

Histidine as a catalyst in organic synthesis: A facile *in situ* synthesis of α , N-diarylnitrones

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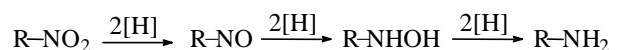
Abstract. α , N-diarylnitrones were synthesized by the reduction of a mixture of nitro- and benzaldehyde derivatives with zinc dust using histidine as a catalyst.

Keywords. α , N-diarylnitrones; zinc dust; organic synthesis; histidine as catalyst.

1. Introduction

Nitrones are versatile synthetic intermediates in organic synthesis^{1–8}. Some nitrones are used for trapping and identification of reactive free radicals⁹, particularly in biomedical research¹⁰. They are also used in the synthesis of many nitrogen-containing biologically active compounds^{11,12}. Recently, we synthesized some α , N-diarylnitrones, which can be used for the synthesis of model and ultimate carcinogens¹².

Nitrones are generally prepared either by the condensation of carbonyl compounds with hydroxylamines¹³ or the oxidation of the corresponding hydroxylamines^{2–7}.



Reduction of nitro- compounds proceeds through intermediate stages involving nitroso and hydroxylamine to form amines. Since N-arylhydroxylamines are less stable because of their photosensitivity¹⁴ and sensitivity to acid, they are further reduced to the corresponding amines. A literature survey reveals that the formation of an amine in addition to hydroxylamine, results in formation of an imine, azoxy compound¹⁵, azobenzene¹⁶ etc., which makes separation difficult and also in low yields of desired product.

To minimise these difficulties, we have made an attempt to synthesize α , N-diarylnitrones (**3a–j**) in good yield by the reduction of a mixture of nitro and benzaldehyde derivatives with zinc dust using histidine as a catalyst. Histidine provides significant buffering power near the neutral pH, which is very essential for the synthesis of α , N-diarylnitrones. Similar reaction was carried out with other amino acids like glycine, alanine, valine, leucine and proline as catalysts but the results were poor because

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of their pK_a values, which are too far away from $pH = 7.0$. Therefore, histidine is a suitable catalyst for this reaction.

2. Experimental

2.1 Materials and methods

All the nitro compounds and carbonyl compounds used were of commercial grade (Aldrich, E-Merck and Acros) and were purified prior to use either by distillation or by recrystallization. Histidine (E-Merck) was used as such. Petroleum ether (Fisher) and ethylacetate (E-Merck) were purified by distillation before use. Double distilled water, HPLC grade DMF and freshly distilled acetic anhydride were used.

^1H NMR spectra were obtained in CDCl_3 at 60 MHz. IR spectra were recorded on FTIR-8300. Melting points were measured on Selaco-605 melting point apparatus and are uncorrected.

2.2 Preparation of **3d** (general procedure)

To a cold solution of equimolar nitrobenzene, benzaldehyde and catalytic amount of histidine in water-ethanol-N, N-dimethylformamide (7:2:1), zinc dust was added in five parts in 60 min by continuous stirring (-5°C). pH of the solution was maintained at 7.2-7.4 throughout the reaction by adding freshly distilled acetic anhydride. Further, the reaction mixture was stirred at -5°C for about 30 min. The reaction mixture was filtered and evaporation of the solvent on a rotary evaporator gave a solid. It was dissolved in 5 ml of an ethylacetate-petroleum ether (1:4) mixture and chromatographed over silica gel-60. Elution with same solvent mixture gave the pure product (**3d**).

3i: ^1H NMR: 2.42 (*s*, 3H, Ar- CH_3); 7.71-7.81 (*m*, 5H, Ar-H); 7.1-7.5 (*m*, 2H, Ar-H); 7.79 (*s*, 1H, CH=N); 8.01-8.32 (*m*, 2H, Ar-H); Analysis - Cald. for $\text{C}_{14}\text{H}_{13}\text{NO}$: C, 79.43; H, 6.15; N, 6.85%. Found: C, 79.4; H, 6.14; N, 6.85%. IR $n_{\text{cm}^{-1}}$: 1572 (C=N), 1200 (NO). GC-MS, m/z : 211 (M^+), 194 (base peak); ^{13}C NMR (DMSO- d_6) δ : 31.14 (C- CH_3), 127.42, 128.47, 128.95, 129.02, 129.95 (CH=N), 130.26, 130.67, 134.63, 144.29, 148.93.

