New Evidence on the Formation of 3-Acylindoles by Reaction of *N*-Phenylnitrones with α,β-Acetylenic Sulfones

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N-Phenylnitrones react with α,β-acetylenic sulfones to give ultimately 3-acylindoles *via* unstable 4-sulfonyl-substituted 2,3-dihydroisoxazoles. In one case, a minor pathway is also operative leading to a different kind of indole derivative. Mechanistic possibilities are discussed.

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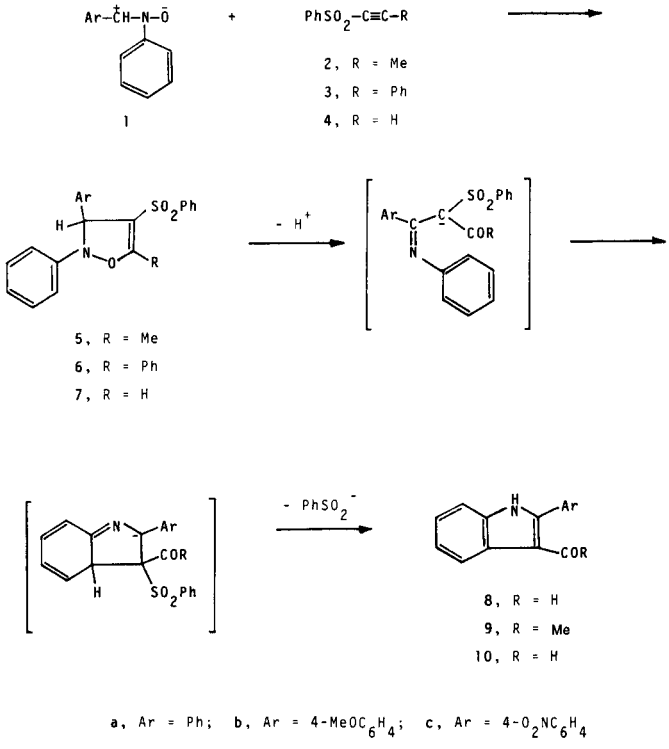
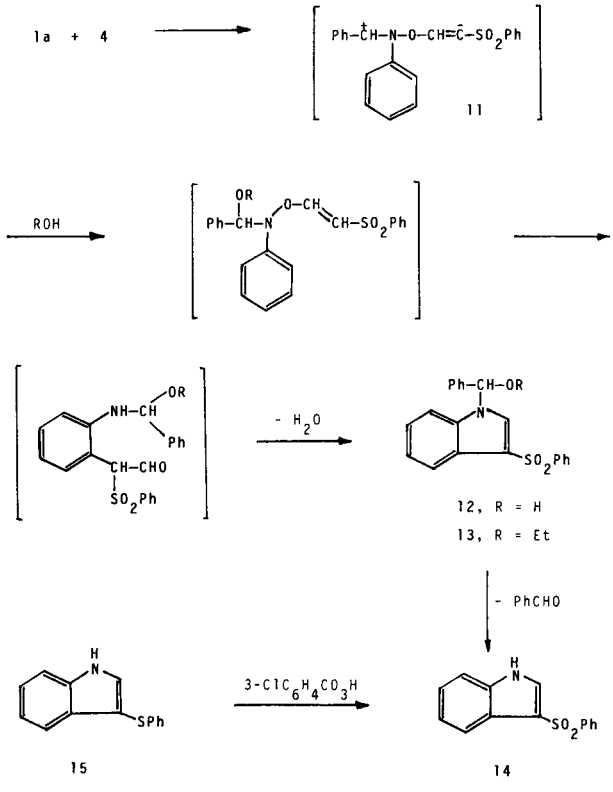
Cycloaddition reactions of nitrones with alkynes constitute an intriguing and fertile field of investigation since the resulting 2,3-dihydroisoxazoles are prone to a variety of synthetically useful transformations [1-4]. Recently [5], on studying the reactions of diphenylnitrone **1a** with α,β-acetylenic sulfones **2** and **3**, we brought to light a novel pathway ultimately leading to 3-acylindoles **8** and **9** (see Scheme 1). Further evidence on this subject is here presented.

