One-Pot Synthesis of Functionalized Nitrones from Nitro Compounds

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Abstract: The zinc-mediated reduction of nitroalkanes and nitroarenes in the presence of aldehydes is an efficient method to synthesize a wide range of nitrones. This method is mild enough to accommodate a variety of functional groups. It is particularly useful when the intermediate hydroxylamines are unstable and/or water-soluble. We used it to prepare several aromatic, aliphatic and highly functionalized sugar-derived nitrones.

Key words: zinc reductions, nitro derivatives, hydroxylamines, carbohydrate derivatives, nitrones

In the last decade, there has been a great deal of interest in the chemistry of nitrones.[1] These compounds are substrates of choice for 1,3-dipolar cycloadditions[2] with alkenes and alkynes, to yield isoxazolidines and isoxazolines, which are easily converted to the corresponding amino-alcohols by N-O bond cleavage.

Another interesting feature of nitrones is their higher stability and better electrophilicity when compared to the corresponding imines which prompted their use as precursors of hydroxylamines and amines through nucleophilic additions onto the C=N bond.[3] Nitrones are also well known as radical spin-trapping agents,[4] thus allowing their use as antioxidants.[5] Recently, they have also been considered as substrate analogs for inhibiting enzymes such as thermolysin.[6]

Several general methods have been proposed for the synthesis of nitrones.[7] The first procedures involved *N*-alkylation of oximes but proved to be poorly selective and significant amounts of *O*-alkylated products contaminated product mixtures.[8] Oxidation of secondary amines,[9] hydroxylamines,[10] or imines[11] also leads to nitrones. However, in the cases of unsymmetric substrates a regioselectivity problem cannot be avoided.

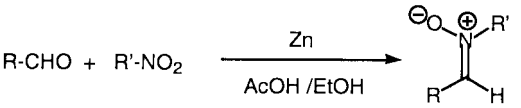
To date, it seems that the mildest and the most selective route to prepare nitrones is the condensation of *N*-alkylhydroxylamines with carbonyl compounds.[12] The major drawback of this method is that only very few *N*-alkyl-hydroxylamines are commercially available. The preparation of *N*-monoalkylhydroxylamines is often not straightforward, and the most general process involves three steps from primary amines.[13] Moreover, *N*-monoalkylhydroxylamines are usually prone to oxidize or disproportionate on standing, and need to be stored as their salts (hydrochloride or oxalate).

In the course of synthetic studies carried out in our laboratories,[14] we were interested in an efficient and general method to prepare aromatic and aliphatic nitrones bearing sterically hindered groups on the nitrogen atom and/or the electrophilic carbon. A wide range of nitro compounds being commercially available, we turned our attention to a one-pot preparation of nitrones from nitroalkanes or nitroarenes and aldehydes under reductive conditions.

Such a process has been previously used to prepare cyclic nitrones by reduction-intramolecular condensation between a nitro group and a carbonyl functionality.[15] Intermolecular examples of this reaction are also known.[16] However, this method received only moderate attention to prepare aliphatic nitrones.

The usual reduction procedure of the nitro compound into hydroxylamine is carried out by a mixture of zinc/acetic acid in ethanol or zinc/ammonium chloride in water. Recently, Kende described a way to reduce nitro derivatives with the more expensive, air-sensitive samarium diiodide.[17]

In this paper, we demonstrate that the *in situ* zinc mediated reduction of nitro compounds in presence of aldehydes (Scheme 1) is mild enough to accommodate a variety of functional groups. We used it to prepare aromatic, aliphatic and highly functionalized sugar-derived nitrones.



Scheme 1

The results obtained from various aromatic aldehydes and nitro derivatives are summarized in Table 1. Depending on the nature of both starting materials, nitrones were isolated with moderate to very good yields.

The general reaction conditions required the use of 1 equivalent of nitro derivative and 2-4 equivalents of zinc at 0 °C during two days. Yield improvements could be achieved by either increasing the temperature (entries 7-8, Table 1) or the number of equivalents of nitro compound and/or zinc (entries 2-3 and 7-9, Table 1).

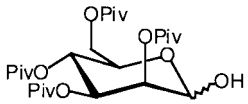
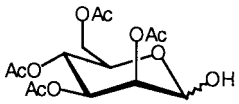
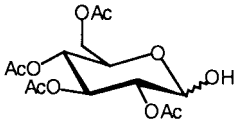
Representative results with different aliphatic and glycosyl aldehydes (Schemes 2 and 3) and the sterically hindered 2-methyl-2-nitropropane are gathered in Table 2. Again, the corresponding nitrones were obtained in moderate to very good yields. Some results could be optimized by increasing the number of equivalents of *t*-$BuNO_2$ and/or zinc. Increasing the temperature or reaction time was not an adequate way to improve yields in these cases.

