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REACTIVITY OF N-SUBSTITUTED p-BENZO AND p-NAPHTHOQUINONEIMINE N-OXIDES TOWARD DIPOLAROPHILES

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Abstract

The dipolar cycloaddition reactivity of N-(1-naphthyl)-1,4- benzoquinoneimine N-oxide and N-phenyl-1,4- naphthoquinoneimine N-oxide are investigated. The latter gives the expected adducts with common dipolarophiles such as acrylonitryle, methyl methacrylate, dimethylacetylene dicarboxylate and N-phenylmaleimide. The reactivity of the former nitrone is found to be minimal. It undergoes, however, an anomalous reaction with DMAD to give, after rearrangement, 1-(4-hydroxyphenyl)-3, 3-dicarboxymethylbenzooxindole.

Introduction

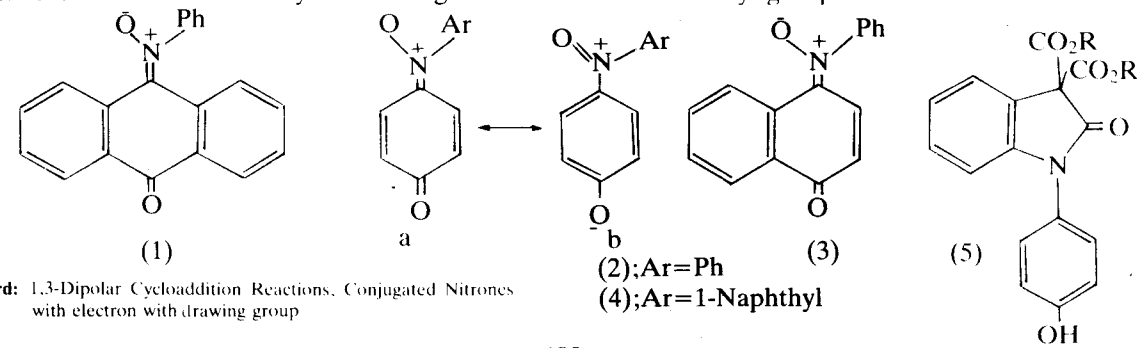
Nitrones are well known for their 1,3-dipolar cycloaddition reactions [1]. Conjugated nitrones, however, received little attention [2,3] and thus far no systematic study of these species have been reported.

Our study of the reactivity of N-phenyl-9, 10-anthraquinoneimine N-oxide (1) shows that this nitrone reacts readily with dipolarophiles and gives the expected 5-membered adducts [4]. N-phenyl-1 , 4-benzoquinoneimine N-oxide (2), on the other hand, is not reactive towards cycloaddition reactions and out of several dipolarophiles, it reacts only with dimethyl or diethylacetylene dicarboxylate to give oxindole (5) [4]. The surprising aspect of oxindole formation is 1,2-carbomethoxy rearrangement, which is apparently very fast.

In this communication we wish to report the synthesis and the test of the reactivity of homologous nitrones, N-phenyl-1,4-naphthoquinoneimine N-oxide (3) and N-(1-naphthyl)- 1,4-benzoquinoneimine N-oxide (4) towards dipolar cycloaddition reactions.

Results and Discussion

Perbenzoic acid oxidation of N-phenyl-1,4-naphthoquinoneimine and N-(1-naphthyl)-1, 4-benzoquinoneimine gave nitrones (3) and (4) respectively in relatively high yields. N-oxidation accompanied by substantial changes in ^1H NMR and IR spectrum of the initial imines, idicated that the carbonyl groups were affected by the formation of the N-oxide. The carbonyl stretching frequency shifted to lower frequency by the N-oxide formation, pointing to the fact that the back donation of diazomethine N-oxide moiety is more pronounced by conjugation with carbonyl group.