Scheme 1



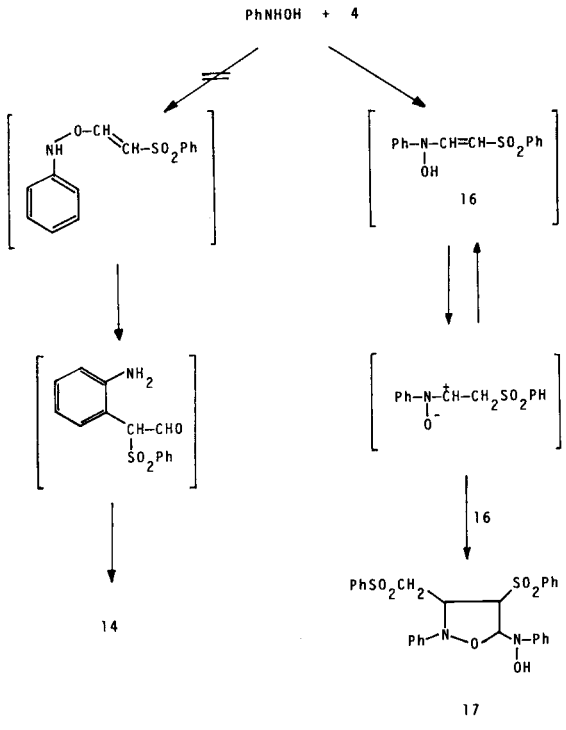
Scheme 2



Results and Discussion.

We thought it worthwhile to investigate the behaviour of the acetylenic substrate **2** towards *C*-aryl-*N*-phenylnitrones **1b,c** with the aim of evaluating the electronic effects of the *C*-substituent. The reactions were carried out in chloroform solution at room temperature. In the case of **1b**, the chromatographic treatment of the product mixture gave the dihydroisoxazole cycloadduct **5b** and the indole derivative **8b** in 29 and 39% yield, respectively. It was then ascertained that compound **8b** was not a primary product; in fact, adduct **5b** was shown to originate **8b** by standing in solution at room temperature as well as upon submission to a silica gel column chromatography. The reaction of **2** with **1c** followed a similar course, but the isolation of the first-formed adduct **5c** was very difficult because this compound showed a more pronounced lability than the related substrate **5b**. The observed difference between **5b** and **5c** clearly indicates that the spontaneous evolution of these dihydroisoxazoles proceeds as easier as more acidic is the hydrogen in the 3-position. Such evidence speaks in favour of the view that compounds **5**

Scheme 3



suffer the heterolytic cleavage of the N-O bond in concertedness with the removal of the 3-hydrogen, thus avoiding the energetically impervious formation of a discrete nitrenium ion. The extensive delocalization of the resulting anionic charge can further facilitate this ionic pathway. The subsequent cyclization step should be seen as an electrocyclic process rather than as a true nucleophilic attack to the phenyl ring. Finally, the aromaticity of the indole system provides a plausible driving force to the elimination of benzenesulfinate anion.

In order to establish whether the above route might be operative also in the case of monosubstituted acetylenes, we examined the reaction of nitrone **1a** with ethynylphenylsulfone **4**. The expected 3-formylindole **10a** was really isolated in fair yield, though no precursor of it could be evidenced even at short times. However, the reaction provided also a small amount of the indole derivative **14**, the structure of which was proven by an independent synthesis *via* oxidation of the known sulfide **15** (see Scheme 2). A mechanistic proposal for the formation of **14** involves the following steps: (i) nucleophilic addition of nitrone **1a** to the electron-poor acetylene **4**, (ii) trapping of the resulting dipolar adduct by moisture, (iii) hetero-Cope rearrangement of the so-formed *N*-phenyl-*O*-vinylhydroxylamine, (iv) cyclocondensation to the indole derivative **12**, and (v) hydrolytic loss of benzaldehyde during the work-up. Alternatively, one may think that benzaldehyde is lost initially upon hydrolysis of the starting nitrone **1a** and that addition of *N*-phenylhydroxylamine to **4** is leading to the final indole **14** (see Scheme 3). This hypothesis must be discarded because the reaction between *N*-phenylhydroxylamine and sulfone **4** was found to follow a different route resulting in the dimeric adduct **17** [6]. On the other hand, the first mechanistic proposal received support when treating **1a** with **4** in the presence of ethanol. Under these conditions, compound **10a** was again the major product, but a new compound was isolated at the expense of **14**. Analytical and spectral data suggested the indole structure **13**, which was confirmed by the acid-promoted hydrolysis to **14**. The obtainment of **13** well harmonizes with the intermediacy of the dipolar adduct **11**. It remains to be noticed that the step sequence given in Scheme 2 finds one precedent in the chemistry of nitrones [10].

