



A green synthesis of nitrones in glycerol

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Abstract. An eco-friendly and efficient synthesis of nitrones is presented by condensation of an equimolar amount of aldehydes and N-substituted hydroxylamine hydrochlorides in glycerol as a recyclable solvent-catalyst. This novel protocol provides rapid and mild access to a series of nitrone derivatives in good to excellent yields in the absence of catalyst and base.

Keywords. Aldehyde; N-substituted hydroxylamines; condensation; nitrone; glycerol; green.

1. Introduction

Nitrones as useful reactive intermediates render a heavily pursued synthetic target.¹ Multifaceted applications of nitrones including 1,3-dipolar cycloaddition to access cyclic compounds and natural product,² biological activity as spin trapping agents,³ bioorthogonal probes⁴ and pharmacological activity as therapeutics in some cancers and antioxidants in age-related disease.⁵

Two main methods used to prepare nitrone compounds are oxidation of secondary hydroxylamines, amines and imines, and condensation of aldehydes with N-monosubstituted hydroxylamines.^{6,7} Since the strategies based on the oxidative formation of nitrones use metal-catalytic systems, harsh conditions and excess amounts of oxidants,⁸ a common and mild method for synthesis of nitrones is based on the C=N bond formation by condensation.⁹ However, this method also has limitation such as forming water during condensation which has decreased the yield of synthesized nitrones.^{10,11} Furthermore, due to the use of hydroxylamines as hydrochloride salts, base-mediated liberation of hydrochloride is commonly required. Relatively long reaction time, tedious chromatographic purifications and the use of toxic organic solvents are other problems. The search for an alternative and novel strategy focused on diminishing the above-mentioned restrictions and improving various

aspects of efficiency and environmental properties of reaction is therefore of interest.^{12,13}

In the last few years, the use of glycerol as a solvent for a large variety of applications or even a catalyst is increasing.¹⁴ Today, most of the petroleum solvents suffer from environmental problems during the preparation of chemicals and this can be replaced with glycerol. Glycerol, as a by-product of biodiesel production, has similar properties with water such as low toxicity, low price, abundance, and renewability. Moreover, like water, glycerol is highly hydrophilic and can dissolve a wide range of organic and inorganic compounds including transition metal catalysts.¹⁵ Glycerol as a hygroscopic compound can attract water in reaction and as it has three hydroxyl groups so it has hydrogen bond donor property. It has to be pointed out that glycerol, in comparison to water, has a high boiling point (298 °C), so it can be used in high temperature-needed reactions. Also, it has a lower vapor pressure and an ability to dissolve organic compounds usually immiscible with water.¹⁶

As the main problem for the development of on-water reactions is the high hydrophobicity of organic substrates, it seems that glycerol can be a good option as the solvent in the organic reaction. Palladium-catalyzed β,β -diarylation of alkyl acrylates through a Mizoroki–Heck reaction,¹⁷ Ring-closing metathesis catalyzed by ruthenium complexes,¹⁸ Multicomponent reactions catalyzed by [Fe(III)-(salen)]Cl¹⁹ and

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Ruthenium-catalyzed reductions of allylic alcohols²⁰ and palladium-catalyzed Heck and Suzuki coupling²¹ are some examples of the use of glycerol as solvent in organic reactions.

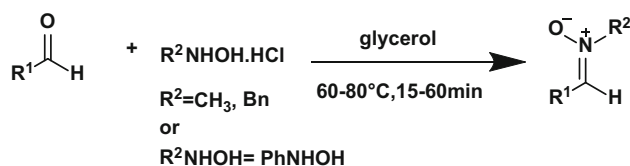
Glycerol can also act as a potential catalyst and proceed with many organic transformations. Some examples of such reactions are, Michael addition of aromatic amines to α,β -unsaturated Ketones,²² the ring-opening of epoxide with the amine under catalyst-free conditions,²³ electrophilic activations of aldehydes in the catalyst-free synthesis of di(indolyl)methanes, xanthene-1,8(2H)-diones and 1-oxo-hexahydroxanthenes.²⁴

According to these reports, glycerol is described as a green solvent and highly efficient promoting medium for the synthesis of different nitrones by direct condensation of aldehydes and N-substituted hydroxylamines under catalyst-free condition (Scheme 1). This new protocol for the preparation of nitrones exhibits pleasant environmental and practical superiority over the others reported in the literature.