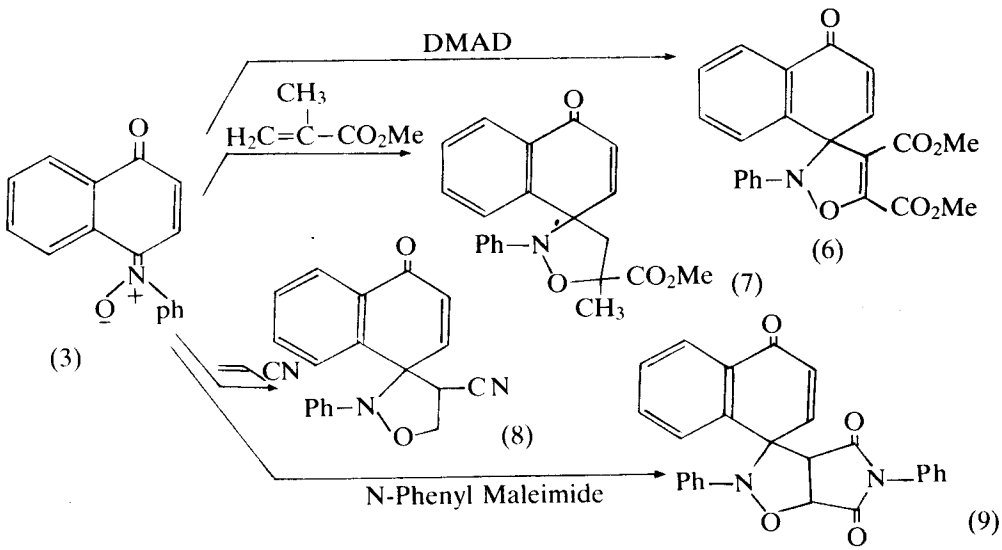
(1) a b (2);Ar=Ph (4);Ar=1-Naphthyl (3) (5)

Key word: 1,3-Dipolar Cycloaddition Reactions, Conjugated Nitrones with electron with drawing group

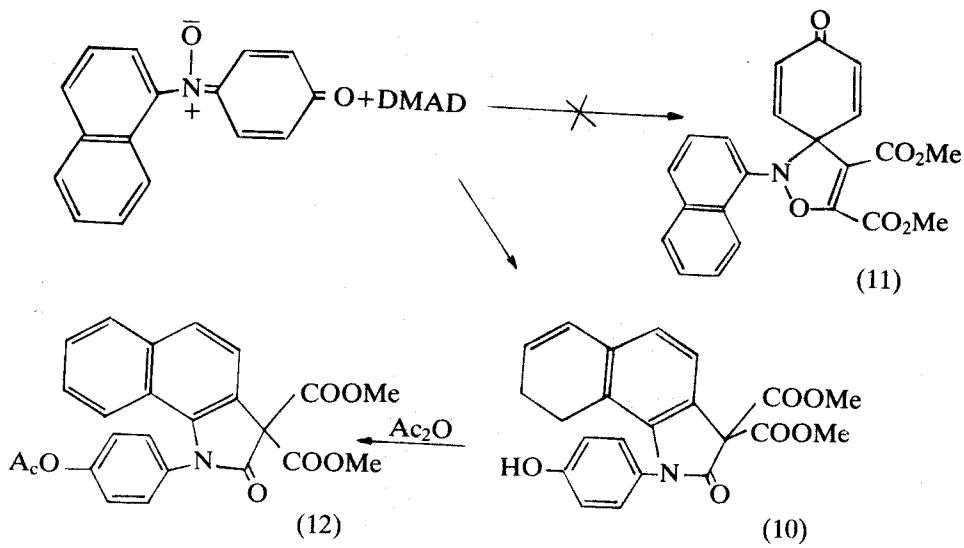
Reaction of nitrone (3) with DMAD in chloroform gave isoxazoline (6). The structure of (6) has been arrived at, on the basis of spectral data. The ^1H NMR spectrum of (6), for example, showed two singlets at δ 3.5 (3H) and 4 (3H), which have been assigned to methyl ester groups positioned at C-4 and C-5 of isoxazoline ring, respectively. Other protons appeared as complex multiplet in δ 6.3-8.2.

Similarly, the reaction of nitrone (3) with ethylenic dipolarophiles gave rise to the expected 5-membered isoxazolidine ring. In the case of non-symmetrical ethylenic dipolarophiles, where the question of regioselectivity arises, nitrone (3) showed a different behaviour. The reaction of nitrone (3), for example, with acrylonitrile gave 4-cyanoisoxazolidine derivative (8). The structure of (8) was established on the basis of mass, IR and ^1H NMR spectroscopy. The IR spectrum of (8) showed, among other peaks, a band at 2250 cm^{-1}, attributed to the nitrile group and a strong absorbtion at 1680 cm^{-1} due to the α,β-unsaturated carbonyl group. The ^1H NMR of compound (8) showed, among other peaks, a multiplet centered at δ 4.5 due to the methylene protons. The ^1H NMR evidence also provides strong evidence that the product is the 4-cyano instead of the isomeric 5-cyano derivative. Reaction of nitrone (3) with methyl methacrylate, on the other hand, gave 5-substituted isoxazolidine (7). The chemical shift of methylene protons in ^1H NMR, centered at δ 2.7, was specially diagnostic and unambiguously allowed the assignment.

