia was evaporated while 300 mL of ether was added. The ethereal extract was filtered and the residual salts were washed twice with 100 mL of ether. The salts were dissolved in water and extracted further with chloroform (2 × 100 mL). The combined organic extracts were dried, concentrated, and distilled to give 16.6 g (94%) of **6**: bp 51–53 °C (0.15 mm); ^{1}H NMR (CCl_4) δ 1.16 (s, keto methyls), 1.19 (s, enol methyls), 3.87 (s, CH_2), 5.24 (s, enol CH), 6.70–7.16 (m, 2 H, PyH-3,5), 7.31–7.55 (m, 1 H, PyH-4), 8.10–8.20 (m, PyH-6 of enol), 8.27–8.37 (m, PyH-6 of keto), and 14.35 (broad s, enol OH) (enol content ca. 50%).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.40; H, 8.49.

2,2,7,7-Tetramethyloctane-3,6-dione (8). To a potassium amide

solution prepared from 2.93 g (75 mg-atoms) of potassium and 300 mL of liquid ammonia was added 7.51 g (75 mmol) of pinacolone followed by a rinse of anhydrous ether (25 mL). The enolate solution was irradiated for 120 min, quenched with excess solid ammonium chloride, and evaporated. The residual salts were triturated repeatedly with anhydrous ether to extract the organic components. The combined ether extracts were concentrated and examined by VPC showing, in addition to unreacted pinacolone, an appreciable amount of **8**. A sample of **8** was collected as a viscous oil: ^{1}H NMR (CCl_4) δ 1.12 (s, 18 H, CH_3) and 2.62 (s, 4 H, CH_2).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found: C, 72.56; H, 11.07.

An experiment similar to the one above was conducted in a foil-wrapped flask in a darkened room for 120 min. After the mixture had been quenched in the dark, an identical workup was followed. VPC analysis showed unreacted pinacolone with no trace of diketone **8**.

Reaction of 1 with Acetone and 2,4-Dimethyl-3-pentanone Enolates. 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added under irradiation to the enolate solution prepared from 2.18 g (37.5 mmol) of acetone, 4.28 g (37.5 mmol) of 2,4-dimethyl-3-pentanone, and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure **A**. VPC analysis showed 2% of **7**, 21% of **3**, and 77% of **4**.

Reaction of 1 with 3-Methyl-2-butanone Enolate. 2-Bromopyridine (**1**, 3.16 g, 20 mmol) was added under irradiation to the enolate solution prepared from 6.46 g (75 mmol) of 3-methyl-2-butanone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After a 15-min irradiation period, the mixture was quenched and worked up by procedure B. VPC analysis showed a moderate amount of 5-hydroxy-2,5,6-trimethyl-3-heptanone along with 3-methyl-1-(2-pyridyl)-2-butanone (**11**) and 3-methyl-3-(2-pyridyl)-2-butanone (**12**) in a ratio of 7:1. Isomeric ketones **11** and **12** were isolated as colorless oils by preparative VPC. Compound **11** showed ^{1}H NMR (CCl_4) δ 1.07 (d, J = 6.6 Hz, keto methyls), 1.16 (d, J = 6.6 Hz, enol methyls), 2.39 (septet, J = 6.6 Hz, isopropyl methine of enol), 2.71 (septet, J = 6.6 Hz, isopropyl methine of keto), 3.80 (s, keto CH_2), 5.17 (s, enol vinyl H), 6.70–7.14 (m, 2 H, PyH-3,5), 7.31–7.56 (m, 1 H, PyH-4), 8.10–8.20 (m, PyH-6 of enol), and 8.30–8.40 (m, PyH-6 of keto) (enol content ca. 37%).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.44; H, 7.92.

Compound **12** showed ^{1}H NMR (CCl_4) δ 1.44 [s, 6 H, $C(CH_3)_2$], 1.84 (s, 3 H, CH_3), 6.94–7.19 (m, 2 H, PyH-3,5), 7.43–7.63 (m, 1 H, PyH-4), and 8.39–8.49 (m, 1 H, PyH-6) (no enol).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.33; H, 7.98.

