Deoxygenation of Pyridine N-Oxide[1]

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The deoxygenation of pyridine, 2-picoline, and 2,6-lutidine N-oxides employing 9-diazofluorene (I) is described. The mechanisms of the reaction and the formation of fluorenone ketazine (VI) are discussed.

Numerous methods have been found for deoxygenating pyridine N-oxides.[2,3] In a previous paper[3] we have shown that dichlorocarbene deoxygenates pyridine N-oxide. However, relatively high conversions of pyridine N-oxide to pyridine were difficult to achieve unless high pyridine N-oxide to halocarbene precursor ratios were maintained. In an effort to achieve a deoxygenation procedure with greater synthetic utility our attention was turned to nonhalocarbene precursors. Fluorene carbene (II) has been postulated to exist in the photochemical[4] and thermal[5] decomposition of 9-diazofluorene (9-DAF, I). The 9-DAF (I) may be prepared in high yield[6] from readily available starting materials and stored under ordinary conditions for extended periods of time.

Table I gives the yields of pyridines obtained when the corresponding pyridine N-oxides were allowed to react with I in benzene or dimethyldiethylene glycol (diglyme) solvent. Yields of the pyridines ranged from 45 to 66% when the I to N-oxide ratio was 4 to 1. These results were obtained by allowing the pyridines formed to distil as I was added; this technique was necessary in order to suppress the side reaction which gave fluorenone ketazine (VI).

TABLE I

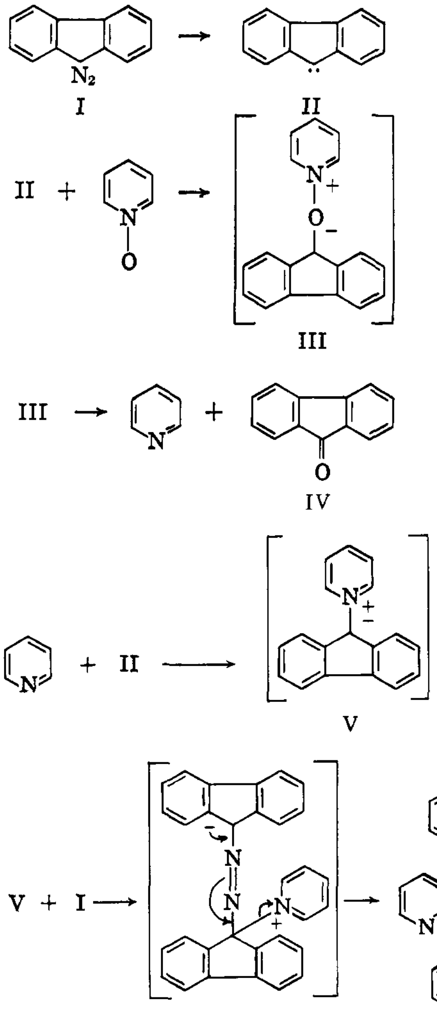
N-oxides	Mole ratio of 9-DAF–N-oxide	Solvent	Time, hr.	% yield of pyridines
Pyridine	1	Benzene	72	16[a]
Pyridine	1.5	Benzene	65	28[a]
Pyridine	2.0	Diglyme	2	39[b]
Pyridine	4.0	Diglyme	2	66[b]
2-Picoline	4.0	Diglyme	2	45[b]
2,6-Lutidine	4.0	Diglyme	2	62[b]

[a] Isolated. [b] Determined as picrate.

TABLE II

Benzene, ml.	Base	9-DAF (I), mole	Bifluorene, %	Fluorenone ketazine (VI), %
15		0.0078	91	4
	Pyridine (20 ml.)	0.0107	5	92
4	Pyridine (0.0021 mole)	0.0021	28	68
4	2,6-Lutidine (0.0021 mole)	0.0021	54	42

Staudinger and Kupfer[7] had previously shown that on decomposing I in refluxing benzene, bifluorene was the only product obtained. On repeating this reaction we obtained 91% bifluorene and 4% of the previously unreported ketazine (VI). A similar reaction using pyridine as the solvent gave 5% of bifluorene and 92% of VI (Table II). When equimolar quantities of I and 2,6-lutidine were allowed to react in benzene, the bifluorene to ketazine VI ratio was 54 to 42%, whereas, in an identical experiment, substituting pyridine for the 2,6-lutidine, the ratio of bifluorene to VI was 28 to 68%. The following mechanism is postulated for the deoxygenation of pyridine N-oxide and for the formation of VI.



