Reactions of the Nitrosonium Ion. VII. Syntheses of Dihydroisoquinolines and Oxazoles from Azides in Nitrile Solvents

Michael P. Doyle (1a), C. David Spoelhof (1b), and Mary A. Zaleta (1c)

Department of Chemistry, Hope College, Holland, Michigan 49423

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N-Alkylnitrilium salts are cleanly produced from alkyl azides by reaction with nitrosonium salts in nitrile solvents. Syntheses of 3,4-dihydroisoquinolines from nitrilium ions formed in this method from 2-phenylethyl azide are described. Oxazoles are readily formed from phenacyl azides by this general method; the advantages of oxazole syntheses through azide nitrosation are discussed.

Nitrilium ions have been widely used in the syntheses of heterocyclic compounds (2). The methods most commonly employed to generate nitrilium ions have been the reactions of alcohols or olefins and mineral acids in nitrile solvents, *N*-alkylation of nitriles by oxonium salts such as triethyloxonium tetrafluoroborate, and Lewis acid-catalyzed reactions between alkyl halides and nitriles (2a,3). When the nitrilium ion possesses an internal nucleophilic site, intramolecular attack at the electrophilic nitrile carbon results in ring-closure. Five- and six-membered nitrogen heterocycles are commonly prepared by this method (2).

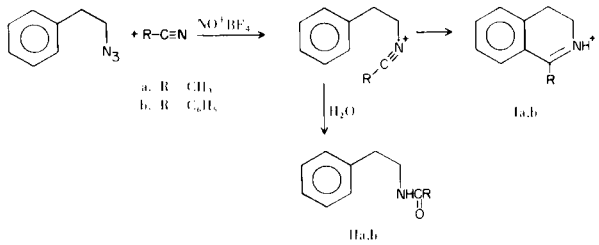
We have previously reported an alternate procedure for nitrilium ion formation by the reaction of alkyl azides with stable nitrosonium salts in nitrile solvents (4). Nitrosation is nearly instantaneous at room temperature and proceeds at acceptable rates even at -30°. The specific advantage of this method is that nitrilium ions are cleanly produced;

$$R\text{-}N_3 + NO^+X^- + R'\text{-}C{\equiv}N: \rightarrow [R\text{-}N{\equiv}C\text{-}R']X^- + N_2 + N_2O$$

$$X^- = BF_4^-, PF_6^-, SbF_6^-$$

the nitrosonium ion reacts at the azido functionality to produce stable gaseous products, nitrogen and nitrous oxide. The nitrosation reaction is general for the formation of *N*-alkylnitrilium salts and does not require either an acid catalyst or a strongly acidic medium. We wish to describe applications of this nitrosation reaction to the syntheses of isoquinolines and oxazoles.

2-Phenylethyl azide was treated with nitrosonium tetrafluoroborate at -15° in acetonitrile; the low temperature was used to minimize side reactions such as hydride abstraction by the nitrosonium ion and hydride migration from the 1-position. After refluxing 1-methyl-3,4-dihydroisoquinoline (Ia, 71%) and *N*-(2-phenylethyl)acetamide (IIa, 29%) were the only detectable reaction products. A similar



proceudre using benzonitrile yielded 1-phenyl-3,4-dihydroisoquinoline (Ib, 54%) and *N*-(2-phenylethyl)benzamide (IIb, 46%). Product yields were reproduceable (± 3%) and comparable to those obtained by alternate procedures (5).

Conversion of the nitrilium ion to I was slow at or below room temperature; ring closure required more vigorous conditions than nitrosation. The production of II was the only important competing reaction. Although care was taken to exclude water and the solvent was rigorously dried, reaction of the nitrilium ion with water did occur (6). However, II could be easily separated from I. *N*-(1-Phenylethyl)acetamide was not detected except from reactions run in chloroform using 5 equivalents of acetonitrile (2-3% yield).

Attempts to form the analogous five- and seven-membered nitrogen heterocycles by nitrosation in acetonitrile of benzyl azide and 3-phenylpropyl azide, respectively, were not successful. After refluxing the acetonitrile solution containing *N*-benzylacetonitrilium tetrafluoroborate (2b) only *N*-benzylacetamide and Friedel-Crafts alkylation products were observed. 3-Phenylpropyl azide gave a mixture of isomeric amide products.

