

Henry Feuer*, James K. Doty and Nathan Kornblum

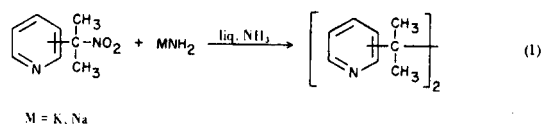
Department of Chemistry, Purdue University, West Lafayette, Indiana 49707

Received June 26, 1978

The reaction of 2-nitro-2-(4-pyridyl)propane (I) with lithium 2-propanenitronate, lithium cyclohexanenitronate, and sodium thiophenoxide affords excellent yields of the C-alkylation products 2-nitro-3-(4-pyridyl)-2,3-dimethylbutane (II), 2-(4-pyridyl)-2-(1-nitrocyclohexyl)propane (V) and 2-thiophenyl-2-(4-pyridyl)propane (VI), respectively. In contrast, the reaction of compound I with sodium azide does not afford the expected tertiary azide; but instead gives the dimer 2,3-bis(4-pyridyl)-2,3-dimethylbutane (III), in near quantitative yield. Evidence has been obtained that all of these transformations proceed *via* electron transfer pathways.

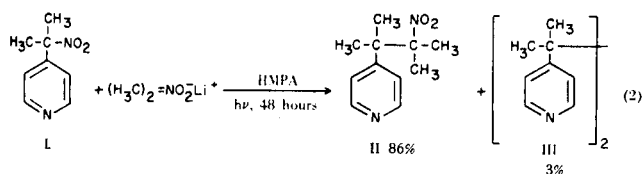
J. Heterocyclic Chem., 15, 1419 (1978)

Recently (1), we reported that the isomeric (nitroisopropyl)pyridines underwent dimerization to the corresponding 2,3-bis-(pyridyl)-2,3-dimethylbutanes when subjected to sodium amide or potassium amide in liquid ammonia (Equation 1). It was proposed that these dimerizations proceeded by electron transfer processes and



were related to the reactions reported by Kornblum and co-workers in which the tertiary nitro group of α , p -dinitrocumene was replaced by a variety of nucleophiles (2). We are now reporting on the reactions of 2-nitro-2-(4-pyridyl)propane (I) with nucleophiles.

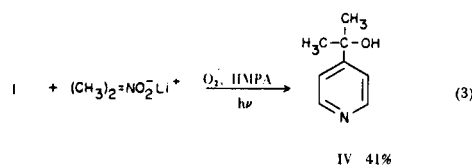
The reactions of compound I with salts of nitroalkanes showed the characteristics of a radical anion-free radical chain process. For example, treatment of I with lithium 2-propanenitronate in hexamethylphosphoric triamide (HMPA) under a "white light source" (3) for 48 hours gave an 86% yield of 2-nitro-3-(4-pyridyl)-2,3-dimethylbutane (II) and 3% of 2,3-bis-(4-pyridyl)-2,3-dimethylbutane (III) (Equation 2). When the reaction was performed under a higher energy "black light source" (4), the rate of the reaction was increased by a factor of 4 and



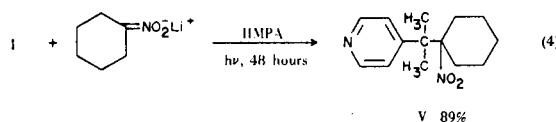
now compounds II and III were obtained in yields of 75% and 20% respectively. The rate of the reaction was found to be very solvent dependent. For instance, in the "white light source" after 72 hours the reaction was only 8% complete when dimethyl sulfoxide was the solvent. Compound I was recovered to the extent of 92%.

In the presence of catalytic amounts of radical inhibitors such as *m*-dinitrobenzene or di-*tert*-butylnitroxide,

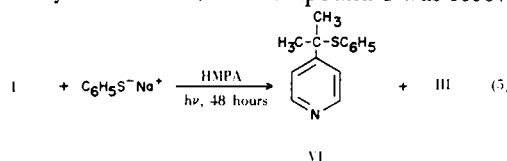
no reaction occurred at all and over 90% of I was recovered. When the reaction was carried out in an oxygen atmosphere, compound I was converted into the tertiary alcohol, 2-(4-pyridyl)-2-propanol (IV) (Equation 3). In the dark, the C-alkylate II was obtained only in 5% yield and 85% of I was recovered.



