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Synthesis of 2-Isoxazolines From Olefins Derived From Norephedrine And Pulegone

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Abstract: In this communication we report the use of (±)-norephedrine and (-)-8-benzylaminomenthol (derived from (+)-pulegone) as chiral adjuvants for the cycloaddition of α,β-unsaturated 1,3-dipolarophiles. 2-Isoxazolines were obtained with low stereoselectivity from the reaction of nitrile oxides with the N-tosyl norephedrine derivative as the dipolarophile. Cycloaddition of nitrile oxide with 2-vinyl-N-benzyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine produced stereoisomeric 2-isoxazolines in a ratio of about 95:5.

Keywords: amino alcohols; asymmetric induction; cycloadditions; isoxazolines

Substituted 2-isoxazolines are an important class of heterocycle, as they can be selectively transformed into 1,3-amino alcohols or β-hydroxy ketones which are useful intermediates in the total synthesis of a wide variety of natural products.[1] It is known that monosubstituted olefins exhibit high regioselectivity in 1,3-dipolar cycloadditions with nitrile oxides to give 5-substituted 2-isoxazolines as the major product.[1] Furthers stereoselective cycloadditions with a high level of asymmetric induction have been reported by Ukaji, Curran, Oppolzer, Kim, and Olsson.[2] Nonetheless, a mixture of 2-isoxazolines regioisomers generally results if unsymmetrical 1,2-disubstituted olefins including α,β-unsaturated esters and ketones are used. The diastereoselectivity in these 1,3-dipolar cycloadditions is also much lower.[1,2b,c,d] Kanemassa and Ukaji have reported better regio- and stereoselectivity in the 1,3-dipolar cycloaddition involving magnesium crotyl alcoholate[3a] and allylic alcohol[3b] by the coordination of benzonitrile oxide with magnesium or zinc ions. The use of α,β-unsaturated aldehydes is restricted due to the formation of a *bis*-cycloadduct resulting from the addition of nitrile oxide to the carbaldehyde group of the initial 2-isoxazoline product.[4a] This problem is alleviated by the use of β-substituted α,β-unsaturated aldehyde equivalents (i.e. acetals and thioacetals). Interestingly, these dipolarophiles are highly regioselective and afford predominantly 2-isoxazolines bearing an acetal group at the C-4 position[4b] or a 2-isoxazoline with a dithiane group at the C-5 position.[4c] In this communication, we report the use of (±)-norephedrine and (+)-pulegone as carbonyl protecting groups. This choice fulfills the following requirements: commercial availability of both

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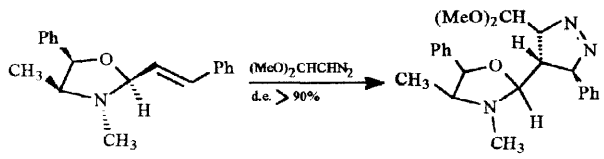
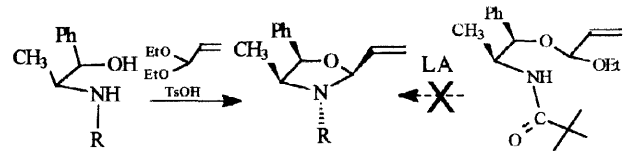
enantiomeric forms of the chiral auxiliary and a high degree of Π-face differentiation in other asymmetric processes.[5] For example, ephedrine has been used as a chiral adjuvant to cinnamaldehyde to induce a high level of asymmetry during a 1,3-dipolar cycloaddition with 1,1-dimethoxy-2-diazomethane (**Scheme 1**).[5a] Thus, it was anticipated that the cycloaddition of 2-alkenyl oxazolidine (derived from (±)-norephedrine) using various nitrile oxides as the dipole should proceed with equal facial selectivity.