Phenacyl azides are readily converted to oxazoles (III) by treatment with nitrosonium tetrafluoroborate in nitrile solvents. Product yields are given in Table I. As expected

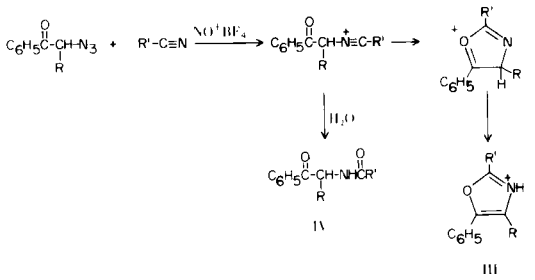


TABLE I

Product Yields from Nitrosation of Phenacyl Azides in Nitrile Solvents.

$C_6H_5COCHRN_3$ R =	R'CN R =	Yield, % III (Isolated yield) (a)	IV
a. H	CH_3	70 (59)	30
b. H	C_6H_5	75	25
c. CH_3	CH_3	>95 (49)	>5
d. C_6H_5	CH_3	80 (65)	20

(a) Isolated yield of purified oxazole after recrystallization.

from the relative nucleophilicities of phenyl compared to the carbonyl group, oxazoles are formed at a faster rate than are dihydrosioquinolines from the appropriate nitrilium ions. Oxazole formation is rapid at room temperature. Again, the only observed competing reaction is amide formation (IV).

4,5-Diphenyloxazoles have been prepared in good yields from desyl chloride and nitriles in reactions catalyzed by stannic chloride (7). This procedure, however, is not general and points to the advantages of using the reaction between azides and nitrosonium salts to generate nitrilium ions. When either anhydrous aluminum chloride or stannic chloride was used with phenacyl bromide in acetonitrile in attempts to form IIIa, no oxazole product was observed even after refluxing for 3-6 hours; IVa was, however, produced in the aluminum chloride catalyzed reaction. Two factors may be advanced to explain the reluctance of the Lewis acid-phenacyl bromide system to form IIIa; destabilization of the incipient carbenium ion by the adjacent carbonyl group preventing formation of the nitrilium ion, and complexation of the carbonyl group of the reactant with the Lewis acid, preventing nucleophilic assistance to ionization of the phenacyl halide and decreasing the reactivity of the internal nucleophilic site towards intramolecular attack at the electrophilic nitrile carbon. Neither of these are problems in heterocyclic syntheses from azides utilizing nitrosonium salts, and oxazole syntheses from nitrilium salts need no longer be limited to 4,5-diphenyloxazoles (2).

EXPERIMENTAL

General.

Instrumentation has been described (4b). Nitrosonium salts were obtained from Ozark Mahoning Co. and were dried over phosphorus pentoxide prior to use. Analytical grade acetonitrile and benzonitrile were distilled from calcium hydride and stored over molecular sieves. The water content of the acetonitrile was determined as previously described (6). Azides were synthesized from the corresponding alkyl halides in good yields by standard procedures using sodium azide in aqueous ethanol (8).

3,4-Dihydroisoquinolines from 2-Phenylethyl Azide. General Procedure.

In a representative procedure 2-phenylethyl azide (0.487 g., 3.31 mmoles) in 3.5 ml. of acetonitrile was added dropwise over a 10-minute period to the nitrosonium tetrafluoroborate (0.392 g., 3.36 mmoles) in 1.5 ml. of anhydrous acetonitrile. The reaction mixture was continually stirred and was cooled at -15° by the use of an ice-acetone bath. After gas evolution was complete (1 hour) the mixture was heated at reflux for 2.5 hours. After cooling to room temperature 10 ml. of ether and 10 ml. of 20% aqueous hydrochloric acid was added, and the aqueous layer was separated after thorough mixing and washed with an additional 10 ml. of ether. Aqueous sodium hydroxide (20%) was then added to the acidic solution until this solution was basic (pH 10). Ether (25 ml.) was added to the basic solution, and the aqueous layer was separated and washed with two 25 ml.-portions of ether. The combined ether solution was passed through anhydrous magnesium sulfate, and the ether was removed under reduced pressure.