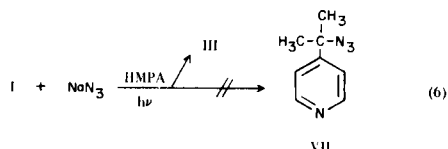
Similar results were observed when compound I was treated with lithium cyclohexanenitronate. After 48 hours under the "white light source" the reaction was complete and afforded an 89% yield of 2-(4-pyridyl)-2-(1-nitrocyclohexyl)propane (V) (Equation 4).



Compound I and sodium thiophenoxide afforded the tertiary thioether, 2-thiophenyl-2-(4-pyridyl)propane (VI), but the rate of the reaction was significantly slower than with the nitronate salts. Under the "white light source" the reaction was only 23% complete after 48 hours and afforded VI and dimer III in yields of 16% and 7%, respectively. However, the reaction rate was substantially increased when a "black light source" was employed. The reaction was now complete after 48 hours. Compounds VI and III were isolated in yields of 73% and 15%, respectively (Equation 5). The presence of small amounts of 4-isopropylpyridine and isopropenylpyridine was ascertained by nmr. When the reaction was carried out in the absence of light for 48 hours, the yield of compound VI was only 3% and 95% of compound I was recovered.



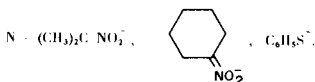
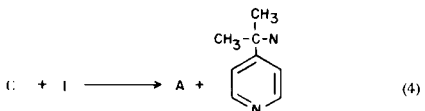
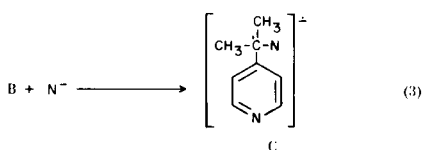
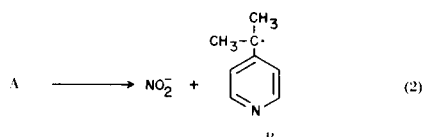
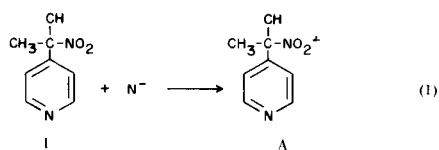
The reaction of compound I with sodium azide did not give the expected tertiary azide, 2-azido-2-(4-pyridyl)-2-propane (VII). Instead, dimer III was obtained in 93% yield (Equation 6). The radical nature of the reaction was apparent because the rate was much faster in the higher energy light source (4). Moreover, no reaction occurred at all in the absence of light.



Discussion.

The results of the investigation have shown that reactions of compound I with nitronate salts and sodium thiophenoxide occur by a radical anion-free radical chain process. This view is supported by the observations that known scavengers of free radicals such as oxygen (5) and di-*t*-butylnitroxide (6) suppress the C-alkylation process (*vide supra*). Similar effects were exhibited by *m*-dinitrobenzene and this is recognized as a diagnostic test for the intermediacy of radical anions (7). The mechanism shown

Scheme I



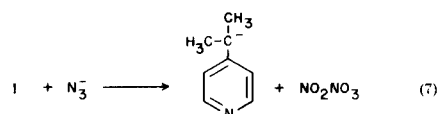
in Scheme I is consistent with the observed results and is similar to the one proposed for the dimerization of isopropylpyridines during the alkyl nitrate nitration (1).

The reaction is initiated by an electron transfer from the nucleophile to compound I to form the radical anion

A (step 1). Radical anion A then collapses into nitrite ion and radical B (step 2), which then couples with the nucleophile to generate the radical anion C of the C-alkylate (step 3). In the final step, the radical chain is propagated by transfer of an electron from radical anion C to compound I, thereby, forming the C-alkylate and regenerating radical anion A.

