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N-Benzyl Aspartate Nitrones: Unprecedented Single-Step Synthesis and [3 + 2] Cycloaddition Reactions with Alkenes

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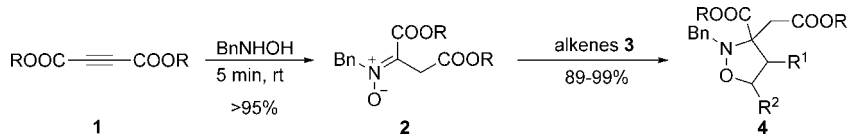
ABSTRACT



***N*-Benzyl aspartate nitrones 2, prepared by addition of *N*-benzylhydroxylamine to dialkyl acetylenedicarboxylates 1, underwent [3 + 2] thermal cycloaddition with a wide range of alkenes to afford isoxazolidines 4 bearing a polyfunctionalized quaternary center. Under these uncatalyzed conditions, the *trans* stereocontrol observed with vinyl ethers is higher than that obtained with all acyclic activated nitrones reported to date. The first asymmetric access to a type-4 pure adduct was achieved starting from the chiral aspartate nitrone derived from (*S*)-α-methylbenzylhydroxylamine.**

Nitrones represent attractive synthetic intermediates since they undergo 1,3-dipolar cycloaddition (1,3-DC) reactions with a wide range of alkenes and alkynes to afford versatile isoxazolidine and isoxazoline products, respectively.[1] These cycloadducts could be opened by N−O bond cleavage via reduction,[2] alkylation,[3] and even oxidation to other nitrones.[4] Condensation of aldehydes/ketones with N-substituted hydroxylamines,[5] oxidation of N,N-disubstituted amine[6]/hydroxylamines[7]/imines,[8] thermal cycloreversion[9] of isoxazolidines, N-alkylation of *O*-trimethylsilyl oximes,[10] and fragmentation of *N*-hydroxyamino sulfonates[11] represent the most common methods for the synthesis of nitrones. α,α-Dialkylnitrones are synthetically important as they could be involved in 1,3-DC reactions to create a quaternary center,

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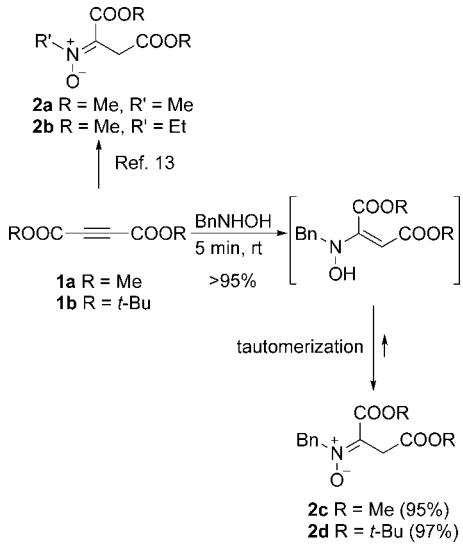
but the 1,3-DC reactions of nitrones containing two differently functionalized side chains were rarely reported.[12] The access to this kind of nitrone such as **2a**,**b** was described by Winterfeldt by Michael addition of *N*-alkylhydroxylamines to dimethyl acetylenedicarboxylate (Scheme 1).[13] Attempts

Scheme 1. Synthesis of Nitrones **2c**,**d**



to prepare *N*-aryl derivatives by the same procedure led to unstable nitrones.[14] We report herein the first extensive study on the reactivity of type-**2** nitrones toward a wide range of alkenes.[15] In this study, we selected *N*-benzyl nitrones **2c**,**d** with the aim to obtain N-protected-3,3-disubstituted isoxazolidines.

The dimethyl and di-*t*-butyl acetylenedicarboxylates **1a**,**b** were chosen as the starting material to react with BnNHOH·HCl since all these compounds are commercially available and the *N*-benzyl group is convenient to handle for the following manipulation. Addition of a stoichiometric amount of BnNHOH to the alkyne in sodium acetate-buffered methanolic medium was achieved in less than 5 min at rt (Scheme 1). The intermediate 2-(*N*-benzyl-*N*-hydroxyamino)butendioate underwent a rapid *N*-hydroxy-enamine−nitrone tautomerization to afford nitrone **2c**,**d** which could be obtained as an oily liquid stable at rt. When a sample of **2c** was heated under argon in toluene for 3 days at 110 °C, no decomposition was detected by ^{1}H NMR. Interestingly, nitrones **2c**,**d** exist at rt in solution of $CDCl_3$ as a unique isomer as shown by ^{1}H NMR (all H−C sp^3 proton signals are singlet, and only one set of these signals was observed). Considering the absence of a NOESY correlation peak between H^{CH2Ph} and $H^{CH2COOMe}$, we thought that these nitrones would adopt a stable *E* configuration. This hypothesis could agree with the fact that the *Z*-isomer encounters two unfavorable interactions including steric interaction between *N*-benzyl and CH_2COOR moieties and repulsion between two negatively charged oxygen atoms of nitrone and 1-carboxylate groups (Figure 1). In contrast, the *E*-isomer appears to be more stable as its