3j: ^1H NMR: 7.2-7.68 (*m*, 5H, Ar-H); 7.7-7.9 (*m*, 2H, Ar-H); 7.83 (*s*, 1H, CH=N); 8.12-8.52 (*m*, 2H, Ar-H); Analysis - Cald. for $\text{C}_{13}\text{H}_{10}\text{NOCl}$: C, 67.24; H, 4.31; N, 6.25%. Found: C, 67.23; H, 4.32; N, 6.23%; IR $n_{\text{cm}^{-1}}$: 1554 (C=N), 1202 (NO); GC-MS, m/z : 231.5 (M^+), 214.5 (base peak); ^{13}C NMR (DMSO- d_6) δ : 127.55, 128.59, 128.94, 129.14, 130.02 (CH=N), 131.93, 132.37, 132.41, 133.17, 148.21, 149.11.

3. Results and discussion

A series of *a*, N-diarylnitrones **3a-j** (table 1) were synthesized by the reduction of nitro- and benzaldehyde derivatives at pH 7.2-7.4 with zinc dust in water-ethanol-N, N-dimethylformamide (7:2:1) containing catalytic amount of histidine.

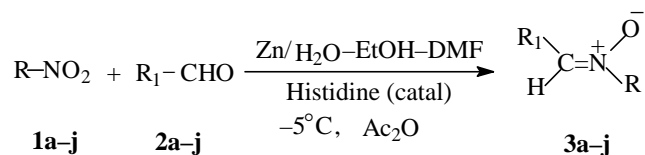


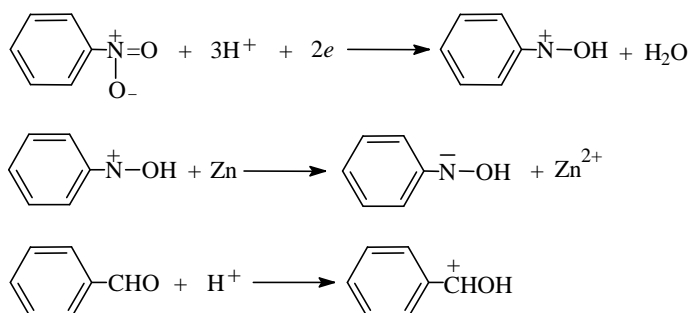
Table 1. Preparation and physical parameters of α , N-diarylnitrones **3a–j**.

Compound	R ₁ CH=N(O)R		m.p.(°C)	Reported m.p. (°C)	Time (min)	Yield (%)
	R ₁	R				
3a	4-NMe ₂ C ₆ H ₄	C ₆ H ₅	138–139	138 ¹⁸	80	81
3b	4-OHC ₆ H ₄	C ₆ H ₅	208	210 ¹⁹	80	83
3c	4-OMeC ₆ H ₄	C ₆ H ₅	118	118 ¹²	85	87
3d	C ₆ H ₅	C ₆ H ₅	115	112–114 ²⁰	90	92
3e	4-ClC ₆ H ₄	C ₆ H ₅	154	153–154 ²¹	90	90
3f	4-NO ₂ C ₆ H ₄	C ₆ H ₅	191	190 ²²	95	89
3g	C ₆ H ₅	4-MeC ₆ H ₄	123–125	124–125 ²³	70	92
3h	C ₆ H ₅	4-ClC ₆ H ₄	180	181 ⁷	75	88
3i	C ₆ H ₅	3-MeC ₆ H ₄	76–79	– ^a	90	79
3j	C ₆ H ₅	3-ClC ₆ H ₄	95–96	– ^a	90	84