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The ir spectra were taken on a Parkin-Elmer 298 spectrophotometer. The nmr spectra were recorded on Varian EM-390 (^{1}H) and Bruker WP80SY (^{13}C) instruments; chemical shifts are given in ppm from tetramethylsilane as internal standard (J in Hz). Mass spectra were measured on a WG-70EQ apparatus.

Compounds **1a-c** [11], **2** [12] and **4** [13] were available according to the literature.

Reaction of Nitrone **1b** with Sulfone **2**.

A solution of nitrone **1b** (10.4 mmoles) and sulfone **2** (10.4 mmoles) in chloroform (80 ml) was stirred at room temperature for 42 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with diethyl ether-light petroleum (1:1) as eluant. First fractions contained 4-methoxybenzaldehyde (19%). Subsequent fractions gave 3-(4-methoxyphenyl)-5-methyl-2-phenyl-4-phenylsulfonyl-2,3-dihydroisoxazole (**5b**) (29%), mp 115° (from ethanol); ir (Nujol): 1650 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.53 (s, 3H), 3.80 (s, 3H), 5.60 (s, 1H), 6.6-7.6 (m, 14H); ms: m/e 407 (M^+).

Anal. Calcd. for $C_{23}H_{21}NO_4S$: C, 67.80; H, 5.20; N, 3.44. Found: C, 67.57; H, 5.31; N, 3.25.

Further elution provided 3-acetyl-2-(4-methoxyphenyl)indole (**8b**) (39%), mp 234° (from chloroform); ir (Nujol): 3220, 1610 cm^{-1}; ^{1}H nmr (CD_3SOCD_3): δ 2.12 (s, 3H), 3.88 (s, 3H), 6.9-7.7 (m, 7H), 8.0-8.3 (m, 1H), 11.9 (br s, 1H, exchangeable); ms: m/e 265 (M^+).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.05; H, 5.49; N, 5.25.

Reaction of Nitrone **1c** with Sulfone **2**.

A solution of nitrone **1c** (5.0 mmoles) and sulfone **2** (5.0 mmoles) in chloroform (40 ml) was stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with dichloromethane-light petroleum (1:1) gave 4-nitrobenzaldehyde (25%), unchanged sulfone **2** (19%) and 5-methyl-3-(4-nitrophenyl)-2-phenyl-4-phenylsulfonyl-2,3-dihydroisoxazole

(**5c**) (10%), mp 105-107° (from diisopropyl ether); ir (Nujol): 1640 cm^{-1}; ^1H nmr (deuteriochloroform) δ 2.59 (s, 3H), 5.67 (s, 1H), 6.92 (d, J = 8, 2H), 7.0-7.6 (m, 10H), 8.01 (d, J = 8, 2H); ms: m/e 422 (M^+).

Anal. Calcd. for $C_{22}H_{18}N_2O_5S$: C, 62.56; H, 4.30; N, 6.63. Found: C, 62.39; H, 4.27; N, 6.85.

Subsequent fractions contained 3-acetyl-2-(4-nitrophenyl)indole (**8c**) (43%), mp 230° (from diethyl ether); ir (Nujol): 3260, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.31 (s, 3H), 7.1-7.6 (m, 3H), 7.95 (d, J = 8, 2H), 8.1-8.3 (m, 1H), 8.41 (d, J = 8, 2H), 12.3 (br s, 1H, exchangeable); ms: m/e 280 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.61; H, 4.20; N, 9.86.