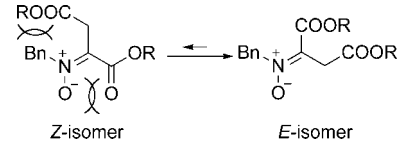


Figure 1. Rationale for the stability of the *E*-isomer.

structure could minimize these unfavorable interactions.

With **2c**,**d** in hand, we investigated the cycloaddition reactions with representative alkenes (Table 1) as dipolarophiles: simple alkenes **3a**,**b**, functionalized alkenes **3c**−**e**, electron-deficient alkenes **3f**,**g**, and electron-rich alkenes **3h**−**k**. In most cases, cycloaddition of nitrones **2c**,**d** gave high yields of expected isoxazolidines **4** (except toward **3b**,**k**) and exhibited a total regioselectivity.

Not surprisingly, reaction times varied considerably depending on the substrate. In general, electron-deficient dipolarophiles **3f**,**g** reacted most rapidly, leading to completion of the reaction after only 4−16 h at 80 °C (entries 6 and 7). Simple alkene **3a** (entry 1) and electron-rich alkenes **3h**−**j** reacted notably more slowly (entries 8−10). Allyl alcohol **3c** gave total conversion only after 10 h at 80 °C (entry 3), more rapidly than its acetate ester **3d** (entry 4) or its homologue **3e** (entry 5). This enhanced reactivity would be possibly due to the formation of a hydrogen bond between the OH group of **3c** and ester oxygens of **2c** in the transition state that could reduce the activation barrier. When the OH group is located further from the reaction site, this assistance would be less effective. Cyclic alkenes **3b**,**k** failed to react probably because of unfavorable steric interaction in the transition state (entries 2 and 13).

The diastereoselectivity was moderate in most cases but, interestingly, very high in the case of alkyl vinyl ethers **3i**,**j** (entries 9−12, Table 1). The corresponding adducts **4i**−**l** were thus obtained as a mixture 92:8 to 98:2 in which the major adducts possess a *trans* relationship between COOR and alkoxy moieties, possibly resulting from an *exo*-selective 1,3-DC reaction involving the nitrones **2c**,**d** in an *E* configuration.

This common relative configuration was readily assigned on the basis of spectral data, including 2D COSY and NOESY NMR spectra, as exemplified in Figure 2 for major adduct **4i**. The presence of three NOESY correlation peaks between H-5 and H-4β, H-4α and H-1, and H-4α and H-2, together with the absence of a correlation peak between H-5 and H-4β, and between H-4β and H-2 helped to deduce the

(12) For the only example of 1,3-DC reaction to our knowledge, between **2a** and 1-tridecene, see: Chiacchio, U.; Piperno, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1998**, *54*, 5695. For the formal 1,3-DC reaction of an α,α-disubstituted nitrone to alkynes, see: (a) Cantagrel, F.; Pinet, S.; Gimbert, Y.; Chavant, P. Y. *Eur. J. Org. Chem.* **2005**, 2694. (b) Pernet-Poil-Chevrier, A.; Cantagrel, F.; Le Jeune, K.; Philouze, C.; Chavant, P. Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1969.

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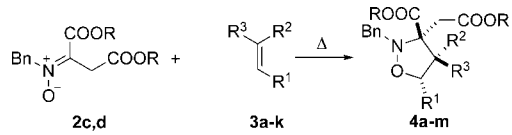
Table 1. Thermal 1,3-Dipolar Cycloaddition Reactions of Nitrones **2c**,**d** with Dipolarophiles **3a**−**j**



