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

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

Keywords. *a*, 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 radicals [9], particularly in biomedical research [10]. They are also used in the synthesis of many nitrogen-containing biologically active compounds [11,12]. Recently, we synthesized some *a*, N-diarylnitrones, which can be used for the synthesis of model and ultimate carcinogens [12].

Nitrones are generally prepared either by the condensation of carbonyl compounds with hydroxylamines [13] or the oxidation of the corresponding hydroxylamines [2–7].

$$R\text{–}NO_2 \xrightarrow{2[H]} R\text{–}NO \xrightarrow{2[H]} R\text{–}NHOH \xrightarrow{2[H]} R\text{–}NH_2,$$

Reduction of nitro- compounds proceeds through intermediate stages involving nitroso and hydroxylamine to form amines. Since N-arylhydroxylamines are less stable because of their photosensitivity [14] 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 compound [15], azobenzene [16] etc., which makes separation difficult and also in low yields of desired product.

To minimise these difficulties, we have made an attempt to synthesize *a*, 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 *p*H, which is very essential for the synthesis of *a*, 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 *p*H = 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 anhydried were used.

^{1}H 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)*

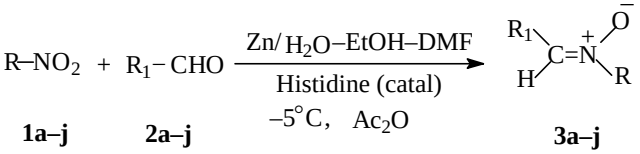
To a cold solution of equimolar nitrobenzene, benzaldehyde and catalytic amount of histidine in water–ethanol–N, N-dimethylformamide (7 : 2 : 1), zinc dust was added in five parts in 60 min by continuous stirring (–5°C). *p*H of the solution was maintained at 7·2–7·4 throughout the reaction by adding 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: ^{1}H 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 $C_{14}H_{13}NO$: C, 79·43 H, 6·15; N, 6·85%. Found: C, 79·4; H, 6·14; N, 6·85%. IR n_{cm}^{-1}: 1572 (C=N), 1200 (NO). GC-MS, *m*/*z*: 211 (M^+), 194 (base peak); ^{13}C NMR (DMSO-d_6) *d*: 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: ^{1}H 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 $C_{13}H_{10}NOCl$: C, 67·24; H, 4·31; N, 6·25%. Found: C, 67·23; H, 4·32; N, 6·23%; IR n_{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 *p*H 7·2–7·4 with zinc dust in water–ethanol–N, N-dimethylformamide (7 : 2 : 1) containing catalytic amount of histidine.



1a–j **2a–j** **3a–j**

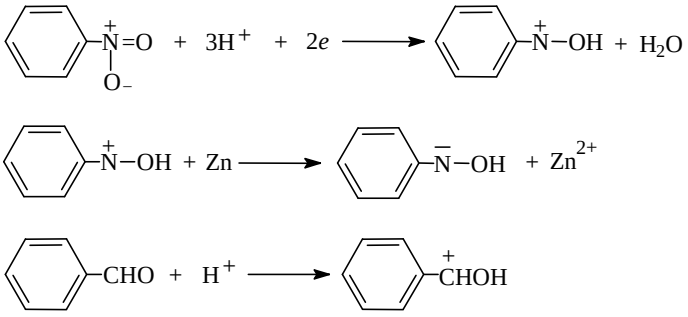
Table 1. Preparation and physical parameters of *a*, N-diarylnitrones **3a–j**.

Compound	$R_1CH=N(O)R$ R_1	R	m.p.(°C)	Reported m.p. (°C)	Time (min)	Yield (%)
3a	4-$NMe_2C_6H_4$	C_6H_5	138–139	138 [18]	80	81
3b	4-OHC_6H_4	C_6H_5	208	210 [19]	80	83
3c	4-$OMeC_6H_4$	C_6H_5	118	118 [12]	85	87
3d	C_6H_5	C_6H_5	115	112–114 [20]	90	92
3e	4-ClC_6H_4	C_6H_5	154	153–154 [21]	90	90
3f	4-$NO_2C_6H_4$	C_6H_5	191	190 [22]	95	89
3g	C_6H_5	4-MeC_6H_4	123–125	124–125 [23]	70	92
3h	C_6H_5	4-ClC_6H_4	180	181 [7]	75	88
3i	C_6H_5	3-MeC_6H_4	76–79	–[a]	90	79
3j	C_6H_5	3-ClC_6H_4	95–96	–[a]	90	84