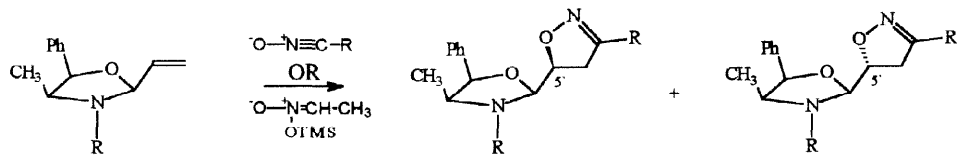


Scheme 1



Scheme 2 **1a-f** **2a-f** **5**

N-Substituted oxazolidines **2a-f** were prepared from the corresponding N-substituted (±)-norephedrines **1a-f** following literature procedures (**Scheme 2**).[6] In the case of the N-pivaloyl derivative **1e**, a diastereomeric mixture of the uncyclized **5** was obtained in 89% yield.[7] The N-pivaloyl oxazoline derivative **2e** was obtained in low yield from the condensation of (±)-norephedrine with acrolein followed by the addition of pivaloyl chloride to the oxazoline formed *in situ*.[8] Olefins **2a-f** were treated with acetonitrile oxide or benzonitrile oxide generated *in situ* under various reaction conditions. The results are summarized in Table 1.



2a-f **3a-f** **4a-f**

Table 1 1,3-Dipolar Cycloaddition of **2a-f** with acetonitrile oxide and phenylnitrile oxide.

No.	Dipolarophile **2a-f**	Dipole Method (eq)	Additive (eq)	Yield[d] (%)	Adduct Ratio (%)[e] (**3a-f : 4a-f**)
		Acetonitrile oxide			
1	**2a**, R=CH_3	b (10)	-	-	
2	**2b**, R=$COCH_3$	a;b;c (2; 5; 2)	-	-	
3	**2c**, R=$CO_2CH_2CF_3$	b (1)	-	28	1 : 1
4	**2d**, R=CO_2iPr	b (10)	-	45	1 : 1
5	**2e**, R=CO_2t-Bu	b (10)	-	57	1 : 1
6	**2f**, R=Ts	a (1.2)	-	31	1 : 1
7	**2f**, R=Ts	b (10)	-	50	1.5 : 1
8	**2f**, R=Ts	b (10)	$MgBr_2•Et_2O$(10eq)[9b]	29	1.3 : 1
9	**2f**, R=Ts	c (6)	$MgBr_2•Et_2O$(1eq)	22	1.4 : 1
10	**2f**, R=Ts	c (5)	$ZnCl_2$ (6eq)	11	1 : 1
		Phenylnitrile oxide			
11	**2f**, R=Ts	b (3)	-	52	1.1 : 1
12	**2f**, R=Ts	b[3a] (10)	MgBrCl(10eq)[9a]	15	1 : 1

a) To a solution of **2a-f** in benzene at RT was slowly added nitroethane, phenylisocyanate and Et_3N in catalytic amounts.
b) To a solution of RCCl=NOH was slowly added a stoichiometric amount of Et_3N, **2a-f** (1eq) in CH_2Cl_2 and the Lewis acid.
c) To a solution of **2a-f** (1eq) in CH_2Cl_2 was added the trimethysilyl ester of aci-nitroetane and the Lewis acid.
For a, b, and c, the reagents were added at 0°C, followed by stirring overnight at room temperature.
d) Isolated yield. e) Determined by ^1H NMR and ^{13}C analysis of the crude reaction mixture.

While the N-methyl and N-acetyl derivatives were found to be unsuitable using the reaction conditions required to generate the nitrile oxide (i.e. by method a, b or c), the carbamate and N-tosyl derivatives led to a mixture of the two epimers at C-5` (i.e. **3a-f** and **4a-f**).[10,11] Method **b**, involving the base conversion of excess α-chloro oxime into nitrile oxide gave higher conversion yields. We observed no asymmetric induction for the carbamate substituent (entry 3-5), while the N-tosyl group gave **3f** with 20% *de* (entry 7-10). Unfortunately, the addition of a Lewis acid had no effect other than to decrease the chemical yield.[9] The stereochemistry of **3f** was unambiguously determined by X-ray diffraction analysis, and in solution, the results of nOe experiments for **3f** and **4f** were consistent with the relative stereochemistry as depicted in ***Figure 1***. From inspection of ***Figure 1***, we attributed the low level of asymmetric induction to the *trans* relationship between the N-tosyl and the C-2 vinyl groups. This leaves the face of the olefin opposite to the tosyl group accessible for a cycloaddition for each reactive conformer.