2. Experimental

2.1 Materials and instrumentations

All reagents were purchased from Merck and Sigma-Aldrich Chemical Companies and used without further purification. phenylhydroxylamine was prepared from the reduction of nitrobenzene in the presence of Zn powder and NH_4Cl . ^1H NMR spectra were acquired using CDCl_3 as solvent running at 500 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl_3 , 7.26 ppm for ^1H NMR). In all ^1H NMR spectra, Data are reported as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constant(s) in hertz and the number of protons for each signal is also indicated. FTIR spectra were recorded using a Nicolet IR100 FT-IR over the 400–4000 cm^{-1} region using spectroscopic grade KBr. Melting points were measured using Büchi B-540 apparatus in open capillary vials. Mass spectra were obtained in a VG Auto Spec Spectrometer in positive electrospray ionization (ESI +). Obtained data are expressed in mass/charge (m/z) units. All solvents were used without previous treatment.



Scheme 1. General scheme of reaction.

2.2 General procedure for the synthesis of nitrone derivatives

To a mixture of a carbonyl compound (1 mmol), and N-substituted hydroxylamine hydrochloride (1 mmol) was added glycerol (1 mL). The reaction mixture was stirred at 60–80 °C for the desired time until the disappearance of the starting material, followed by TLC. After that, the reaction mixture was extracted with a mixture of water/ethyl acetate and the upper organic phase was dried with Na_2SO_4 and evaporated under reduced pressure. In order to the purification of prepared nitrones, the residue was purified by recrystallization from ethyl acetate/n-hexane the identity of the products was confirmed by comparison of their spectroscopic data with literature data.

3. Results and Discussion

To determine whether the glycerol is a promoting medium for this process, initially, we selected the reaction of benzaldehyde **1a** and N-methyl hydroxylamine hydrochloride **2b.HCl** in the presence of glycerol as a model. In order to optimize the reaction conditions, a series of experiments in the presence and absence of a base in a different solvent were investigated and were compared with glycerol (Table 1).

Only a trace amount of nitrone **3ab** was provided in the solvents including toluene, THF, CH_3CN , CH_2Cl_2 and solvent-free condition due to the lack of free hydroxylamine (entries 1–5). Water was capable to promote the reaction up to 25% yield (entry 6). The change of solvent to an alcoholic solvent such as MeOH produced moderate yields (entry 7). The addition of 1 equivalent of bases such as NaHCO_3 , NEt_3 and Na_2SO_4 in MeOH had a significant effect on the reactivity because the instantaneous liberation of hydroxylamine hydrochlorides has happened in the presence of the base (entries 8–10). We then attempted to examine the possibility of using glycerol as a solvent for this reaction. As expected, a promising yield was obtained under this condition with 83% yield in 15 min (entry 11). As the yield of reaction provided in the presence of glycerol was nearly similar to those observed in the presence of the base, our system is superior from the viewpoint of the traditional problem of base-mediated reaction, that hampers the simultaneous nucleophile and electrophile activation and have the tedious workup.¹²

Following the optimization of reaction conditions, we specified an optimum temperature. When the reaction was carried out in room temperature, only 40% yield was obtained. By increasing the

Table 1. Optimization of the reaction condition to form N-methyl nitrones **3ab** starting from **2b.HCl**.