A decreased yield of the ketazine (VI) and an increased yield of bifluorene on using 2,6-lutidine instead of pyridine as the precursor for the ylid of type V (Table

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[1] Acknowledgment is made of support from the University of Delaware Research Foundation.

[2] (a) T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1917 (1962); (b) D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962), and references cited therein.

[3] E. E. Schweizer and G. J. O'Neill, *ibid.*, **28**, 2460 (1963).

[4] W. von E. Doering and M. Jones, Jr., *Tetrahedron Letters*, **No. 12**, 791 (1963).

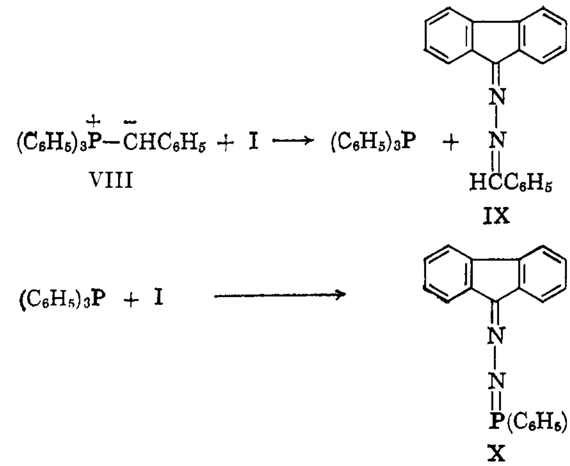
[5] (a) W. E. Parham, H. G. Braxton, Jr., and D. R. Theissen, *J. Org. Chem.*, **27**, 2632 (1962); (b) A. Schonberg, A. Mustafa, and M. Latif, *J. Am. Chem. Soc.*, **75**, 2267 (1953); (c) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4675 (1952).

[6] C. D. Nenitzescu and E. Solomonica, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 496.

[7] H. Staudinger and O. Kupfer, *Ber.*, **44**, 2197 (1911).

II) supports the postulation of the 1-(9-fluorenyl)-pyridinium ylid (V) as an intermediate, because one would expect that steric hindrance in the lutidine reaction would enhance the formation of bifluorene owing to the slowing down of the ylid V formation.[8] The postulation of V as an intermediate is further supported by the following facts: Pinck and Hilbert[9] suggested the formation of V as an intermediate when 1-(9-fluorenyl)pyridinium bromide (VII) is treated with 10% aqueous sodium hydroxide in ethanol. On treating essentially equimolar portions of VII and 9-DAF (I) with base, in the manner described by Pinck and Hilbert, at room temperature, an 87% yield of VI was obtained.

Benzylidenetriphenylphosphorane[10] (VIII) was allowed to react with I in an attempt to show similarities between this reaction and that described by Markl,[11] who demonstrated that aliphatic diazo ketones will form ketazines on reaction with phosphine methylenes. On allowing VIII to react with I, a 22% yield of the expected[11] fluorenonebenzal hydrazone (IX) was obtained. A 26% yield of the expected[11] triphenylphosphine fluorenone azine (X) from the reaction of triphenylphosphorus and I was also found. Thus I in the presence of pyridine bases undergoes reactions which are characteristic for I and phosphorus ylids.



As shown by our suggested mechanistic scheme (1–5) fluorenone (IV) must be a major by-product of the deoxygenation of pyridine N-oxides by this procedure. Under suitable reaction conditions pyridine N-oxide can serve as a useful species for donating oxygen to a carbene[3]; a maximum yield of 69% of IV was isolated (see Table III).

