The Reaction of Nitrosobenzene with Phenylhydrazones. A New Synthesis of Nitrones

D. W. Berry, R. W. Bryant, J. K. Smith, and R. G. Landolt[1]

Department of Chemistry, Muskingum College,
New Concord, Ohio 43762

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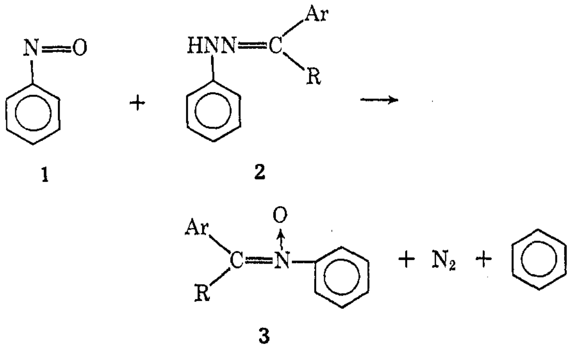
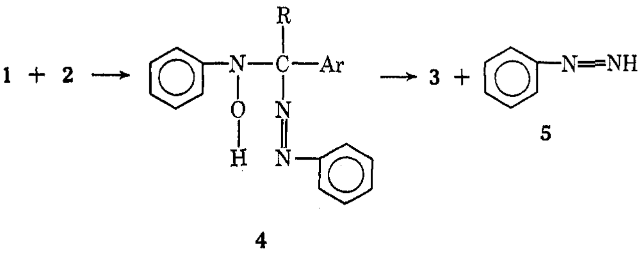
Syntheses of nitrones utilizing nitroso compounds as reagents with a variety of substrates have been developed.[2,3] These procedures are somewhat limited by availability of reagents or severity of required reaction conditions. The reaction of nitrosobenzene (**1**) with a readily available substrate series, the phenylhydrazones of aromatic aldehydes (**2**, R = H) and ketones (**2**, R = Ar), takes place under mild conditions to give good yields of the corresponding nitrones (**3**). By-products are benzene and nitrogen.



Reaction was found to occur at ambient temperatures, either neat or in a variety of solvents. Most reactions were run in a nitrogen atmosphere owing to the known propensity of phenylhydrazones to react with oxygen.[4] A pronounced increase in nitrone production was noted when the nitrosobenzene–phenylhydrazone ratio was increased (Table I, expt A, B, C and D; compare also L and M). Nitrogen was trapped and identified from reactions run in air, and the yield of nitrone was increased. (Compare expt A and E.) In diethyl ether, the yield of benzene approximated that of nitrone (expt F).

A probable reaction sequence is illustrated in Scheme I. Intermediate **4** is analogous with compounds isolated from the reaction of phenylhydrazones with alkoxycarbonylazo derivatives.[5] Phenyldiazene (**5**) is a short-lived species known to decompose to benzene and nitrogen.[6] It also reacts with oxygen and benzoquinone. Formation and subsequent interaction of phenyldiazene with nitrosobenzene may account for the excess of the latter required to achieve high yields of nitrones. Phenyldiazene may react also with phenylhydrazones, but the recovery of the latter in good yields from a number of reactions reduces the probability that this is a major factor in determining product yields. Azoxybenzene, presumably formed by interaction of **1** with N-phenylhydroxylamine (a possible product of the reaction of nitrosobenzene and phenyldiazene), was isolated in expt D. In an air atmosphere, oxygen would intercept phenyldiazene, accounting for increased yield of nitrone in expt E.

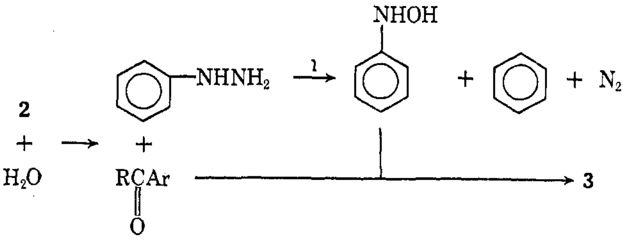
Scheme I



A reaction incorporating benzoquinone as a potential phenyldiazene trap failed to yield useful data, perhaps owing to interaction of the quinone with starting materials.[7]

An alternate pathway that could lead to products of the reaction of phenylhydrazones with nitrosobenzene involves hydrolysis of the former to phenylhydrazine and the parent aldehyde or ketone (Scheme II). Reaction of nitrosobenzene with phenylhydrazine yields benzene, nitrogen, and probably N-phenylhydroxylamine,[8] which is known to react with aldehydes and ketones to give nitrones.