Reaction of Acetone Enolate with 1 and Bromobenzene. A mixture of bromobenzene (1.57 g, 10 mmol) and **1** (1.58 g, 10 mmol) was added in the dark to 75 mmol of potassioacetone in 300 mL of liquid ammonia. The mixture was irradiated with one 12.5-W output lamp for 7 min, quenched, and worked up by procedure A. VPC analysis showed complete reaction of **1** and partial consumption of the bromobenzene to give phenylacetone and **3** in a ratio of 0.27:1.00.

Reaction of Acetone Enolate with 1 and 2-Chloroquinoline. A mixture of **1** (1.58 g, 10 mmol) and 2-chloroquinoline (1.64 g, 10 mmol) was added in the dark to 75 mmol of potassioacetone in 300 mL of liquid ammonia. After the mixture had been irradiated for 1.5 min with one lamp (12.5-W output), it was quenched and worked up by procedure A. VPC analysis showed complete recovery of **1** and, along with some 2-chloroquinoline, 66% of 2-acetonylquinoline.[2]

3-Acetonylpyridine (14). 3-Bromopyridine (3.16 g, 20 mmol) was added to 75 mmol of acetone enolate prepared from 4.36 g (75 mmol) of acetone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure B. VPC analysis showed no 3-bromopyridine and 65% of **14**, which was collected as a colorless oil: ^{1}H NMR (CCl_4) δ 2.10 (s, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 7.04–7.19 (m, 1 H, PyH-5), 7.32–7.46 (m, 1 H, PyH-4), and 8.23–8.37 (m, 2 H, PyH-2,6) (no enol).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.94; H, 6.64.

4-Acetonylpyridine (15). 4-Bromopyridine hydrochloride (3.89 g, 20 mmol) was dissolved in ice water, neutralized with sodium bicarbonate, and extracted four times with cold ether (25 mL). The combined ethereal extracts were dried, filtered, and added to an acetone enolate solution prepared from 4.36 g (75 mmol) of acetone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 15 min, it was quenched and worked up by procedure B. VPC analysis showed an appreciable amount of unreacted 4-bromopyridine along with 28% of liquid keto6e **15**: ^{1}H NMR ($CCl)_4$ δ 2.10 (s, 3 H, CH_3), 3.61 (s, 2 H, CH_2), 6.94–7.03 (m, 2 H, PyH-3,5), and 8.30–8.40 (m, 2 H, PyH-2,6) (no enol).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.90; H, 6.78.

2,6-Bis(pivaloylmethyl)pyridine (16). A solution of 2.37 g (10 mmol) of 2,6-dibromopyridine in 25 mL of ether was added to the enolate solution prepared from 7.51 g (75 mmol) of pinacolone and 75 mmol of potassium amide in 300 mL of liquid ammonia. After the mixture had been irradiated for 60 min, it was quenched and worked up by procedure B. VPC analysis showed a trace of **6** and 89% of **16**.

A similar reaction with 1.48 g (10 mmol) of 2,6-dichloropyridine in place of the 2,6-dibromopyridine produced **16** in 86% yield.

A preparative experiment conducted with 25 mmol of 2,6-dichloropyridine and 150 mmol of the potassium enolate of pinacolone afforded a 44% isolated yield of **16**:[20] bp 155–162 °C (0.5 mm); mp 47.5–49 °C; ^{1}H NMR (CCl_4) δ 1.17, 1.19, and 1.20 (singlets, 18 H, *tert*-butyl methyls of keto and enol), 3.81 and 3.82 (singlets, CH_2 of keto and enol), 5.22 (s, CH of enol), 6.62–7.05 (m, 2 H, PyH-3,5), 7.31–7.52 (m, 1 H, PyH-4), and 14.15 (broad s, enol OH) (enol content ca. 53%).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.18; H, 9.17.