2c,d 3a-k 4a-m

entry	nitrone	R	alkene	R^1	R^2	R^3	equiv alkene/conditions	adduct	diastereomeric ratio[a]	yield (%)[b]
1	**2c**	Me	**3a**	*n*-C_5H_{11}	H	H	10/toluene, 110 °C, 76 h	**4a**	73:27	95
2	**2c**	Me	**3b**	-$CH_2(CH_2)_2CH_2$-	H	H	10/toluene, 110 °C, 120 h	**4b**	-	0
3	**2c**	Me	**3c**	CH_2OH	H	H	10/80 °C, 10 h	**4c**	50:50	97
4	**2c**	Me	**3d**	CH_2OAc	H	H	10/80 °C, 48 h	**4d**	63:37	96
5	**2c**	Me	**3e**	$(CH_2)_2OH$	H	H	10/100 °C, 72 h	**4e**	62:38	93
6	**2c**	Me	**3f**	COOMe	H	H	10/80 °C, 16 h	**4f**	52:48	96
7	**2c**	Me	**3g**	COOEt	H	COOEt	2/80 °C, 4 h	**4g**	72:28	97
8	**2c**	Me	**3h**	OAc	H	H	2/80 °C, 48 h	**4h**	80:20	89
9	**2c**	Me	**3i**	OEt	H	H	10/80 °C, 72 h	**4i**	92:8[c]	95
10	**2c**	Me	**3j**	O-*t*-Bu	H	H	3/80 °C, 72 h	**4j**	98:2[c]	92
11	**2d**	*t*-Bu	**3i**	OEt	H	H	10/80 °C, 72 h	**4k**	95:5[c]	99
12	**2d**	*t*-Bu	**3j**	O-*t*-Bu	H	H	3/80 °C, 72 h	**4l**	98:2[c]	99
13	**2c**	Me	**3k**	-$O(CH_2)_2CH_2$-		H	10/90 °C, 120 h	**4m**	-	0

[a] Determined by ^{1}H NMR 400 MHz of the crude product. [b] Isolated yield [c] *trans* configuration assigned to the major isomer.

trans relationship between ethoxy and carbonyloxymethyl moieties in major adduct **4i**.

Possibly resulting from an *exo*-selective approach of dipolarophiles **3i**,**j** on *E*-nitrones **2c**,**d**, the level of *trans* stereocontrol observed for adducts **4i**−**l** is notably higher than any other *trans* stereocontrol ever obtained in the uncatalyzed 1,3-dipolar cycloaddition between alkyl vinyl ethers and activated acyclic nitrones.[16,17] Interestingly, this level of stereocontrol is comparable to those obtained with (*E*)-geometry-fixed activated nitrones.[18] It must be also mentioned that such a high *trans* selectivity was rarely observed under Lewis acid conditions which could favor the *endo* approach of a chelated acyclic (*Z*)-nitrone: as shown by Tamura's group with Eu(fod)$_3$, high *trans* selectivities with α-alkoxycarbonylnitrones required the use of a bulky diphenylmethyl N-protecting group.[17]

Encouraged by this favorable stereochemical outcome, we searched for an asymmetric extension (diastereofacially selective) of such a 1,3-dipolar cycloaddition since it could represent a promising starting point for the enantioselective synthesis of highly functionalized derivatives containing a quaternary stereogenic center.

The first approach was attempted with the achiral nitrone **2a** and the chiral vinyl ethers **3l**−**n** (Table 2) derived from (−)-menthol, D-(−)-pantolactone, and (*R*)-methyl mandelate. Interestingly, in all cases, the cycloaddition gave the desired adducts in excellent yields (90−96%) and with a good-to-high *trans* selectivity and global *trans*:*cis* ratios ranging from 5:1 to 19:1.

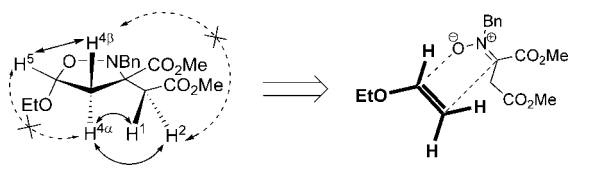
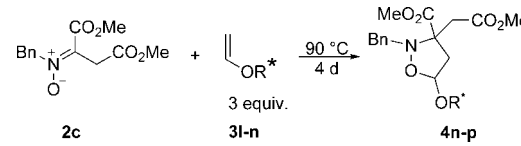
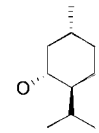
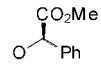
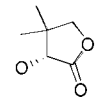


Figure 2. 2D NOESY correlation for major adduct **4i**.