Scheme II



Control experiments G and H were run to investigate the possible role of water as a reactant. The results indicate that, if anything, the yield of nitrone was enhanced by arid conditions and that hydrolysis of the phenylhydrazone was unimportant. As a check to see if nitrone production *via* N-phenylhydroxylamine was taking place, the reaction of phenylhydrazine with nitrosobenzene in the presence of benzaldehyde was run under conditions similar to those in expt A. α-Phenyl-N-phenyl nitrone was isolated, but in inferior yield compared with the yields of the reactions of Table I (29%), and the phenylhydrazone of benzaldehyde was isolated in 48% yield. The nitrone in this case probably resulted from interaction of nitrosobenzene with phenylhydrazone formed *in situ*.

Experiments I, J, K, and M illustrate that the reaction of nitrosobenzene with phenylhydrazones has potential as a synthetic procedure.

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[1] Author to whom inquiries should be sent.

[2] Reviews of nitrone chemistry: J. Hamer and A. Malcaluso, *Chem. Rev.*, **64**, 473 (1964); G. R. Delpierre and M. Lamchen, *Quart. Rev.* (London), **19**, 329 (1965).

[3] J. E. Baldwin and R. G. Pudussery, *Chem. Commun.*, 1361 (1968).

[4] A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 2788 (1965).

[5] E. Fahr and H. D. Rupp, *Angew. Chem. Intern. Ed. Engl.*, **3**, 693 (1964).

[6] P. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, **90**, 2367 (1968).

[7] An extremely complex mixture resulted. Quinones are known to react with nitroso compounds: W. Gruendel and R. Pummerer, *Justus Liebigs Ann. Chem.*, **529**, 11 (1937).

[8] H. Minato and T. Fujisawa, *Bull. Chem. Soc. Jap.*, **39**, 1054 (1966).

TABLE I

INTERACTION OF NITROSOBENZENE WITH PHENYLHYDRAZONES. REACTION CONDITIONS AND RESULTS

Expt[a]	Phenylhydrazone	Registry no.	**1**/**2**, mmol	Yield of **3**,[b] % (mp, °C)[c]
A	Benzaldehyde	588-64-7	1:1	65 (112, lit.[d] 114)
B	Benzaldehyde		1.25:1	71
C	Benzaldehyde		1.50:1	86
D	Benzaldehyde		2.00:1	100[e]
E[f]	Benzaldehyde		1:1	~90[g]
F[h]	Benzaldehyde		1:1	35[i]
G	Benzaldehyde		1:1[j]	56
H	Benzaldehyde		1:1[k]	63
I	*p*-Nitrobenzaldehyde	2829-27-8	1:1	63 (187–188, lit.[d] 189)
J	*m*-Nitrobenzaldehyde	7539-23-3	1:1	63 (149–150, lit.[d] 154)
K	*p*-Chlorobenzaldehyde	2829-26-7	1:1	38[c] (153, lit.[l] 153–154)
L[m]	Fluorenone	15718-00-0	1:1	17 (192–193, lit.[n] 195–196.5)
M[o]	Fluorenone		2:1	49

[a] A 2-hr reaction time, benzene solvent, nitrogen atmosphere, except as noted. [b] Material recovered directly from chromatography, except as noted. [c] After recrystallization. [d] O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, **78**, 3363 (1956). [e] Traces of azoxybenzene isolated. [f] Air atmosphere. [g] Includes some crude material from which traces of impurities could not be removed. [h] Diethyl ether solvent. [i] Benzene produced in 39% yield. [j] Water added, H_2O/nitrosobenzene = 5 mmol. [k] Solvent benzene dried over sodium and distilled directly into reaction vessel. [l] V. Bellavita, *Gazz. Chim. Ital.*, **65**, 889 (1935). [m] A 19-hr reaction time. [n] A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963). [o] A 15-hr reaction time.