Entry	Base (equiv)	Solvent	Yield (%)
1	—	Toluene	<5
2	—	THF	<5
3	—	CH ₃ CN	<5
4	—	CH ₂ Cl ₂	<5
5	—	—	<5
6	—	H ₂ O	25
7	—	MeOH	40
8	NaHCO ₃ (1)	MeOH	85
9	NEt ₃ (1)	MeOH	80
10	Na ₂ SO ₄ (1)	MeOH	90
11	—	Glycerol	83

1a: 1 mmol, **2b.HCl:** 1 mmol, solvent: 1 cc.

temperature, the reaction goes forward, so the best optimum yield of nitrone was attained in 60–80 °C. Above this temperature range, no significant progression in reaction time and yield of product was observed. So, in an optimized reaction, benzaldehyde **1a** (1.0 mmol) reacted with N-methyl hydroxylamine hydrochloride **2b.HCl** (1.0 mmol) in glycerol (1 mL) at 60–80 °C during 15 min, yielding **3a** in 83% yield.

Optimization studies led us to investigate the scope and limitation of reaction in the presence of different carbonyl compounds as well as N-methyl, N-benzyl hydroxylamine hydrochloride and free N-phenyl hydroxylamine (Table 2, entries 1–16). In all the cases, substituted benzaldehydes were converted to the corresponding nitrones in nearly quantitative yields in a few minutes. On the other hand, a small difference of yield was gained with respect to the nature and position of the substituent on the aromatic ring (entries 1–12). To extend our methodology, we also examined heteroaromatic aldehydes (entries 13 and 14) and the result was also obtained in good to excellent yields under these conditions. Not only aromatic aldehydes but also aliphatic aldehydes provided excellent yields of the product (entries 15 and 16). Unfortunately, all efforts to synthesize ketonitrones from ketones such as acetophenone under this condition failed (entry 17).

With these promising results, we can deduce the role of glycerol as an electrophilic activator of aldehydes. Mechanism of this activation involves the generation of

the hydrogen bond between three hydroxyl group of glycerol and carbonyl group of aldehyde. Also, the hygroscopic property of glycerol enabled it to absorb the water produced during the reaction and hampered the hydrolysis of formed nitrone.

In order to study the reusability of glycerol for this reaction, we diluted the mixture of reaction with hexane-ethyl acetate. After complete isolation of the product, the glycerol phase was directly reused four times. The results indicated that the efficiency of glycerol was preserved and nitrone **3ab** was obtained in remarkable yield after four runs (Table 3).

Finally, with the comparison of our method (reaction conditions, time and yield) with other previously reported for the prepared nitrones,^{10–13,25–28} determined that the yields and times obtained with this system are comparable or superior to others for the given nitrone. From the perspective of the environment, our method is eco-friendly. Furthermore, our strategy is cost-efficient due to the availability of glycerol as a waste during the production of biodiesel, which is sometimes, cheaper than water.¹⁷

4. Conclusions

In summary, we have developed a simple, efficient and catalyst-free strategy to form nitrones from the condensation of several aldehydes with N-substituted

Table 2. Synthesis of different nitrones derived from various carbonyl compound and N-substituted hydroxylamine in glycerol.