Short Irradiation of 2,6-Dichloropyridine with Pinacolone Enolate. An ethereal solution of 2,6-dichloropyridine (1.48 g, 10 mmol) was added in the dark to 75 mmol of pinacolone potassium enolate in 300 mL of liquid ammonia. After the mixture had been irradiated for 0.75 min, it was quenched and worked up by procedure B. VPC analysis showed 2,6-dichloropyridine and **16** in a 1:3 ratio. Although a trace of **6** was seen, no **17** was detected.

Preparative Scale Synthesis of 2-Acetonylpyridine (3). A potassium amide solution was prepared in a cylindrical Pyrex vessel from 47 g (1.2 g-atoms) of potassium, 2.5 L of liquid ammonia, and a small amount of ferric nitrate nonahydrate. Acetone (69.7 g, 1.2 mol) was added over a period of 10 min and rinsed into the vessel with 50 mL of anhydrous ether. After the enolate solution had been stirred for 15 min, irradiation was begun and 63.2 g (0.40 mol) of **1** was added during a 10-min period and rinsed into the vessel with 50 mL of ether. After the mixture had been irradiated for 90 min, the orange-yellow solution was poured into a 4-L beaker and quenched with excess solid ammonium chloride. Ether (500 mL) was added while the ammonia was evaporated with the aid of a warm water bath. After 500 mL of water had been added, dilute HCl was added to pH <1 and the mixture was shaken. Excess solid sodium bicarbonate was added in portions to neutralize the acid, and the ethereal layer was separated. The aqueous layer was extracted with chloroform (3 × 250 mL). The combined organic extracts were dried, concentrated, and vacuum fractioned to yield, after a forerun of 4-hydroxy-4-methyl-2-pentanone (18.8 g), 45.3 g (83.8%) of 2-acetonylpyridine (**3**) as a yellow liquid: bp 49 °C (0.1 mm) [lit.[21] bp 92 °C (1.5 mm)]; IR (neat) ν 1710 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.93 (s, CH_3 of enol), 2.09 (s, CH_3 of keto), 3.78 (s, CH_2), 5.20 (s, CH of enol), 6.70–7.16 (m, 2 H, PyH-3,5), 7.37–7.62 (m, 1 H, PyH-4), 8.13–8.23 (m, PyH-6 of enol), 8.37–8.47 (m, PyH-6 of keto), and 14.17 (broad s, enol OH) (enol content ca. 28%); mass spectrum *m/e* (rel intensity) 135 (5), 120 (5), 94 (6), 93 (100), 92 (18), 66 (12), 65 (13), 43 (32), and 39 (12).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.87; H, 7.00; N, 10.46.

The 4-hydroxy-4-methyl-2-pentanone forerun was identical with an authentic sample:[22] ^{1}H NMR (CCl_4) δ 1.18 [s, 6 H, $C(CH_3)_2$], 2.11 (s, 3 H, CH_3), 2.52 (s, 2 H, CH_2) and 3.74 (broad s, 1 H, disappeared on shaking with D_2O, OH).

Small amounts of 2,6-dihydroxy-2,6-dimethyl-4-heptanone were obtained by preparative VPC on the crude reaction mixture: mp 57–57.5 °C [lit.[23] mp 56.4 °C; lit.[24] mp 57–58 °C]; ^{1}H NMR (CCl_4) δ 1.21 [s, 12 H, $C(CH_3)_2$], 2.53 (s, 4 H, CH_2), and 3.38 (broad s, 2 H, disappeared on shaking with D_2O, OH).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.21; H, 10.20.

Registry No.—**1**, 109-04-6; **2**, 25088-58-8; **3**, 6302-02-9; **4**, 62415-76-3; **5**, 3311-57-7; **6**, 34552-04-0; **8**, 27610-88-4; **9**, 62415-77-4; **10**, 62415-80-9; **11**, 10330-59-3; **12**, 62415-78-5; **13**, 626-55-1; **14**, 6302-03-0; **15**, 6304-16-1; **16**, 62415-79-6; **21**, 62415-85-4; 2-chloropyridine, 109-09-1; 2-fluoropyridine, 372-48-5; 4-bromopyridine HCl, 19524-06-2; potassio-2,4-dimethyl-3-pentanone, 62415-81-0; potassiocyclohexanone, 62415-82-1; sodioacetone, 62415-83-2; lithioacetone, 62415-84-3; 2-chloroquinolone, 612-62-4; 2,6-dibromopyridine,

626-05-1; 2,6-dichloropyridine, 2402-78-0; 2,6-dihydroxy-2,6-dimethyl-4-heptanone, 3682-91-5.