Experimental Section

Reagents.—Unless otherwise specified, commercially available reagents and solvents were used without purification. Melting points are corrected. Most nitrosobenzene was supplied by Aldrich; one batch was synthesized, mp 61–65° (lit.[9] mp 64–67°), by the method of Coleman, *et al.*[9] Phenylhydrazones were prepared according to the procedure outlined by Shriner, *et al.*[10]

Reaction of Nitrosobenzene with Benzaldehyde Phenylhydrazone. Neat Reaction.—Benzaldehyde phenylhydrazone (0.392 g, 2.0 mmol) was added to a three-necked flask fitted with a pressure-equalizing dropping funnel. The flask was flushed with nitrogen and cooled with an ice bath. A 0.214-g (2.0 mmol) portion of nitrosobenzene was added, but no change was noted until the ice bath was removed, at which time a sudden and highly exothermic reaction occurred and the mixture grew very dark. After 10 min, the reaction mixture was taken up in 30 ml of ether (previously flushed with nitrogen), and the solution was stirred briefly. The ether solution was evaporated, and the residue was taken up in a minimum amount of benzene. Chromatography on silica gel using benzene and benzene–methanol as solvents yielded 0.179 g of benzaldehyde phenylhydrazone (46% recovery) and 0.029 g of α-phenyl-N-phenyl nitrone (14% conversion).

Identification of the nitrone was made on the basis of its melting point, 112° from cyclohexane (lit.[11] mp 114°), infrared spectrum (bands matching those reported by Shindo and Umezawa[12]), and ultraviolet spectrum (λ_{max} matching those reported by Wheeler and Gore[11]). The nitrone was found to be stable to column chromatographic conditions described.

Nitrogen was produced from both neat and solution reactions; it was trapped over water and identified by diffusion-rate molecular-weight determination. Equimolar amounts of reagents in benzene liberated *ca.* $^2/_3$ mol of nitrogen. A heterogeneous surface (conveniently provided by 10–20 mg of charcoal per 1 mmol of reagent) enhanced the rate of gas production but not the volume.

Reactions of Phenylhydrazones with Nitrosobenzene in Solution.—A reaction using diethyl ether as a solvent was run in order to check for benzene production. Benzaldehyde phenylhydrazone (0.196 g, 1.0 mmol) was introduced into a three-necked flask fitted with magnetic stirrer, pressure-equalizing dropping funnel, and drying tube protected condenser. A 45-ml portion of dry ether was added to the funnel and degassed with dry nitrogen which proceeded *via* the funnel side-arm to flush the reaction flask before being emitted through the condenser. After 20 min, 15 ml of the ether was added to the reaction flask with stirring, and nitrosobenzene (0.107 g, 1.0 mmol) and 1.5 mmol of cyclohexane were dissolved in ether remaining in the dropping funnel. The nitrosobenzene solution was added in one portion to the reaction vessel, and immediate gas production was noted. The reaction mixture was stirred under a nitrogen atmosphere for 2 hr, and an aliquot was analyzed by vpc (6 ft × 0.25 in. SE-30 on firebrick column). With cyclohexane as an internal standard, benzene was found to be produced in 39% yield. The bulk of the reaction mixture was evaporated and subjected to column chromatography. The yield of nitrone was *ca.* 65 mg (35%), and *ca.* 60% of the phenylhydrazone of benzaldehyde was recovered.

The series of reactions run in benzene utilized essentially the same procedure as that outlined above, except that the nitrosobenzene in benzene was added dropwise to phenylhydrazone in benzene over a period of 20 min. Results are summarized in Table I, along with results of reactions of substituted phenylhydrazones with nitrosobenzene.

Reaction of Phenylhydrazine with Nitrosobenzene in the Presence of Benzaldehyde.—A solution of 0.107 g (1.0 mmol) of nitrosobenzene and 0.106 g (1.0 mmol) of benzaldehyde in 30 ml of dry, degassed benzene was added dropwise to a solution of 0.108 g (1.0 mmol) of phenylhydrazine in dry, degassed benzene. Upon chromatographic work-up, 57 mg (29%) of nitrone and 95 mg (48%) of crude benzaldehyde phenylhydrazone were isolated.

Registry No.—Nitrosobenzene, 586-96-9.

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[9] G. H. Coleman, C. M. McCloskey, and F. A. Stuart, *Org. Syn.*, **25**, 80 (1945).

[10] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 147. Melting points corresponded to tables in the text.

[11] Footnote *d*, Table I.

[12] H. Shindo and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 492 (1962).

Direct Fluorination of Secondary Nitronate Salts[1]

KURT BAUM

Environmental Systems Division,
Aerojet-General Corporation, Azusa, California

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A number of 1-fluoro-1,1-dinitro alkanes have been prepared by the direct fluorination of aqueous solutions

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