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Unprecedented base-promoted nucleophilic addition of diazoesters to nitrones

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ABSTRACT

A novel and efficient nucleophilic addition of metalated α-diazoacetates to a variety of nitrones is described. This approach provides a series of stable unprecedented β-alkylhydroxyamino-α-diazoesters with great synthetic potential.

Nitrones represent one of the most useful and versatile nitrogenated substrates in organic synthesis.[1] Due to their dipolar structure they have been largely exploited in [3+2]-cycloaddition reactions with alkenes.[2] Also, due to their highly polarized C–N double bond, nitrones show a pronounced electrophilic reactivity compared to imines and hence are privileged substrates for nucleophilic addition reactions. However, although a number of organometallic additions to nitrones have been previously reported,[1a–d] to the best of our knowledge, there has been no report on the direct nucleophilic addition of α-diazoesters onto nitrones.

A wide array of transformations can be performed with α-diazo carbonyl substrates.[3] Particularly interesting reactions are those involving decomposition of diazo moiety catalyzed by transition metal complexes. Through metallocarbene species, a wide number of reactions including C–H or X–H insertion processes, cyclopropanations, cycloadditions, and Wolff rearrangement can be observed.

In connection with our ongoing research program devoted to the development of new methodologies and synthetic applications involving nitrones,[4] we became interested in exploring the reactivity of nitrones with α-diazo acetates, which are useful C-2 substrates for the incorporation of diazo moiety. This approach would provide densely functionalized hydroxylamines with great potential in organic synthesis.

Inspired by the reported conditions for nucleophilic addition of ethyl diazoacetate (EDA, **2a**) to carbonyl compounds[5,6] and imines,[5,7] we commenced our study with a brief screening of bases to form hydroxylamine **3a** from ethyl *N*-benzyl nitrone (**1**) (Table 1). Although 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzes the condensation of EDA with aldehydes and imines[5] no reaction was observed with nitrone **1**, even after prolonged stirring for several days (Table 1, entry 1). Using potassium hexamethyldisilazide (KHMDS) as base also failed (entry 2). Changing the base to sodium hexamethyldisilazide (NaHMDS)[7e] gave the desired hydroxylamine **3a** in a modest 53% yield (entry 3). However, significant improvement was observed with lithium hexamethyldisilazide (LiHMDS) or lithium diisopropylamide (LDA)[6,7e] as bases, affording the addition product in 93% and 94% yields respectively (entries 4 and 5). We selected the conditions using LiHMDS as base (commercially available solution), THF as solvent, at −78 °C for 1.5 h reaction time to study the scope of the nucleophilic addition.[8]

The addition of other commercial alkyl diazoesters to nitrone **1** was next tested using the previously optimized conditions (Scheme 1). Pleasingly, with *t*-butyldiazoester (**2b**) and benzyl diazoester (**2c**), hydroxylamines **3b** and **3c** were obtained in quantitative yields.

Encouraged by these preliminary results, we next extended the addition of lithiated ethyl diazoacetate to a variety of nitrones.[9] As shown in Table 2 (entries 1–4), the reaction proceeded smoothly with aliphatic aldonitrones, producing the corresponding hydroxylamines in good to excellent yields. Interestingly, the reaction also worked well with ketonitrone **8**, furnishing the corresponding

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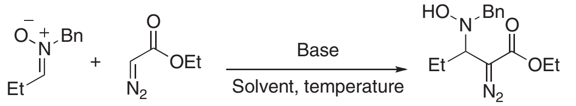
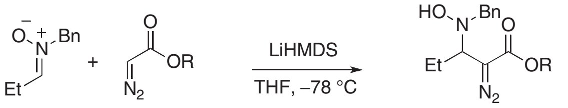
Table 1
Screening of bases in the reaction of EDA (**2a**) and ethyl *N*-benzyl nitrone (**1**)[a]



1 **2a** **3a**

Entry	Base	Solvent	*T* (°C)	Time	Yield[b] (%)
1	DBU (10 mol %)	MeCN	rt	7 d	0[c]
2	KHMDS (1.5 equiv)	THF	−78	1.5 h	0[c]
3	NaHMDS (1.5 equiv)	THF	−78	1.5 h	53[c]
4	LiHMDS (1.5 equiv)	THF	−78	1.5 h	93
5	LDA (1.5 equiv)	THF	−78	1.5 h	94

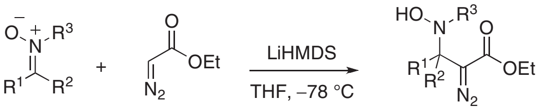
[a] Reactions were carried out with 1.0 equiv of **1** and 1.5 equiv of diazoester **2a**.[8]
[b] Isolated yield after column chromatography.
[c] Starting nitrone was recovered.



1 **2b**, R = *t*-Bu **3b**, R = *t*-Bu (100%)
2c, R = Bn **3c**, R = Bn (100%)

Scheme 1. Addition of *t*-butyl and benzyl diazoesters to nitrone **1**.