Reaction of nitrone (4) with dimethyl acetylenedicarboxylate (DMAD) in CH_2Cl_2 at reflux temperature, however, led to a 1:1 adduct. The IR spectrum of this adduct consisted of strong band at 3480 cm^{-1} which could be attributed to NH or OH groups. Furthermore, the bands at 1765, 1730 and 1710 cm^{-1} showed three different carbonyl groups. In ^1H NMR spectrum of the adduct, a complex pattern, appeared at δ 6.4-7.9, comprising of 10 protons, which was assigned to aromatic protons. Furthermore, only one singlet (δ 3.85, 6H) was observed in the aliphatic region, indicating that the two methyl ester groups of DMAD in the adduct are in equivalent chemical environments. On the basis of the above observation, the structure (10) was assigned to the product, instead of isoxazoline (11). Acetylation of (10) in boiling acetic anhydride furnished a further proof for benzooxindole structure (10). The IR spectrum of acetylated product (12) showed no bands above 3100 cm^{-1} and in ^1H NMR spectrum a new singlet comprising of 3 protons appeared at δ 2.3. In conclusion, the above evidence together with those reported in our previous paper [4], suggest that the back donation of the negative charge of diazomethine N-oxide moiety in N-arylbenzoquinoneimine N-oxide and the contribution of structure (2a) and (4a) are important resonance structures. Thus, the non-reactivity of the nitrones of this type toward dipolarophiles and their anomalous reactions with dialkyl acetylenedicarboxylate could be accounted for by the above consideration.



In complete contrast, N – (1-naphthyl) benzoquinoneimine N-oxide (4) did not form the 1,3-cycloadducts with various dipolarophiles. Heating nitrone (4) with several ethylenic dipolarophiles led to the deoxygenated nitrone and some polymeric products. Naphthoquinoneimine oxide (3) and its anthraquinone analogue (1), on the other hand, are reactive in dipolar cycloaddition reactions. It implies that the back donation of negative charge is not strong enough and hence, these nitrones undergo a typical



(2+3) cycloaddition reactions.

Experimental Section

Melting points are taken in open glass capillaries and are uncorrected. IR spectra were recorded in Nujol on a Beckman Acculab 3 spectrophotometer. ^{1}H NMR (60 MHz) spectra were obtained with Perkin Elmer 248 spectrometer, and the shifts are given in scale with Me_4Si as the internal standard. Mass spectra were run by Varian MAT 311 mass spectrometer.

N-(1-Naphthyl)-1, 4-benzoquinone monoimine N-oxide (4).- To N-(1-naphthyl)-1, 4-benzoquinone monoimine [5] (0.46g, 2mmol) dissolved in $CHCl_3$ (15 ml), was added dropwise a solution of perbenzoic acid (0.4g, 3 mmol) in chloroform (15 ml). The reaction mixture was stirred at room temperature overnight and was extracted with 5% NaOH (2×20 ml). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in rotatory evaporator. The residue was recrystallized several times from ethanol to give the red needles of N-oxide (4) (0.49g, 98% yield), m.p.164-166°C; IR ν_{max} (nujol) 1625, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.8-6.55 (m, 4H), 7.2-7.9 (m,7H); mass spectrum m/z 233 (M^+), corresponding to deoxygenated N-oxide (4).

4', 5'-Dicarboxymethyl-1-oxo-2'-phenyl spiro (1,4-dihydronaphthalene-3', 4-isoxazoline)(6).- A mixture of nitrone (3)[6](0.6g, 2mmol) and dimethyl acetylenedicarboxylate (0.4g, 2.8 mmol) in dichloromethane (5 ml) was heated under reflux for 8 hours. The solvent was removed in vaccuo and ether (5 ml) was added. Cooling the mixture gave a white precipitate which was recrystallized from ether to give the spiroadduct (6), m.p. 108-109° C, as white crystals (0.4g, 44% yield); IR ν_{max} (Nujol) 1760, 1720, 1675, 1655 and 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.5 (s, 3H), 4 (s, 3H), 6.2-8.2 (m, 11H); mass spectrum, m/z 391 (M^+).