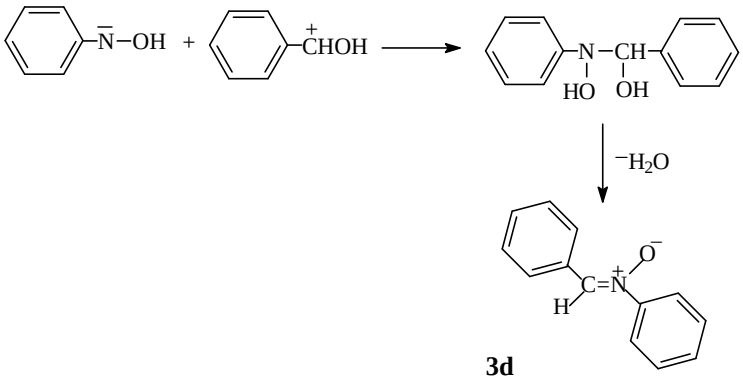
[a]not reported

3.1 *Reduction of nitrobenzene and benzaldehyde*

When nitrobenzene, benzaldehyde, zinc dust and catalytic amount of histidine in water–ethanol–N, N-dimethylformamide of *p*H 7·2–7·4 maintained by the addition of acetic anhydride and this was stirred at –5°C gave *a*, N-diarylnitrone **3d**. The reaction appears to proceed through the following mechanism.

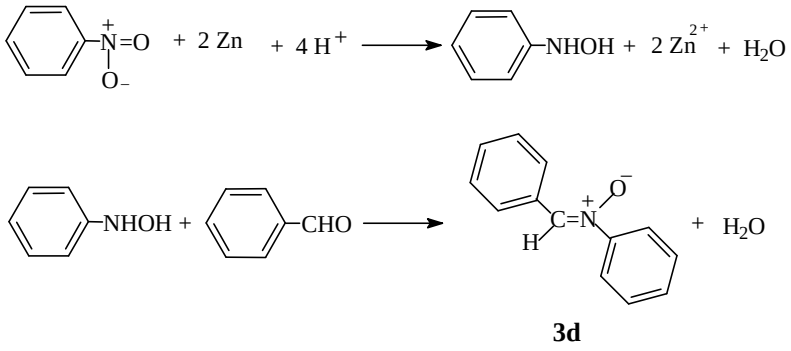


The first phase of reduction followed by the reaction of Ph–$\bar{N}$–OH and Ph–$\overset{+}{C}$HOH results **3d**.



3d

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



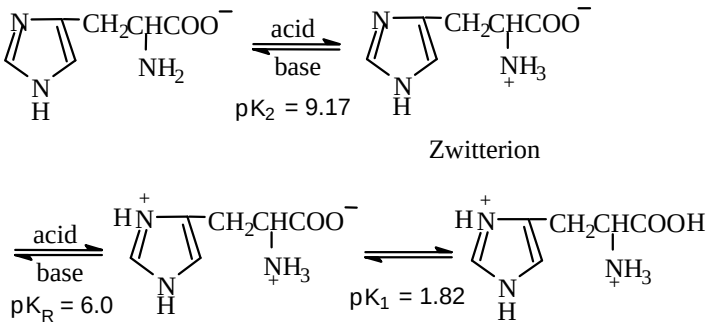
3d

3.2 *Role of histidine*

A mixture consisting of nitrobenzene, benzaldehyde, zinc dust, water–ethanol–N, N-dimethylformamide (7 : 2 : 1) at *p*H about 5·3, yields products aniline, nitrosobenzene, azobenzene, hydrazobenzene, azoxybenzene and 10% of **3d**. Condensation of nitrosobenzene and aniline give azoxybenzene [16], which is reduced by zinc dust to hydrazobenzene. Azoxybenzene, which may be produced by disproportionation of phenylhydroxylamine [15] 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 *p*H ≈ 5·3, and hence the *p*H 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 *p*H. All other amino acids have pK_a values too far away from *p*H 7·0. In order to improve the yield of product, histidine was used as a catalyst and the *p*H 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–C$\bar{H}$OH 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 *p*H range 7·2–7·4 through its zwitterions [17]. We did not observe the presence of benzyl alcohol at *p*H 7·2–7·4. Thus, combining two oppositely charged ions is most favourable in the presence of histidine in the 7·2–7·4 *p*H 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 $NMe_2 > OH > OMe > H > Cl > NO_2$, i.e. the order of their electron-releasing properties. In *p*-substituted nitrobenzene the ease of formation of $R-\bar{N}OH$ is Cl > Me and *m*-substituents have little effect.

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