The reaction of I with sodium azide, which afforded only dimer III and none of the tertiary azide, does not follow the course observed when α ,*p*-dinitrocumene reacts with sodium azide; in this latter case the product is *p*-nitrocumyl azide and not a trace of the cumyl dimer is formed (7).

Regarding the formation of dimer III, from sodium azide and I, several possible pathways could be envisioned. For example, the electron transfer could be initiated by the carbanion of 4-isopropylpyridine formed by direct displacement of the nitro group by azide ion (Equation 7). A similar pathway has been proposed for the dimerization of I in the presence of amide ion in liquid ammonia (1). However, the intermediacy of this carbanion (8) was not very probable because dimer III was isolated in near quantitative yield when the reaction between I and sodium azide was conducted in methanolic HMPA. Not a trace of 4-isopropylpyridine could be detected.



The formation of dimer III could conceivably have arisen by photolytic decomposition of the tertiary azide VII. However, this possibility was ruled out because VII was recovered unchanged when treated with sodium azide under the lights (9). Furthermore, VII was recovered in 90% yield from a reaction in which compounds I, VII and sodium azide were subjected to photolysis for 18 hours under the lights (4). Dimer III was obtained in 75% yield and 18% of I was recovered. Moreover, not a trace of VII could be detected when aliquot samples were taken at various stages of the reaction of I with sodium azide and analyzed by glpc.

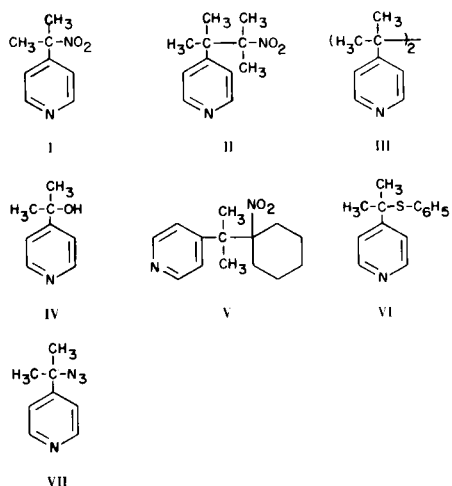
Evidence for the intermediacy of the 2-(4-pyridyl)-2-propyl radical B was provided by conducting the reaction of I with sodium azide in an oxygen atmosphere. The formation of dimer III was completely suppressed and, instead, compound I was converted into the tertiary alcohol IV (16%).

It is proposed that the formation of dimer III occurs by the coupling of radicals B as shown in Scheme II. Apparently, the dimerization of radicals B is faster than the coupling with azide ion. This tendency is reversed in the reactions of I with the nucleophiles shown in Scheme I.

Scheme II



Formula Sheet



EXPERIMENTAL

Equipment.

All infrared spectra were taken with a Perkin Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on either an Aerograph A-350B or A-700 using either 10% QF-1, SF-96, or FFAP on acid washed Chromosorb W 10 ft. columns. Solvents were evaporated on a Buchler flash evaporator. Titrations were carried out with a Beckman Zeromatic pH meter.

Materials.

HMPA (DuPont Chem. Corp.) was distilled from calcium hydride at reduced pressure (10). 2-Nitropropane (IMC Chemical Group Inc.) 99.9% was distilled prior to use. Nitrogen and argon were Airco high purity. Sodium Azide (Baker Analyzed) was used as received. *m*-Dinitrobenzene (Matheson, Coleman and Bell) was recrystallized from 95% ethanol prior to use. Di-*t*-butylnitroxide (11), lithium 2-propanenitronate (12), lithium cyclohexanenitronate (12) and 2-nitro-2-(4-pyridyl)propane (1) were prepared by methods described in the literature.

Sodium Thiophenoxide.