4'-Cyano-1-oxo-2'-phenylspiro (1, 4-dihydronaphthalene-4, 3'-isoxazolidine)(8).- Nitrone (3) (200 mg, 0.8 mmol) and acrylonitrile (70 mg, 1.6 mmol) were dissolved in dichloromethane (10 ml) and the reaction mixture was heated under reflux for 18 hours. The solvent was removed, using a rotatory evaporator and the resulting solid was chromatographed (silica gel, chloroform-petroleum ether 40-60° (1:1)), giving a white solid. This solid was further purified by recrystallization from ether to give adduct (8), m.p. 146-147°c, as colorless crystals (67 mg, 28% yield); IR ν_{max} (Nujol) 2250, 1680, 1645 and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.8 (m, 2H), 4.0 (m, 1H), 6.3-8.3 (m, 11H); mass spectrum m/z 302 (M^+).

5'-Carbomethoxy-5'-methyl-1-oxo-2'-phenylspiro (1,4-dihydronaphthalene-3', 4-isoxazolidine) (7).- Nitrone (3) (100 mg, 0.4 mmol) was added to methyl methacrylate (25 ml) and the reaction mixture was heated under reflux for 2 hours. The excess methyl methacrylate was evaporated in vaccuo and the residue was recrystallized from ether to give adduct (7), m.p. 137-138°C, as pale yellow crystals (53 mg, 38% yield); IR ν_{max} (nujol) 1730, 1665 and 1600 cm^{-1}); ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3H), 2.5 (d, 1H), 2.7 (d, 1H), 3.9 (s, 3H), 6.25 (m, 11H) mass spectrum m/z 349 (M^+).

1, 4′, 6′- Trioxo - 2′, 5′- diphenylspiro (1,4 - dihydronaphthalene - 3, 4′- perhydropyrrolo (3, 4 - d) isoxazolidine)(9). The mixture of nitrone (3)(400 mg, 1.6 mmol) and N-phenylmaleimide (300 mg, 1.7 mmol) in dry benzene (25 ml) was heated under reflux for 2 hours. The solvent was removed under reduced pressure and the resulting solid was passed through the column (silica gel, chloroform-aceton (97:3)) and further recrystallized from ethanol to give adduct (9), m.p. 172-174°C, as colorless crystals (216 mg, 32% yield): IR V_{max} (nujol) 1730, 1660 and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) §3.9 (d, 1H), 5.35 (d, 1H), 6.3-8.0 (m, 16H); mass spectrum m/z 422 (M^+).

1-(4-Hydroxyphenyl)-3, 3-dicarboxymethyl-6, 7-benzooxindole (10).- Nitrone (4)(250 mg, 1 mmol) dissolved in dichloromethane (10 ml) and dimethyl acetylenedicarboxylate (170 mg, 1.2 mmol) was added dropwise and the reaction mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and the resulting gum was treated with pet.ether (40-60°) and the solid thus obtained was recrystallized several times from ethanol to give oxindole (10), m.p.192-193°C, as a colorless solid (245 mg, 63% yield); IR ν_{max} (Nujol) 3480,1765,1735and 1710cm^{-1}; ^1H NMR($CDCl_3$)§ 3.8(s, 6H) 6-7.8 (m, 11H); mass spectrum m/z 391 (M^+).

1-(4-Acetoxyphenyl)-3, 3-dicarboxymethyl - 6, 7-benzooxindole (12).- The mixture of oxindole (10)(100 mg, 0.12 mmol), acetic anhydride (0.2 ml) and acetic acid (4 ml) were heated under reflux for 2 hours.The mixture was cooled to room temperature and water (20 ml) was added. The precipitate thus obtained, was recrystallized from ethanol to give acetylated oxindol (12), m.p.183-184°C (80 mg, 95% yield); IR ν_{max} (nujol) 1730, 1655, 1630 and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) § 2.3 (s, 3H), 3.8 (s, 6H), 7.3 (m, 4H), 7.65 (s, 5H); mass spectrum m/z 433 (M^+).

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