Product analyses were performed both prior to the addition of aqueous hydrochloric acid to determine the yields of dihydroisoquinoline and amide products and after workup. Amide products were identified from their pmr spectrum through comparison with an authentic sample. The dihydroisoquinolines were identified from their characteristic ir and/or pmr spectrum; their physical properties corresponded with those reported (9).

1-Methyl-3,4-dihydroisoquinoline.

Pmr (carbon tetrachloride): δ 7.6-6.8 (m, 4H), 3.65 (triplet of quartets, 2H, J = 7 Hz (triplet), J = 1.2 Hz), 2.65 (t, 2H, J = 7 Hz) and 2.37 (t, 3H, J = 1.2 Hz). Ir (carbon tetrachloride): 3060, 3020, 2950, 2900, 2843, 1627, 1600, 1450, 1247, 860, and 695 cm^{-1}.

1-Phenyl-3,4-dihydroisoquinoline.

Pmr (carbon tetrachloride): 7.9-7.0 δ (m, 9H), 3.85 (t, 2H), and 2.75 (t, 2H).

When the nitrosation reaction was run in chloroform using 5 equivalents of acetonitrile (based on azide) gas evolution was slow even at room temperature, and amide products predominated (65% of total).

Oxazoles from Penacyl Azides. General Procedure.

In a representative procedure α-azidoacetophenone (1.29 g., 8.03 mmoles) was added dropwise over a 20-minute period to the nitrosonium tetrafluoroborate (1.23 g., 10.5 mmoles) in 5 ml. of anhydrous acetonitrile, continually stirred at room temperature. Gas evolution was immediate and continuous throughout the period of addition of azide. After gas evolution was complete 50 ml. of a saturated solution of sodium bicarbonate and 30 ml. of methylene chloride were added. After thorough shaking the aqueous layer was separated and washed twice with 20 ml.-portions of methylene

chloride. The combined methylene chloride solution was washed four times with 20-ml. portions of 15% hydrochloric acid to remove the oxazole. The combined acidic solution was made basic (*p*H 10) with the addition of 50% sodium hydroxide solution and then washed three times with 50-ml.portions of methylene chloride. The combined methylene chloride solution containing the oxazole product was passed through anhydrous magnesium sulfate, and the solvent was removed under reduced pressure.

Product analyses were performed both prior to the addition of aqueous bicarbonate to determine the yields of oxazole and amide products and after workup. Amide products were identified from their pmr and ir spectra. Oxazoles were identified from their characteristic pmr and ir spectra and by comparison of their physical properties with those of known samples.

2-Methyl-5-phenyloxazole.

Pmr (deuteriochloroform): δ 7.9-7.3 (m, 5H), 7.25 (s, 1H) and 2.53 (s, 3H); ir (potassium bromide): 3130, 3060, 2940, 1660, 1580, 1560, 1485, 1450, 1210, 1055, 750, and 680 cm^{-1}; m.p. 52.5-53.0° (lit. (10) m.p., 55-57°).

2,4-Dimethyl-5-phenyloxazole.

Pmr (deuteriochloroform): δ 7.8-7.3 (m, 5H), 2.50 (s, 3H), and 2.42 (s, 3H); ir (potassium bromide): 3060, 2930, 2860, 1640, 1580, 1570, 1490, 1440, 1280, 1230, 1060, 750, and 680 cm^{-1}; m.p. 41.5-43.0° (lit. (11) m.p., 45-46°).

2,5-Diphenyloxazole.

Pmr (deuteriochloroform): δ 8.4-8.1 (m, 2H), 7.9-7.3 (m, 9H).

2-Methyl-4,5-Diphenyloxazole.

Pmr (carbon tetrachloride): δ 7.9-7.2 (m, 10H), and 2.44 (s, 3H); ir (film): 3060, 2935, 2860, 1610, 1590, 1485, 1440, 1270, 1120, 1055, 760, and 690 cm^{-1}; m.p. 22-24° (lit. (12) m.p. 28°).

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