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Heterodienophiles. 8.[1] Acid-Catalyzed Reactions of Benzal- and Methylenebisurethanes with α-Phellandrene. Structural and Stereochemical Studies

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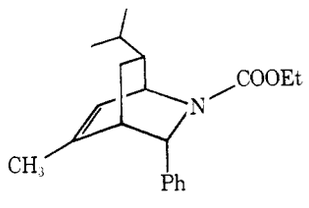
Received February 2, 1977

The boron trifluoride/copper bromide catalyzed reactions of benzal- and methylenebisurethane with α-phellandrene (**3**) have been investigated. Benzalbisurethane (**4**) affords a 37/63 mixture of 3-*endo*- and -*exo*-phenyl-5-methyl-7-isopropylisoquinuclidines (**1** and **6**), the products of regiospecific 1,4-cycloaddition of benzaliminourethane (**5**) to α-phellandrene (**3**). Methylenebisurethane **17** and α-phellandrene (**3**), however, afford *N*-carbethoxy-1-methyl-4-isopropenyl-6-azabicyclo[3.2.1]octane (**19**) and *N*-carbethoxy-3,7,7-trimethyl-9-azabicyclo-[4.3.0]non-2-ene (**20**), products derived by formal 1,3-cycloaddition of iminourethane to *p*-menthadiene isomers of α-phellandrene (**4**); thus, methylenebisurethane **17** and α-terpinene also afforded **19** and **20**. Ozonolysis of **19** completed a two-step synthesis of *N*-carbethoxy-1-methyl-6-azabicyclo[3.2.1]oct-4-one (**21**). Camphene (**29**) and **17** afforded amidoalkylation product **31**.

The Diels–Alder cycloaddition of imines with conjugated dienes offers a convenient synthetic route to diverse azacyclic and azabicyclic molecules.[1-4] Surprisingly, however, questions of regiochemistry and stereochemistry in these additions have been little explored.[3] In one study by Harter and Liisberg[3g] a regioisomeric mixture of *anti*-isopropyl, *endo*-phenylisoquinuclidines **1** and **2** of unspecified relative amounts has been



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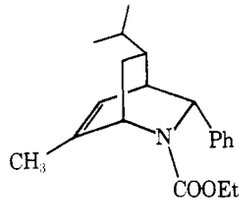

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reported from the reaction of α-phellandrene (**3**) with benzalbisurethane (**4**), a precursor of the iminourethane **5**.

We decided to continue the study of alkylidenebisurethane reactions with cyclic terpenes for several reasons. We doubted the regiochemical and stereochemical assignments given to the mixture of **1** and **2**. Cycloaddition reactions of iminourethane **5** with cyclohexa-1,3-diene do not afford 3-*endo*-phenylisoquinuclidine (**7**) only; they afford a 3-*endo*/*exo*-phenylisoquinuclidine **7**/**8** mixture with the 3-*exo*-phenyl isomer **8** predominating.[1g] Also, considerations of relative carbonium ion stabilities in a stepwise addition of an immonium ion[1b,f,g] to α-phellandrene might favor regioisomer **1** to the exclusion of **2**. Cyclic terpenes are readily available and facile synthetic access to the ring skeletons of several alkaloid[5,6] systems is available by direct cycloaddition[2i] or rearrangement[4] of initially formed adducts. We hoped to extend the scope of these syntheses.

Results and Discussion

Reactions of α-Phellandrene and Benzalbisurethane. Reaction of α-phellandrene (**3**) with benzalbisurethane (**4**) in