Further elution provided unchanged nitrone **1c** (11%).

Reaction of Nitrone **1a** with Sulfone **4**.

A) A solution of nitrone **1a** (11 mmoles) and sulfone **4** (11 mmoles) in chloroform (90 ml) was stirred at room temperature for 18 hours. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column by eluting with a mixture of light petroleum-dichloromethane-diethyl ether (3:2:1). First fractions contained benzaldehyde (33%). Subsequent fractions gave compound **14** (4%) (*vide infra*). Further elution afforded 3-formyl-2-phenylindole (**10a**) (29%), mp 253° (from chloroform); ir (Nujol): 3200, 1625 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.1-7.9 (m, 8H), 8.1-8.3 (m, 1H), 10.02 (s, 1H), 12.2 (br s, 1H, exchangeable); ms: m/e 221 (M^+).

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.20; H, 4.89; N, 6.41.

B) A solution of nitrone **1a** (14 mmoles) and sulfone **4** (14 mmoles) in 9:1 chloroform-ethanol (110 ml) was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with a mixture of light petroleum-dichloromethane-diethyl ether (3:2:1) gave benzaldehyde (35%) followed by 1-(α-ethoxybenzyl)-3-phenylsulfonylindole (**13**) (5%), mp 126° (from pentane-chloroform); ^1H nmr (acetone-d_6): δ 1.22 (t, J = 7, 3H), 3.3-3.9 (m, 2H), 6.87 (s, 1H), 7.1-7.6 (m, 11H), 7.8-8.1 (m, 3H), 8.27 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.7 (q), 65.0 (t), 87.7 (d), 111.8 (d), 116.6 (s), 120.0 (d), 122.8-132.5, 136.3 (s), 137.2 (s), 143.2 (s); ms: m/e 391 (M^+).

Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.61; H, 5.58; N, 3.77.

Subsequent fractions contained compound **10a** (32%).

Independent Synthesis of Compound **14**.

A solution of sulfide **15** [14] (0.45 g) and 3-chloroperbenzoic acid (1.22 g) in dichloromethane (35 ml) was stirred at room temperature for 18 hours. The mixture was washed with aqueous solutions of sodium metabisulfite and sodium hydrogen carbonate, dried over sodium sulfate and evaporated. The residue was taken up with pentane. Filtration gave 3-phenylsulfonylindole (**14**) (0.40 g), mp 147° (from pentane-benzene); ir (Nujol): 3280 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.1-7.5 (m, 6H), 7.7-8.1 (m, 4H), 9.5 (br s, 1H, exchangeable); ms: m/e 257 (M^+).

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.51; H, 4.09; N, 5.40.

Hydrolytic Treatment of Compound **13**.

A solution of compound **13** (0.10 g) in 60% aqueous ethanol (15 ml) was treated with concentrated hydrochloric acid (0.2 ml) and refluxed for 48 hours. The solvent was partly removed under reduced pressure and the residue was diluted with water and extracted with chloroform. The organic solution was dried over sodium sulfate and evaporated. Addition of pentane and subsequent filtration gave compound **14** (0.055 g).

Reaction of *N*-Phenylhydroxylamine with Sulfone **4**.

A solution of *N*-phenylhydroxylamine (7.3 mmoles) and sulfone **4** (7.3 mmoles) in chloroform (60 ml) was stirred at room temperature for 2 hours. Removal of the solvent under reduced pressure gave practically pure **17** [7] (92%); ^1H nmr (deuteriochloroform): δ 3.78 (d, J = 6.5, 2H, exchangeable), 4.86 (dd, J = 5.5 and 2, 1H, exchangeable), 5.05 (dt, J = 6.5 and 2, 1H, s after deuteriation), 6.08 (d, J = 5.5, 1H, s after deuteriation), 6.2 (br s, 1H, exchangeable), 6.8-8.0 (m, 20H).

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[6] The latter result matches that previously described by other authors [7]. Compound **17** was obtained as a single diastereoisomer, albeit the relative configuration of the three stereocentres was not determined. It can be mentioned that proton coupling constants in the isoxazolidine ring are not clear-cutting for stereochemical assignments [8,9].

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