To 250 ml. of absolute methanol, cooled in an ice bath (0-5°), was added 7.60 g. (0.33 mole) of sodium under a nitrogen atmosphere. After all of the sodium had reacted, 39.8 g. (0.36 mole) of thiophenol was poured into the clear solution and the reaction mixture allowed to warm to room temperature. Then it was concentrated *in vacuo*, 250 ml. of benzene added and the benzene-methanol azeotrope removed *in vacuo*. This procedure was repeated three times. The resulting white powder was slurried in ether, filtered, washed with 300 ml. of ether and dried at 60° (0.5 mm) for 18 hours. Potentiometric titration of a sample dissolved in water with 0.1009N hydrochloric acid gave an equivalent weight

of 131.0, theoretical 132.0.

General Procedure for the Removal of Oxygen by the Freeze-Pump-Thaw (F.P.T.) Technique.

Into a 3-necked round-bottom flask fitted with a stopper, stopcock adapter, side arm addition tube and mechanical stirrer were placed the nucleophile and HMPA (10). In the side arm addition tube was placed 2-nitro-2-(4-pyridyl)propane (I). Then, the assembly was placed on a freeze-pump-thaw apparatus, evacuated and argon introduced. This process was repeated three times. Then the contents of the flask were frozen in a liquid nitrogen bath and the side arm addition tube was frozen in a Dry-ice acetone bath. While the system was being evacuated, the reagents were allowed to thaw by replacing the cooling baths with water baths (30°). When no more bubbles arose from the solution, argon was reintroduced into the system. The F.P.T. procedure was repeated four times, the stopcock of the adapter closed and the assembly removed from the F.P.T. apparatus.

The Reaction of 2-Nitro-2-(4-pyridyl)propane (I) with Lithium 2-Propanenitronate.

The following is representative of the general procedure employed in the reactions of compound I with nucleophiles.

A. In the White Light Source (3).

Into a 300 ml. round-bottom 3-necked flask were placed 4.75 g. (50 mmoles) of lithium 2-propanenitronate and 100 ml. of HMPA, and in the side arm addition tube was placed 1.66 g. (10 mmoles) of compound I. After the contents of the assembly were subjected to the F.P.T. procedure, the reaction was started by inverting the addition tube and by placing the flask in the light source at 30°.

After 48 hours, the reaction mixture was poured into 250 ml. of water layered with 100 ml. of ether-benzene (50:50, v:v) and the aqueous phase extracted with 4 x 100 ml. portions of the ether-benzene mixture. The combined extracts were washed with 4 x 100 ml. portions of water, dried (magnesium sulfate) and concentrated *in vacuo* to yield 1.92 g. of material. Nmr analysis indicated the presence of 2-nitro-3-(4-pyridyl)-2,3-dimethyl-butane (II) (95%) and 2,3-bis(4-pyridyl)-2,3-dimethylbutane (III) (3%). Recrystallization from hexane afforded 1.80 g. (86%) of pure II, m.p. 96-97°; ir (potassium bromide): 1603 (C=N), 1543 and 1348 cm⁻¹ (NO₂); nmr (deuteriochloroform): δ 1.50 (s, 6, CH₃), 1.55 (s, 6, CH₃), 7.20 (m, 2, pyr C₃H, C₅H) and 8.60 (m, 2, pyr C₂H, C₆H); ms (75 ev): m/e (relative intensity) 208 (19), 162 (100), 120 (100), and 106 (94).

Anal. Calcd. for C₁₁H₁₆N₂O₂: C, 63.45; H, 7.71; N, 13.45. Found: C, 63.34; H, 7.49; N, 13.21.

B. In the Black Light Source (4).

The general procedure was employed except that 4.8 g. (50 mmoles) of lithium 2-propanenitronate, 1.67 g. (10 mmoles) of compound I and 100 ml. of HMPA were used. After 12 hours at 30°, the reaction mixture was worked up to yield 2.00 g. of material. Column chromatography over neutral alumina afforded two fractions: fraction 1 (ether), 1.75 g. (75%) of II, m.p. 97° (mixture melting point determination with the sample obtained in experiment A showed no depression); Fraction 2 (acetone), 0.25 g. (25%) of dimer III, m.p. 204-205° (lit. (1) m.p. 205°) (a mixture melting point determination with an authentic sample showed no depression).