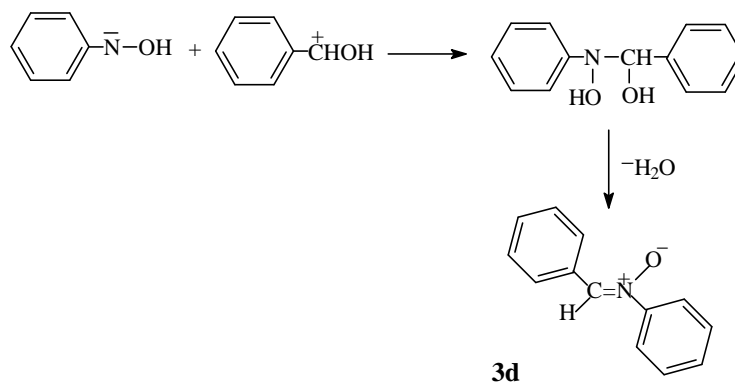
^anot reported

3.1 Reduction of nitrobenzene and benzaldehyde

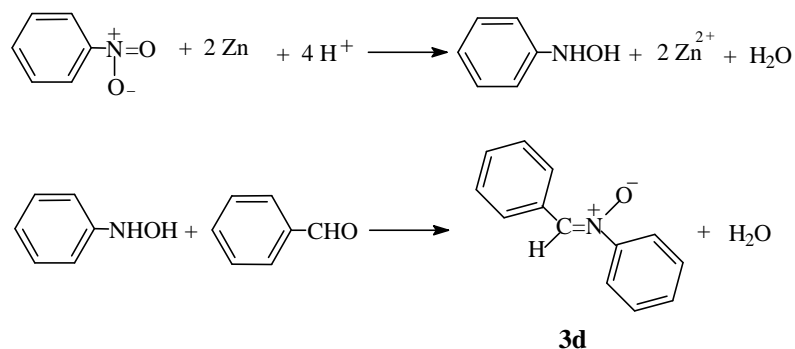
When nitrobenzene, benzaldehyde, zinc dust and catalytic amount of histidine in water-ethanol–N, N-dimethylformamide of pH 7.2–7.4 maintained by the addition of acetic anhydride and this was stirred at –5°C gave α , N-diarylnitronone **3d**. The reaction appears to proceed through the following mechanism.



The first phase of reduction followed by the reaction of Ph–N[–]OH and Ph–C⁺HOH results **3d**.



The above reaction is affected by an intermediate of phenylhydroxylamine which reacts with benzaldehyde to also give **3d**.

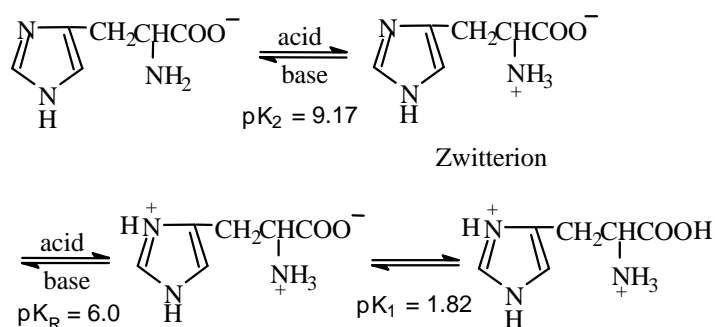


3.2 Role of histidine

A mixture consisting of nitrobenzene, benzaldehyde, zinc dust, water-ethanol-N, N-dimethylformamide (7:2:1) at pH about 5.3, yields products aniline, nitrosobenzene, azobenzene, hydrazobenzene, azoxybenzene and 10% of **3d**. Condensation of nitrosobenzene and aniline give azoxybenzene¹⁶, which is reduced by zinc dust to hydrazobenzene. Azoxybenzene, which may be produced by disproportionation of phenylhydroxylamine¹⁵ or by condensation of nitrobenzene and phenylhydroxylamine^{15a}, may also be the precursor of hydrazobenzene. Thus, the desired product **3d** is obtained in low yield at pH \approx 5.3, and hence the pH of the reaction media plays an important role. Of the 20 standard amino acids, only histidine has a side chain ($pK_a = 6.0$) providing significant buffering power near the desired pH. All other amino acids have pK_a values too far away from pH 7.0. In order to improve the yield of product, histidine was used as a catalyst and the pH was increased and maintained constantly in the range 7.2–7.4 by the addition of acetic anhydride. The addition of acetic anhydride rapidly produces the basic product Ph-N-OH which reacts with Ph-CHOH to give **3d**. These two oppositely charged ions are acid sensitive. Therefore, balanced concentration of H⁺ ions in the media is most favourable for the formation of **3d**. This was effectively achieved by the addition of catalytic amounts of histidine which balances the concentration of H⁺ ions at pH range 7.2–7.4 through its zwitterions¹⁷. We did not observe the presence of benzyl alcohol at pH 7.2–7.4. Thus, combining two oppositely charged ions is most favourable in the presence of histidine in the 7.2–7.4 pH range to obtain **3d**.

3.3 Temperature and solvent

Nitrobenzene was also reduced by zinc dust at room temperature and gave only 5% of **3d**. This implies that the efficiency of the reaction is particularly interesting if it operates at -5°C . Poor results were obtained when **1a–j** and **2a–j** are reduced by zinc dust using any one of the solvents water, ethanol, chloroform, ether or dimethylformamide individually. Best results were obtained in a solvent mixture of water-ethanol-N, N-dimethylformamide in the ratio of 7:2:1.



3.4 Reduction of substituted nitro derivatives

The order of ease of reduction of *p*-substituted benzaldehyde is $\text{NMe}_2 > \text{OH} > \text{OMe} > \text{H} > \text{Cl} > \text{NO}_2$, i.e. the order of their electron-releasing properties. In *p*-substituted nitrobenzene the ease of formation of $\text{R}-\bar{\text{N}}\text{OH}$ is $\text{Cl} > \text{Me}$ and *m*-substituents have little effect.

Acknowledgements

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