Table 2. Cycloaddition of Nitrone **2c** with Alkenes **3l**−**n**



2c 3l-n 4n-p

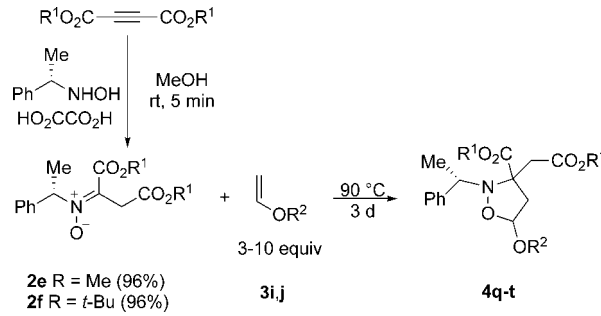
entry	alkene	OR*	adduct	diastereomeric ratio[a] *trans*1:*trans*2:*cis*1:*cis*2	yield (%)[b]
1	**3l**		**4n**	50:45:5:0	95
2	**3m**		**4o**	49:46:5:0	96
3	**3n**		**4p**	68:16:16:0	90

[a] Determined by ^{1}H NMR of the crude product. [b] Isolated yield.

However, a diastereofacial selectivity for the *trans* adduct was observed in the sole case of *O*-vinyl pantolactone **3n**,

(16) Jensen, K. B.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.

Table 3. Cycloaddition of Nitrones **2e**,**f** with Alkenes **3i**,**j**



entry	nitrone	R^1	alkene	R^2	adduct	diastereomeric ratio[a] *trans*1:*trans*2:*cis*1:*cis*2	yield[b] (%)
1	**2e**	Me	**3i**	Et	**4q**	69:31:0:0	99
2	**2e**	Me	**3j**	*t*-Bu	**4r**	72:28:0:0	92[c]
						96:4:0:0	53[d]
3	**2f**	*t*-Bu	**3i**	Et	**4s**	67:33:0:0	99
4	**2f**	*t*-Bu	**3j**	*t*-Bu	**4t**	72:28:0:0	97

[a] Determined by ^{1}H NMR of the crude product. [b] Isolated yield. [c] Global yield of isolated adduct **4r**. [d] Isolated yield of major adduct **4r** after diastereomeric separation.

with a 4.3:1 ratio (entry 3). Unfortunately, in this critical case, the major *trans* adduct **4p** could not be separable by column chromatography.

The second approach was made with achiral vinyl ethers **3i**,**j** and chiral nitrones **2e**,**f** bearing a chiral N-protecting group such as α-methylbenzyl. These nitrones were prepared in excellent yields in the same manner by addition of (*S*)-α-methylbenzylhydroxylamine[19] to the corresponding dialkyl dicarboxylates **1a**,**b**. Interestingly, the thermal 1,3-DC reaction of these nitrones was carried out smoothly at 90 °C and led to the desired adducts after 3 days with excellent yields and total *trans* selectivity. An increase of bulkiness of the nitrone N-protecting group (Table 1, entries 9−12 vs Table 3, entries 1−4) seems to improve the overall *trans* selectivity. This fact is in good agreement with our rationale for the stability of the *E*-isomer (Figure 1) and our hypothesis of an *exo*-selective approach.

The facial selectivities were found to be moderate, with an approximate 7:3 ratio whatever the vinyl ether used. Replacing the methyl group of the ester functions with more hindered *t*-Bu did not modify this selectivity. This facial differentiation could be limited by free rotation around the C−N bond of the chiral nitrone. However, the mixture of cycloadducts was separable in the more favored case (entry 2, Table 3) to afford the major *trans* adduct **4r** in good isolated yields.[20]

In this study, N-protected nitrones **2c**−**f** were synthesized in excellent yields by a simple addition of *N*-benzylhydroxylamines to the corresponding dialkyl acetylenedicarboxylates. Their 1,3-dipolar cycloaddition reactions with alkenes afforded a set of original isoxazolidines in excellent yields and regioselectivities under thermal cycloaddition. These original cycloadducts **4**, obtained in two steps from commercial sources in 85−97% global yields, could be considered as a masked form of α,α-disubstituted α-amino acids bearing two different functionalized side chains. In the cases of alkyl vinyl ethers, valuable *trans* selectivities were observed. Asymmetric versions have been tried with chiral nitrones or chiral alkyl vinyl ethers, resulting in excellent yields and good to excellent *trans* selectivities. If facial control proved to be never better than moderate, the use of a chiral aspartate nitrone was found to lead to a first **4**-type adduct with high enantio- and diastereopurity. Further application of these promising adducts is currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Absolute configuration not yet determined.