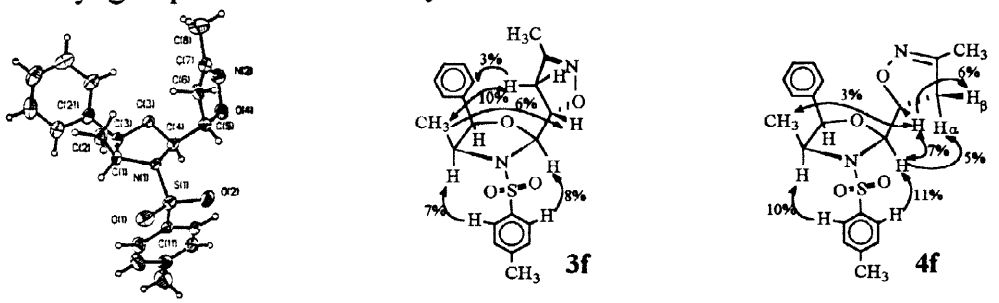
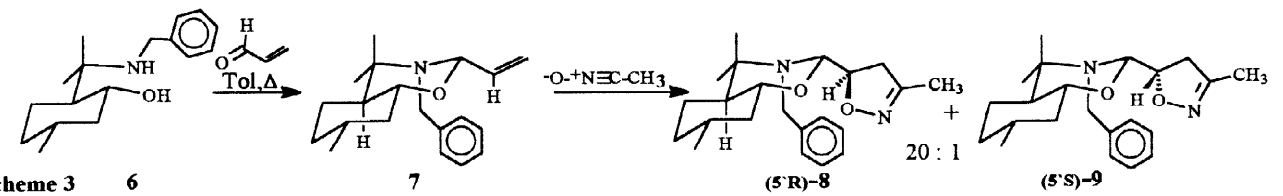


Figure 1 Left: X-ray crystal structure of isoxazoline **3f**. Right: Relevant nOe signals in **3f** and **4f**.

Having demonstrated that oxazolidines can serve as chiral adjuvants for α,β-unsaturated 1,3-dipolarophiles we decided to use a more conformationally rigid auxiliary such as the *trans*-fused octahydrobenzoxazine **7**, derived from (+)-pulegone. Eliel`s[12a] procedure for the preparation of (-)-8`-benzylaminomenthol **6**, was used followed by the condensation of **6** with acrolein to afford **7**.[12b] The conformation of the equatorial C-2 vinyl group and the axial N-benzyl residue was confirmed by nOe experiments.[13] The 1,3-dipolar cycloaddition of acetonitrile oxide with **7** gave a mixture of diastereomers **8** and **9**, and was found to be highly stereoselective (i.e., 90% *de* in favor of **8**, see **Scheme 3**). The absolute stereochemistry at the C-5` center for the epimeric



Scheme 3 **6** **7** **(5`R)-8** **(5`S)-9**

2-isoxazolines **8** and **9** is supported by nOe experiments.[13] Assuming that the reactive conformation in the cycloaddition is close to that highly favored in the ground state, the (5`R) stereochemistry of the major epimer **8** is readily explained by the cycloaddition of the nitrile oxide on the *Re*-face of the olefin, **7**, opposite to the N-benzyl substituent.