TABLE III

9-DAF (I), mole	Pyridine N-oxide, mole	Benzene, ml.	Fluorenone (IV), %	Ketazine (VI), %
0.0156	0.250	0	33	57
0.0156	0.250	30	55	41
0.0156	0.250	60	69	23

Experimental[12]

Materials.—9-Diazofluorene (I) was prepared according to the method described by Nenitzescu and Solomonica.[6] The N-oxides[13] were distilled *in vacuo* under a nitrogen atmosphere prior to use. Fluorenone ketazine (VI) was prepared according to Arcus and Barrett.[14] The benzene used was anhydrous and thiophene free. The alumina used for chromatography was powdered, catalyst grade AL-0102-P, obtained from the Harshaw Chemical Co., Cleveland, Ohio.

Deoxygenation of Pyridine N-Oxides (Table I). A. In Benzene.—A mixture of 14.3 g. (0.074 mole) of 9-diazofluorene (I), 4.7 g. (0.050 mole) of pyridine N-oxide, and 95 ml. of benzene was refluxed for 65 hr. The mixture was chilled with an ice-water bath and 7.0 g. of fluorenone ketazine (VI), m.p. 273–274°, lit.[14] m.p. 273–274°, was filtered off.

The filtrate was extracted with three 20-ml. portions of 10% hydrochloric acid and the combined aqueous layers were saturated with potassium hydroxide pellets. This strongly basic solution was extracted with three 20-ml. portions of ether which were fractionally distilled to give 1.10 g. (28%) of pyridine, b.p. 114–116°, $n^{25}D$ 1.5076. Infrared spectrum, melting point, and mixture melting point of the picrate were identical with those of an authentic sample.

B. In Diglyme.—The following method is the general deoxygenation method using 4:1 molar ratio of 9-diazofluorene (I) to the N-oxide.

Into a 100-ml., three-necked flask equipped with a thermometer and a Vigreux column (77 × 12 mm.) with distilling head and condenser were placed 0.0204–0.0210 mole of the N-oxide and 25 ml. of anhydrous diglyme. The mixture was heated until distillation of diglyme (162–163°) occurred. After approximately 5 ml. of diglyme had been distilled, a solution of 16 g. (0.0834 mole) of 9-diazofluorene (I) in 120 ml. of diglyme was added dropwise concurrent with distillation. When a few drops of the distillate no longer gave a precipitate when treated with a saturated solution of picric acid in ether, the reaction was considered to be complete.

The calculation of the yield and the analysis of 2,6-lutidine picrate from 0.0204 mole of lutidine N-oxide are the same for all the N-oxides. An aliquot (7.01 g.) of the diglyme distillate (88.25 g.) was treated with a saturated solution of picric acid in ether. The resulting dry picrate (melting point and mixture melting point identical with an authentic sample and the infrared spectrum was superimposable on the spectrum of an authentic sample) weighed 0.341 g. The total yield of 2,6-lutidine picrate, 4.28 g. (62.3%), was calculated accordingly and is listed in Table I (see p. 1744): (wt. of picrate)/(wt. of aliquot) × (total wt. of distillate) = (total wt. of picrate).

9-Diazofluorene (I) in Refluxing Benzene[7] (Table II).—A solution of 1.5 g. (0.0078 mole) of 9-diazofluorene (I) and 15 ml. of benzene was refluxed for 48 hr. with stirring. The solution was taken to dryness on a steam bath and petroleum ether (b.p. 30–60°) was added to the residue. Column chromatography of the petroleum ether solution on 200 g. of alumina gave 1.18 g. (91%) bifluorene, m.p. 190–192° (lit.[6] m.p. 187–188°), with petroleum ether eluent, and 0.055 g. (4%) of fluorenone ketazine (I), m.p. 276–277° (lit.[14] m.p. 273–274°), with benzene as an eluent.

9-Diazofluorene (I) and Pyridine in Benzene (Table II).—A solution of 0.41 g. (0.0021 mole) of 9-diazofluorene (I), 0.168 g. (0.0021 mole) of pyridine, and 4 ml. of benzene was refluxed for 72 hr., cooled, and diluted with petroleum ether. A residue of 0.225 g. of fluorenone ketazine (VI) was recovered by filtration and the petroleum ether–benzene filtrate was chromatographed on 70 g. of alumina to give 0.10 g. (28%) of bifluorene (melting point and mixture melting point identical with authentic sample) with petroleum ether eluent. An additional 0.035 g. of fluorenone ketazine (VI) was also obtained. Total yield of azine is 0.26 g. (68%), melting point and mixture melting point identical with that of an authentic sample.