C. In the Absence of Light.

The general procedure was employed except that 4.62 g. (50 mmoles) of lithium 2-propanenitronate, 1.66 g. of compound I

and 100 ml. of HMPA were used. The flask was wrapped with three layers of aluminum foil to exclude light, and the reaction allowed to proceed at 27° for 48 hours. Nmr analysis of the crude material (1.58 g.) indicated that compound II had formed in 8% yield and that 92% of compound I had not reacted. Chromatographing over neutral alumina afforded 1.43 g. (86%) of I, n_D^{20} 1.5212 (lit. (1) n_D^{20} 1.5213) (fractions 7-10, pentane), and 0.102 g. (5%) of II, m.p. 97-98° [fractions 13-16, pentane-ether (80:20, v:v)].

Inhibition Studies. The Reaction of 2-Nitro-2-(4-pyridyl)propane (I) with Lithium 2-Propanenitronate.

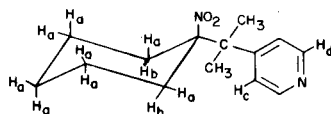
Experiment A was repeated in the presence of 0.086 g. (0.51 mmole) of *m*-dinitrobenzene. After 48 hours, the reaction mixture was poured into 150 ml. of water layered with 150 ml. of benzene. The aqueous portion was extracted with 150 ml. of benzene and 2 x 150 ml. portions of ether. The combined extracts were washed with 4 x 100 ml. portions of water and treated with 3 x 25 ml. portions of 10% hydrochloric acid. The hydrochloric acid extracts were basified with sodium hydroxide pellets, extracted with 4 x 100 ml. portions of ether, dried (magnesium sulfate) and concentrated *in vacuo* to yield 1.50 g. (91%) of recovered I. The glpc retention time was identical to that of an authentic sample of I.

Experiment A was repeated again except this time in the presence of 0.075 g. (0.51 mmole) of di-*t*-butylnitroxide. After 48 hours, the reaction mixture was worked up as in experiment A to yield 1.52 g. (92%) of unreacted I. The glpc retention time was identical to that of an authentic sample.

The Reaction of 2-Nitro-2-(4-pyridyl)propane (I) and Lithium Cyclohexanenitronate.

A. In the White Light Source (3).

The general procedure was employed except that 1.36 g. (10 mmoles) of lithium cyclohexanenitronate, 0.34 g. (2.05 mmoles) of compound I and 20 ml. of HMPA were used. The reaction was carried out at 28° for 48 hours and worked up to yield 0.495 g. of material. Sublimation of the crude material at 85° (0.05 mm) afforded 0.45 g. (89%) of pure 2-(4-pyridyl)-2-(1-nitrocyclohexyl)propane (V), m.p. 82-83°; ir (potassium bromide): 1597 (C=N), 1524 and 1335 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 0.66-1.96 (m, 8, H_a), 1.43 (s, 6, CH_3), 2.30-2.80 (m, 2, H_b), 7.15 (m, 2, H_c), and 8.50 (m, 2, H_d).



Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.78; H, 8.03; N, 11.16.

B. In the Absence of Light.

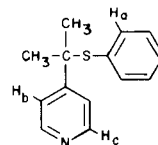
The general procedure was used except that 1.37 g. (10.1 mmoles) of lithium cyclohexanenitronate, 0.33 g. (2.00 mmoles) of compound I and 20 ml. of HMPA were used. Nmr analysis of the crude reaction mixture (0.36 g.) indicated that V formed in 7% yield and that 90% of I had not reacted.

The Reaction of 2-Nitro-2-(4-pyridyl)propane (I) with Sodium Thiophenoxide.