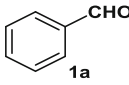
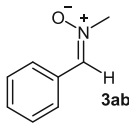
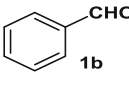
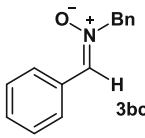
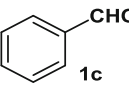
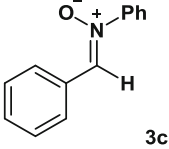
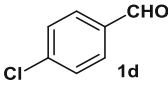
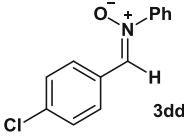
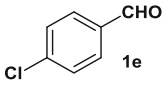
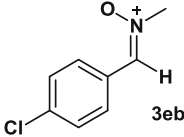
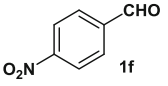
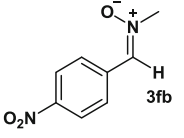
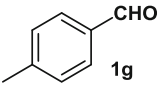
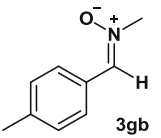
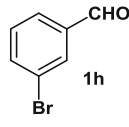
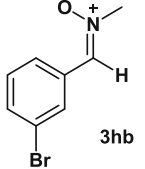
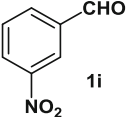
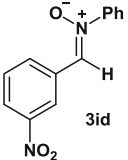
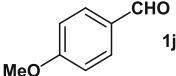
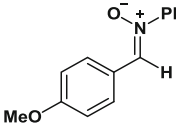
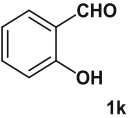
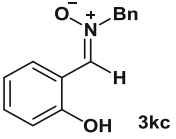
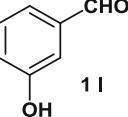
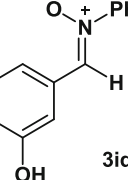
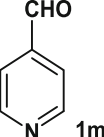
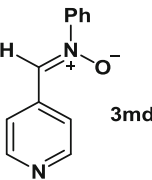
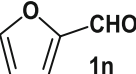
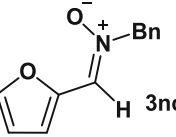
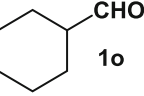
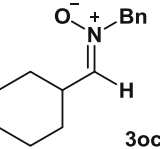
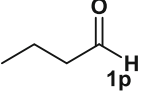
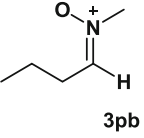
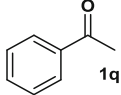
$ \begin{array}{c} \text{R}^1-\text{C}(=\text{O})-\text{H} \\ \text{1a-p} \end{array} + \begin{array}{c} \text{R}^2-\text{N}(\text{OH})-\text{H} \\ \text{HCl} \\ \text{2b.HCl } \text{R}^2=\text{CH}_3 \\ \text{2c.HCl } \text{R}^2=\text{Bn} \\ \text{2d } \text{R}^2=\text{Ph} \end{array} \xrightarrow[60-80^\circ\text{C}, 15-60 \text{ min}]{\text{Glycerol}} \begin{array}{c} \text{O}^--\text{N}^+\text{R}^2 \\ \parallel \\ \text{R}^1-\text{C}=\text{H} \\ \text{3ab-pb} \end{array} $					
Entries	Aldehyde (1)	N-substituted hydroxylamine (2)	Product (3)	Time (min)	Yield (%) ^b
1		2b.HCl		15	83
2		2c.HCl		20	88
3		2d		15	98
4		2d		20	92
5		2b.HCl		25	90
6		2b.HCl		30	93
7		2b.HCl		60	83
8		2b.HCl		60	93

Table 2. (Continued.)

9		2d		20	85
10		2d		35	83
11		2c.HCl		30	80
12		2d		40	95
13		2d		15	90
14		2c.HCl		20	75
15		2c.HCl		40	78
16		2b.HCl		60	40
17		2b.HCl	-	12h	0

^aReactions were carried out with various aldehydes **1a–p** (1 mmol) and ketone **1q**, R²NHOH.HCl R²:CH₃, Bn and free PhNHOH (1 mmol) in glycerol (1 mL).

^bYields are given for isolated product.

Table 3. Reusability of glycerol in the synthesis of **3ab**.

Reaction cycle	1st	2nd	3rd	4th
Yield (%)	88	88	83	80

^aReaction condition: benzaldehyde (1 mmol), N-methylhydroxylamine Hydrochloride (1 mmol), 15 min.

^bYield of isolated pure product.

hydroxylamine hydrochlorides in the presence of glycerol as dual solvent-catalyst. Using glycerol has advantages including (i) the reaction performs in base/metal-free condition that leads to simplifying the work-up procedure, (ii) environmental compatibility and sustainability, (iii) reusability without previous purification for further condensation reaction.

Supplementary Information (SI)

Analytical data and ¹H NMR of the compounds are available at www.ias.ac.in/chemsci.

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