9-Diazofluorene (I) and 1-(9-Fluorenyl)pyridinium Bromide.—To a solution of 0.81 g. (0.0025 mole) of 1-(9-fluorenyl)pyridin-

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[8] The authors recognize the possibility of forming intermediates III and V by direct displacement of the nitrogen from 9-DAF (I) by the oxygen of pyridine N-oxide or the nitrogen of pyridine, respectively; however, they favor initial carbene formation.[4,5]

[9] L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 2011 (1946).

[10] G. Markl, *Tetrahedron Letters*, **No. 22**, 1027 (1692).

[11] G. Markl, *ibid.*, **No. 22**, 811 (1961).

[12] All melting points and boiling points are uncorrected. The infrared spectra were obtained with a Perkin-Elmer spectrophotometer, Model 137.

[13] Reilly Tar and Chemical Corporation, Indianapolis 4, Ind.

[14] C. L. Arcus and G. C. Barrett, *J. Chem. Soc.*, 2098 (1960).

ium bromide (VII) prepared according to Pinck and Hilbert[9] and 0.50 g. (0.0026 mole) of 9-diazofluorene (I) dissolved in 30 ml. of ethanol was added dropwise with swirling approximately 2 ml. of aqueous 10% sodium hydroxide. A dark blue color characteristic of 1-(9-fluorenyl)pyridinium ylid (V)[9] appeared with the addition of each drop of base, and gradually changed to colorless upon swirling. Addition of the base required approximately 0.5 hr. and the mixture was allowed to stand for 15 min. before 0.81 g. (0.0023 mole, 87.4% yield) of fluorenone ketazine (VI, melting point and mixture melting point checked with an authentic sample) was recovered by filtration.

9-Diazofluorene (I) and Benzylidine Triphenylphosphorane (VIII).—To a stirred mixture of benzyltriphenylphosphonium bromide (10.8 g.) and 125 ml. of anhydrous benzene was added 10.6 g. of 14.98% by weight of butyllithium in hexane. A deep red color, characteristic of triphenylphosphorus ylids, developed immediately. This mixture was stirred for 15 min. and then 9-diazofluorene (I, 3.68 g.) was added. Stirring was continued overnight during which time the color changed from deep red to golden yellow. The reaction mixture was heated until it boiled and filtered hot, and 200 ml. of petroleum ether was added to the cooled benzene filtrate. A golden yellow precipitate of triphenylphosphine fluorenone azine (X) was filtered off, 2.3 g. (26.5%), m.p. 210–215°, lit.[15] m.p. 209–210°. Recrystallization from benzene gave an analytically pure sample which had m.p. 210–215°.

Anal. Calcd. for $C_{31}H_{23}N_2P$: C, 81.77; H, 5.06; N, 6.16; P, 6.88. Found: C, 81.68; H, 5.09; N, 6.26; P, 6.48.

The infrared spectrum was identical with that of an authentic sample.

The benzene–petroleum ether filtrate was reduced on a steam bath to a red oil which gave an orange-yellow solid upon being chilled in an ice–water bath. Recrystallization once from ethanol gave 1.2 g. (22.2%) of fluorenone benzalhydrazone (IX), m.p. 91–94°, lit.[16] m.p. 91–94°, mixture melting point with that of an authentic sample prepared according to Curtius and Kof[16] was undepressed.