Table 2
Addition of EDA to a variety of nitrones[a]

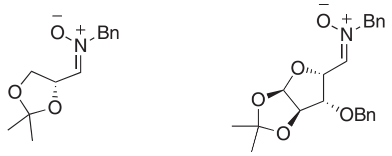


Entry	Nitrone[b]	Hydroxylamine	Yield[c] (%)
1	**4**: $R^1 = Me_2CHCH_2$, $R^2 = H$, $R^3 = Bn$	**12**	59
2	**5**: $R^1 = Me_2CH$, $R^2 = H$, $R^3 = Bn$	**13**	98
3	**6**: R^1 = *t*-Bu, $R^2 = H$, $R^3 = Bn$	**14**	77
4	**7**: R^1 = cyclohexyl, $R^2 = H$, $R^3 = Bn$	**15**	80
5	**8**: R^1–R^2: $-(CH_2)_5-$, $R_3 = Bn$	**16**	74
6	**9**: $R^1 = Ph$, $R^2 = H$, $R^3 = Bn$	**17**	61[d]
7	**10**: R^1 = *p*-$MeOC_6H_4$, $R^2 = H$, $R^3 = Bn$	**18**	46[e]
8	**11**: R^1 = *p*-ClC_6H_4, $R^2 = H$, $R^3 = Ph$	**19**	92

[a] For typical procedure see Ref. 8.
[b] For the preparation of nitrones **4**–**11**, see Ref. 9.
[c] Isolated yield after column chromatography.
[d] 39% of **9** was recovered.
[e] 34% of **10** was recovered.

hydroxyamine **16** in 74% yield (entry 5). In the case of *C*-aromatic *N*-benzyl nitrones, the isolated yields of compounds **17** and **18** are slightly lower (entries 6 and 7). In these cases substantial amounts of starting nitrones were recovered. With *N*-phenyl nitrone **11** (entry 8) the addition product was obtained in excellent yield (92%).

We also examined the diastereoselectivity of this nucleophilic addition using chiral *N*-benzyl nitrones **20** (derived from D-glyceraldehyde)[10] and **21** (prepared from D-glucose)[11] (Fig. 1).

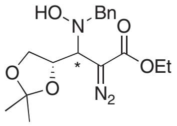
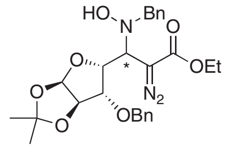


20 **21**

Figure 1. Chiral *N*-benzyl nitrones **20** and **21**.

The reaction proceeded smoothly with nitrone **20** furnishing the corresponding hydroxylamine **22** in 92% yield as a 75:25 mixture of diastereomers (Table 3). It can be assumed that the major product is the *syn* isomer based on the previously reported organometallic additions to the same nitrone.[12] The level of diastereoselectivity is consistent with that observed in the addition of the lithium enolate of methyl acetate to nitrone **20**.[12e] With nitrone **21**, a 60:40 mixture of hydroxylamine **23** was obtained in 83% yield. This result also matches with those observed in vinylation reactions (low selectivities)[13] but it contrasts with the addition of lithiated heteroaromatic nucleophiles to the same nitrone, which showed a much higher diastereoselectivity (>90:10).[14] No attempt to improve the diastereoselectivity of these reactions was undertaken.

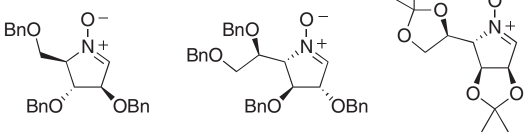
Table 3
Addition of EDA onto chiral non racemic *N*-benzyl nitrones

Entry	Nitrone	Hydroxylamine	Yield[a] (%)	Dr[b] (%)
1	**20**	 **22**	92	75:25
2	**21**	 **23**	83	60:40

[a] Isolated yield after column chromatography.
[b] Diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture.

We next turned our attention to sugar-derived cyclic nitrones. This class of nitrones, and particularly five-membered cyclic nitrones are useful building blocks for the synthesis of bioactive iminosugars.[1e,15] The nucleophilic addition of lithiated ethyl diazoacetate was performed on nitrones **24**,[4c,16] **25**,[17,18] and **26**[19,20] (obtained respectively from L-xylose, D-glucose, and D-mannose, Figure 2). Gratifyingly, the corresponding hydroxylamines **27**, **28**, and **29** were obtained in excellent chemical yields and with total diastereocontrol (Table 4). This result is in agreement with the general trend observed in the nucleophilic addition to these cyclic nitrones in which high diastereoselectivities are obtained through an *anti* attack with respect to the C-3 alkoxy substituent.

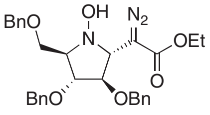
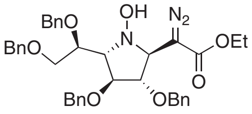
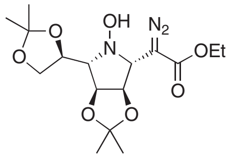
In summary, we report an efficient, high yielding nucleophilic addition of lithiated alkyl diazoesters with a variety of nitrones. The selectivity observed with sugar-derived endocyclic nitrones opens new perspectives for the synthesis of novel bioactive iminosugars. The study of the reactivity of these novel hydroxyamino diazoesters through the formation of metallocarbenoids is ongoing in our laboratory and will be reported in due course.



24 **25** **26**

Figure 2. Structures of sugar-derived nitrones **24**, **25**, and **26**.

Table 4
Addition of EDA onto cyclic sugar-derived nitrones

Entry	Nitrone	Hydroxylamine	Yield[a] (%)	Dr[b] (%)
1	**24**	 **27**	100	>99:1
2	**25**	 **28**	100	>99:1
3	**26**	 **29**	92	>99:1

[a] Isolated yield after column chromatography.

[b] A single diastereomer was observed by ^{1}H NMR analysis of the crude reaction mixture.

Supplementary data

Supplementary data (complete characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.044. These data include MOL files and InChiKeys of the most important compounds described in this article.

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