A. In the Black Light Source (4).

The general procedure was employed except that 7.00 g. (55 mmoles) of sodium thiophenoxide, 1.83 g. (11 mmoles) of compound I and 100 ml. of HMPA were used. The reaction was carried out at 30° for 48 hours and worked up to yield 2.13 g. of

material. Chromatographing on neutral alumina afforded 0.05 g. (4%) of a mixture consisting of 4-isopropylpyridine and 4-isopropenylpyridine (hexane) (determined by nmr) and 1.68 g. (73%) of 2-thiophenyl-2-(4-pyridyl)propane (VI) [hexane-ether (80:20; v:v)], n_D^{20} 1.6052; ir (neat): 1592 (C=N) and 750 cm^{-1} (C-S); nmr (deuteriochloroform): δ 1.65 (s, 6, CH_3), 7.20 (m, 7, H_a and H_b) and 8.50 (m, 2, H_c).



Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{NS}$: C, 73.45; H, 6.54; N, 6.11; S, 13.90. Found: C, 73.35; H, 6.52; N, 6.20; S, 13.68.

The final component (0.18 g., 15%) was identified as dimer III (acetone), m.p. 205° (lit. (1) m.p. 205°).

B. In the White Light Source (3).

The general procedure was used except that 0.685 g. (5.2 mmoles) of sodium thiophenoxide, 0.43 g. (2.53 mmoles) of compound I and 20 ml. of HMPA were used. Nmr analysis of the reaction product (0.468 g.) indicated the presence of unreacted I (76%), dimer III (7%) and thioether VI (16%).

C. In the Absence of Light.

The general procedure was employed except that 1.385 g. (10.4 mmoles) of sodium thiophenoxide, 0.337 g. (2.03 mmoles) of compound and 20 ml. of HMPA were used. Nmr analysis of the product (0.34 g.) indicated the presence of unreacted I (95%) and thioether VI (3%).

The Reaction of 2-Nitro-2-(4-pyridyl)propane (I) with Sodium Azide.

A. In the White Light Source (3).

The general procedure was employed except that 0.60 g. (9 mmoles) of sodium azide, 0.141 g. (0.85 mmole) of compound I and 25 ml. of HMPA were used. The reaction was carried out at 30° for 180 hours. Nmr analysis of the crude reaction product (0.105 g.) indicated that dimer III was formed in 82% yield and 18% of compound I had not reacted. Recrystallization of the crude product from hexane afforded 0.076 g. (74.5%) of III, m.p. 203-204°. Concentrating the hexane filtrates *in vacuo* afforded 0.022 g. of unreacted I.

B. In the Black Light Source (4).

The general procedure was employed except that 0.158 g. (0.95 mmole) of compound I, 0.65 g. (10 mmoles) of sodium azide and 25 ml. of HMPA were used. The reaction was allowed to proceed at 30° for 24 hours.

The reaction product was recrystallized from hexane to yield 0.107 g. (73%) of dimer III.

C. In the Absence of Light.

The general procedure was employed except that 0.166 g. (1 mmole) of compound I, 0.65 g. (10 mmoles) of sodium azide and 25 ml. of HMPA were used. The reaction was allowed to proceed at 25° for 24 hours. The reaction mixture was worked up to yield 0.152 g. (92%) of unreacted I.

D. In the Presence of Methanol.

The general procedure was employed except that 0.17 g. (1.03 mmoles) of compound I, 0.65 g. (10 mmoles) of sodium azide and 25 ml. of HMPA were used. After the F.P.T. procedure, 0.32 g. (10 mmoles) of methanol was added by weight difference from a

2 ml. syringe and the addition tube containing compound I was inverted. The reaction was allowed to proceed in the black light source (4) at 26° for 18 hours.

Nmr analysis indicated the presence of compounds I (28%) and of dimer III (72%).

The Reactions of 2-Nitro-2-(4-pyridyl)propane (I) with Nucleophiles in an Oxygen Atmosphere.