9-Diazofluorene (I) and Pyridine N-Oxide (Table III).—A mixture of 3.00 g. (0.0156 mole) of 9-diazofluorene (I), 24 g. (0.25 mole) of pyridine N-oxide, and 30 ml. (or 60 ml.) of benzene was refluxed for 5 days. The reaction mixture was extracted with two 100-ml. portions of distilled water and two 15-ml. portions of 10% hydrochloric acid. The benzene layer (when applicable) was added to a suitable volumetric flask and diluted to the mark. An aliquot was then taken and evaporated to dryness on a steam bath under a stream of air. The ether-insoluble residue, fluorenone ketazine (VI, melting point and mixture melting point checked with an authentic sample), was recovered and the filtrate was evaporated to dryness in a sublimation apparatus. The residue was sublimed at a bath temperature of 85° (2–3 mm.) overnight to give fluorenone (IV, melting point and mixture melting point checked with an authentic sample). The total yield of fluorenone (IV) was calculated according to the following equation and is given in Table III: total volume of benzene solution in volumetric flask/ml. of aliquot × wt. of fluorenone sublimed = total wt. of fluorenone.

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[15] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 627 (1919).

[16] T. Curtius and K. Kof, *J. prakt. Chem.*, **86**, 113 (1912).

Phosphonium Salts. II. 2-Bromophenetole and Triphenylphosphorus as Novel Phosphonioethylation Precursors

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Triphenylphosphorus (I) and β-bromophenetole (II) in alcohol solvents gave high yields (45–88%) of the alkoxyethyltriphenylphosphonium bromides (IV). In nonhydroxylic solvents (and *t*-butyl alcohol) 1,2-ethylenebis(triphenylphosphonium bromide) (III) was obtained. Vinyltriphenylphosphonium bromide (V) was isolated (92%) and allowed to react with ROH, -SH, and -NH substrates.

Anionic, or Michael-type additions, have been observed with vinylsulfonium salts[1] and vinyldiphenylphosphine oxide.[2] Grayson and Keough[3] have recently shown that base-catalyzed reactions of vinyltributylphosphonium salts with compounds containing active hydrogens also undergo Michael-type additions (phosphonioethylations[3]) to give 2-substituted ethyl phosphonium salts. Wittig and Duffner[4] proposed vinyltriphenylphosphonium bromide (V) as an intermediate in the reaction of 1,2-ethylenebis(triphenylphosphonium bromide) (III) with lithium piperidide to give triphenyl(β-N-piperidinoethyl)phosphonium bromide, although the vinyl salt V was not isolated.

Pursuing our interest in the Wittig reaction,[5] we were led to undertake a study of the preparation of phosphorus salts of 2-substituted 1-bromoalkanes. The results of our studies of the reaction of triphenylphosphorus (I) with β-bromophenetole (II) in a variety of solvents showed this system to be a unique phosphonioethylation[3] precursor.

The preparation of 2-phenoxyethyltriphenylphosphonium bromide (IVf) was attempted by allowing triphenylphosphorus (I) and 2-bromophenetole (II) to react in a variety of nonprotonic solvents (Table I). The only products that were identifiable in these (and simple fusion) reactions were the unexpected 1,2-ethylenebis(triphenylphosphonium bromide) (III) and phenol.

$$\underset{\text{I}}{(C_6H_5)P} + \underset{\text{II}}{C_6H_5OCH_2CH_2Br} \xrightarrow[\text{and fusion}]{\substack{\text{nonprotonic}\\ \text{solvents}}} \underset{\text{III}}{\overset{-}{\text{Br}}(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3\overset{-}{\text{Br}}} + C_6H_5OH \quad (1)$$

On employing methanol, ethanol, 1-butanol, benzyl alcohol, 2-propanol, or phenol as the solvent in the reaction of triphenylphosphorus (I) with 2-bromophenetole (II), the corresponding 2-alkoxy- or 2-phenoxyethyltriphenylphosphonium bromide (IV) was obtained in high yield (Table II).

The 2-phenoxyethylphosphonium bromide (IVf) decomposed readily, on heating in ethyl acetate (or ben-

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[1] W. von E. Doering and K. C. Schreiber, *J. Am. Chem. Soc.*, **77**, 514 (1955).

[2] M. I. Kabachnik, T. Y. Medved, Y. M. Polikarpov, and K. S. Yudena, *Izv. Akad. Nauk, SSSR Otd. Khim. Nauk*, **9**, 1584 (1962).

[3] M. Grayson and P. T. Keough, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 640.

[4] G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958).

[5] Paper I: E. E. Schweizer and R. Schepers, *Tetrahedron Letters*, **15**, 979 (1963).