Table 1 Synthesis of nitrones from aromatic aldehydes and various nitro derivatives

Entry	R-CHO (1 equiv.)	R'-NO_2 (x equiv.)	Zn (y equiv.)	Conditions	Yield
1	PhCHO	*i*-PrNO_2 (2)	3	0°C / 48h	61%
2	"	*t*-BuNO_2 (1)	4	r.t. / 18h	45%
3	"	*t*-BuNO_2 (2)	3	r.t. / 21h	85%
4	"	*p*-Me-PhNO_2 (1)	3	0°C / 48h	93%
5	*p*-MeO-PhCHO	*i*-PrNO_2 (2)	3	0°C / 48h	50%
6	"	PhNO_2 (2)	3	0°C / 48h	89%
7	R^1-CHO[a]	*t*-BuNO_2 (1)	2	r.t. / 48h	68%
8	"	*t*-BuNO_2 (1)	2	50°C / 48h	80%
9	"	*t*-BuNO_2 (1)	4	r.t. / 66h	96%
10	*o*-furyl-CHO	*i*-PrNO_2 (2)	3	0°C / 48h	66%

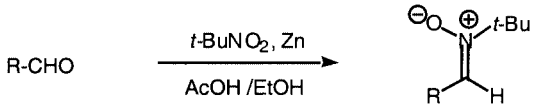
(a) : R^1 = *o*-(2'-Br-PhCH_2O)-Ph-

Table 2 Synthesis of nitrones from aliphatic aldehydes and 2-methyl-2-nitropropane

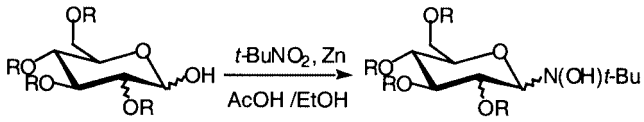
Entry	R-CHO (1 equiv.)	*t*-BuNO_2 (x equiv.)	Zn (y equiv.)	Conditions	Yield
11	HO-$(CH_2)_4$-CHO	2	3	r.t. / 19h	85%
12	Et-CHO	2	3	r.t. / 29h	88%
13	*i*-Bu-CHO	1	4	r.t. / 20h	95%
14	Ph-$(CH_2)_2$-CHO	2	3	r.t. / 72h	79%
15	Ph-CH=CH-CHO	1	4	r.t. / 25h	58%
16		2	2	r.t. / 72h	59%
17		2	3	r.t. / 48h	60%
18		3	3	r.t. / 24h	45%

It is worth pointing out that attempts to prepare such functionalized nitrones by the usual condensation reaction (aldehyde / *t*-butylhydroxylamine)[12] were unsatisfactory; at room temperature, very slow conversions were observed, and degradation of the starting materials occurred on heating.

The method described herein allowed the synthesis of an α,β-unsaturated nitrone derived from cinnamaldehyde (entry 15, Table 2) with a satisfactory yield (58%). No product resulting from cyclization was observed.



Scheme 2



Scheme 3

Concerning the sugar-derived nitrones (entries 16, 17 and 18, Table 2), they were obtained as glycosyl hydroxylamines, resulting from the cyclization of the C_5 oxygen onto the C_1 carbon of the nitrone.

In conclusion, we have demonstrated that the one-pot reduction-condensation of nitroalkanes or nitroarenes with aldehydes constitutes a direct and efficient method to synthesize a wide range of nitrones. The major advantages of this method are the following:

i. Numbers of nitro compounds are commercially available or easily synthesized.
ii. It can easily be scaled up to prepare large amounts of nitrones (50 mmol).
iii It is compatible with sensitive functionalities like α,β-unsaturated or sugar-derived aldehydes.
iv. It has proved to be especially useful for the preparation of nitrones derived from: - quaternary and aromatic hydroxylamines which are usually not commercially available and are unstable;[18] - low molecular weight and/or water soluble hydroxylamines which are difficult to isolate.

General procedure

To a stirred solution of the aldehyde (1 mmol) in 10 mL of 95% ethanol were added the nitroalkane or the nitroarene (x equiv, see Tables 1 and 2) and zinc powder (y equiv, see Tables 1 and 2) at 0 °C under argon atmosphere. Glacial acetic acid (6 mmol) was then introduced dropwise. Reaction temperature was kept at 0 °C during evolution of the reaction or raised to room temperature. The conversion of the starting materials was followed by TLC. After filtration on a celite pad and evaporation of the filtrate under vacuum, the crude material was purified by flash chromatography on silica gel. All new compounds gave spectroscopic and analytical data in agreement with the assigned structures.

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