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7. The intermediate **5** shows an absorption band at 3286 cm^{-1} in the IR and two resonances at δ 6.25 (s) and 6.28 (s) in the ^1H NMR spectrum for the free N-H function. Attempts to cyclize **5** to its corresponding isoxazoline, **2e**, under acidic conditions led to decomposition (i.e. PPTs, TsOH, $BF_3 \bullet Et_2O$).
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9. a) While we found an acceleration and a good regiocontrol for the cycloaddition of Ph-C≡N^+-O$^-$MgBr to crotyl magnesium alcoholate, the use of Ph-C≡N^+-O$^-$MgBr as described by Kamenasa[3a] had no effect on product distribution and a low conversion yield was observed. b) In the case of the reaction with CH_3-C≡N^+-O$^-$MgBr generated under the same conditions no cycloaddition took place.
10. All new compounds gave the correct high resolution mass spectra and suitable spectroscopic data (ir, nmr, ms). The crystallographic structure for **3f** will be published in *Acta Crystallographica*.
11. Spectroscopic data for isoxazoline **4f**; ^1H NMR ($CDCl_3$): δ 7.84 (d, 2H, *J*=8.2, Ar), 7.39 (d, 2H, *J*=8.5, Ar), 7.27 (m, 3H, Ar), 7.13 (dd, 2H, *J*=1.7, *J*=7.8, Ar), 5.16 (d, 1H, *J*=3.3, H-2), 4.88 (dq, 1H, $J_{5'\text{-}2}$=3.7, $J_{5'\text{-}4'\alpha}$=6.6, $J_{5'\text{-}4\beta}$=10.6 H-5'), 4.34 (d, 1H, *J*=5.5, H-5), 4.16 (t, 1H, *J*=6.6, *J*=6.0, H-4), 3.23 (dd, 1H, $J_{4'\alpha,5'}$=6.4, *J*=17.5, H-4'α), 3.13 (dd, 1H, $J_{4'\beta5'}$ =10.8, *J*=17.2, H-4'β), 2.47 (s, 3H, Ph-CH_3), 2.07 (s, 3H, CH_3-3'), 0.86 (d, 3H, *J*=6.8, CH_3-4); ^{13}C NMR: δ 130.1 (Ar), 128.1 (Ar), 128.3 (Ar), 127.9 (Ar), 126.1 (Ar), 155.4 (Ar), 144.6 (Ar), 135.1 (Ar), 134.9 (Ar), 91.1 (C2), 81.8 (C5), 80.4 (C5'), 58.7 (CH-4), 40.5 (C4'), 21.7 (CH_3-Ar), 16.7 (CH_3-3'), 13.0 (CH_3-4).
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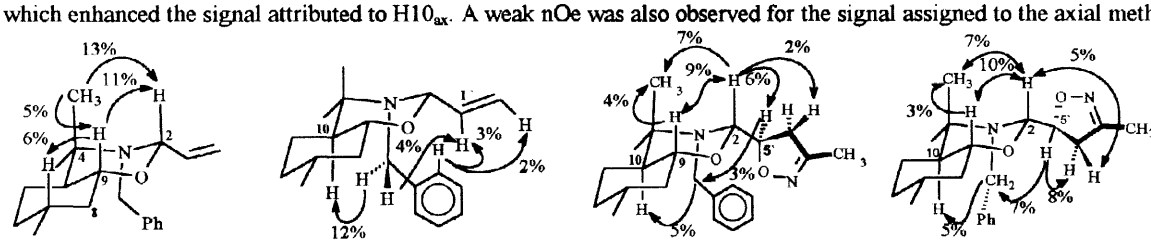
13. Eliel and Pedrosa first reported an equatorial [12a,c,e] and later an axial[12b,d] stereochemistry for the N-benzyl group in 2-alkyl perhydrobenzoxazines similar to **7**. We found that the irradiation of benzylic protons in **7**, **8** and **9** caused a strong nOe which enhanced the signal attributed to $H10_{ax}$. A weak nOe was also observed for the signal assigned to the axial methyl at C4.



7 **7a** **(5'R)-8** **(5'S)-9**

Based on these results, we concluded that the N-benzyl substituent is located mainly in the axial position. An axial position for proton H-2 in compounds **7**, **8** and **9** is supported by the observation of nOe enhancement of the signals attributed to $H\text{-}9_{ax}$ and the axial methyl at C-4. The C-2 vinyl group is therefore in the equatorial position. The assignation of resonances for H-2, 8, 9 and 10 was supported by COSY and HMQC cross peak correlations.