A. Lithium 2-Propanenitronate.

Into a 300 ml. round-bottom flask were placed 4.57 g. of lithium 2-propanenitronate and 100 ml. of HMPA. After the solution was purged with oxygen for 15 minutes, 1.66 g. (10 mmoles) of compound I was added. The reaction was carried out in the white light source (3) for a total of 96 hours, and the oxygen flow maintained for the entire time period. After 48 hours, an additional 4.5 g. of lithium 2-propanenitronate was added to the reaction mixture. Ninety-six hours after the reaction was initiated, it was worked up according to the general procedure to yield 2.56 g. of crude material. Chromatographing on neutral alumina with ether as the eluent afforded 0.818 g. (50%) of unreacted I, 0.879 g. of 2,3-dinitro-2,3-dimethylbutane, m.p. 214-215° (lit. (13) m.p. 216°); nmr (deuteriochloroform): δ 1.75 (s); and 0.548 g. (41%) of 2-(4-pyridyl)-2-propanol (IV), m.p. 130° (lit. (14) m.p. 132°). A mixture melting point determination with an authentic sample (1) showed no depression.

B. Sodium Azide.

Experiment A was repeated except that 0.65 g. (10 mmoles) of sodium azide, 0.17 g. (1.03 mmoles) of compound I and 25 ml. of HMPA were used. The reaction was allowed to proceed in the black light source (4) at 25° for 18 hours. The material was chromatographed by thin-layer chromatography using EM Silica Gel PF 254 as the support with ether as the eluent. The following fractions were obtained: Fraction 1, 0.135 g. (80%) recovery of I; Fraction 2, 0.021 g. (16%) of alcohol IV.

Acknowledgment.

We thank the IMC Chemical Group, Inc. and the National Science Foundation for their generous support.

REFERENCES AND NOTES

- (1) H. Feuer, J. Doty and J. P. Lawrence, *J. Org. Chem.*, **38**, 417 (1973).
- (2a) N. Kornblum, S. C. Carlson, J. Widmer, M. J. Fifolt, B. H. Newton and R. G. Smith, *ibid.*, **43**, 1394 (1978); (b) N. Kornblum, *Angew. Chem. Int. Ed. Engl.*, **14**, 734 (1975).
- (3) The "white light source" consisted of two 20-watt General Electric F20T12 daylight fluorescent lights.
- (4) The "black light source" consisted of two 20-watt General Electric F20T12 black light fluorescent lights.
- (5a) N. Kornblum, G. W. Earl, N. L. Holy, J. W. Manthey, M. T. Musser, D. H. Snow and R. T. Swiger, *J. Am. Chem. Soc.*, **90**, 6221 (1968); (b) G. A. Russell and W. C. Danen, *ibid.*, **90**, 347 (1968); (c) G. A. Russell and A. G. Bemis, *ibid.*, **88**, 5491 (1966).
- (6a) N. Kornblum and S. D. Boyd, *ibid.*, **92**, 5784 (1970); (b) A. K. Hoffman, A. M. Feldman, E. Gelblum and W. G. Hodgson, *ibid.*, **86**, 642 (1964); (c) E. G. Rozantsev and V. D. Sholle, *Synthesis*, 406 (1971).
- (7) N. Kornblum, *Proc. Int. Cong. Pure Appl. Chem.*, **23rd**, **4**, 81 (1971).
- (8) I. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85**, 2183 (1963).
- (9) The preparation of VII from 2-chloro-2-(4-pyridyl)propane will be discussed in a forthcoming paper.
- (10) **CAUTION!** HMPA should be handled with care since it has been reported to cause nasal tumors in rats; *Chem. Eng. News*, **54** (5), 3 (1976).
- (11) A. K. Hoffman, A. M. Feldman, E. Gelblum and A. Henderson, *Org. Synth.*, **48**, 62 (1968).
- (12) N. Kornblum, S. D. Boyd and N. Ono, *J. Am. Chem. Soc.*, **96**, 2580 (1974).
- (13) G. A. Russell, R. K. Norris and E. J. Panek, *ibid.*, **93**, 5838 (1971).
- (14) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 41 (1941).