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1,3-Dipolar Cycloaddition of Enantiopure γ-Oxygenated-α,β-Unsaturated Phenyl Sulfones with Nitrile Oxides†

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Abstract:. The 1,3-dipolar cycloadditions of several enantiopure γ-oxygenated-α,β-unsaturated sulfones with acetonitrile and benzonitrile oxides have been studied. The reactions occurred at room temperature with moderate yields (31-65%), complete regioselectivity in favour of the isoxazolines with the phenylsulfonyl group at C-4, and moderate or high *anti*-stereoselectivity. After reductive elimination of the sulfonyl group and further reduction of N-O bond, enantiomerically pure β-hydroxyketones or 1,3-aminoalcohols were obtained.

Although not so thoroughly studied as the asymmetric Diels-Alder reaction, asymmetric 1,3-dipolar cycloadditions have received considerable attention during the last years.[1] Specially, nitrile oxides are among the most useful 1,3-dipoles due to their easy "in situ" preparation, their remarkable reactivity and the great synthetic interest of the resulting isoxazolines as versatile intermediates in organic synthesis.[2] For instance, reductive cleavage of isoxazolines can be controlled to give either γ-amino alcohols or β-hydroxyketones. The last transformation stands as a very interesting alternative to the aldol condensation.

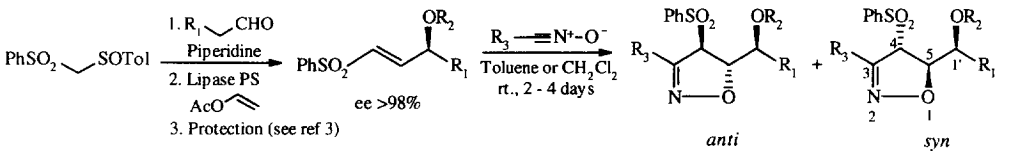
In connection with our current interest concerning the use of the readily available enantiomerically pure γ-hydroxy-α,β-unsaturated phenyl sulfones as versatile starting materials in asymmetric synthesis,[3] we describe herein some examples of their 1,3-dipolar cycloadditions with nitrile oxides. Moreover, it is interesting to note that the 1,3-dipolar cycloaddition between nitrile oxides and vinylsulfones has scarcely been studied even with achiral vinylsulfones.[4] To the best of our knowledge, there are not precedents of the use of chiral vinylsulfones in this kind of cycloaddition.

In the table are shown the results obtained in the 1,3-dipolar cycloaddition of several enantiopure γ-oxygenated-α,β-unsaturated sulfones with acetonitrile oxide[5] and benzonitrile oxide.[6] The substrates (*S*)-**1** to (*S*)-**4** were prepared following our usual procedure: condensation of phenylsulfonyl *p*-tolylsulfinyl methane with an aldehyde,[3d] further Lipase PS mediated enantioselective acetylation,[3c] and subsequent protection of the hydroxyl group.

Reactivity: All substrates reacted at room temperature but, although a great excess of dipole was used (2-4 equiv), the reactions were not complete (conversions of 36-68%) due to the competitive dimerization of the nitrile oxide to give furoxans. Longer reaction times, higher temperatures or very slow addition of the nitrile oxide precursors did not afford significantly better conversions.[7] The resulting ixozazolines **5-10** and the unreacted vinylsulfones **1-4** were readily separated by flash chromatography, affording good yields of transformed products. As it can be deduced from entries 1-3, the protection of the hydroxyl group as the MOM

derivative is more suitable than the protection as the acetate or the TBDMS derivative in terms of conversion and yields.

Table. Reaction of (*S*)-**1** to (*S*)-**4** with nitrile oxides:



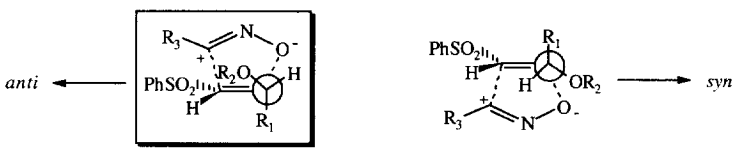
Entry	Substrate	R_1	R_2	R_3	Conversion (%)[a]	Product	*anti:syn*[a]	Yield (%)[b]
1	(*S*)-**1**	*i*-Pr	Ac	Me	60	**5**	1:1	59 (78)
2	(*S*)-**2**	*i*-Pr	TBDMS	Me	36	**6**	>15:1	31 (45)[c]
3	(*S*)-**3**	*i*-Pr	MOM	Me	68	**7**	>15:1	65 (93)
4	(*S*)-**3**	*i*-Pr	MOM	Ph	57	**8**	3:1	48 (75)
5	(*S*)-**4**	Et	MOM	Me	59	**9**	5:1	52 (89)
6	(*S*)-**4**	Et	MOM	Ph	57	**10**	3:1	[d]

[a] Determined by ^{1}H-NMR on the crude mixtures. [b] In pure isoxazolines after flash chromatography. In brackets are shown the yields in converted product after recuperation of unreacted substrates (*S*)-**1** to (*S*)-**4**. [c] After desilylation with $Bu_4N^+F^-$. [d] (*S*)-**4** and **10** could not be completely separated by flash chromatography.

Regioselectivity: Unlike other previously reported 1,3-dipolar cycloadditions of nitrile oxides to vinylsulfones affording mixtures of both regioisomers,[4] the reactions shown in the table were highly regioselective, the only regioisomers detected by ^{1}H-NMR being those with the phenylsulfonyl group at C-4.

Stereoselectivity: The stereoselectivity was dependent on the nature of substituents R_1, R_2, and R_3; however with the exception of entry 1, which afforded a nearly equimolecular mixture of *syn/anti* adducts, the *anti* adduct always predominated and in the cases of entries 2 and 3 was the only adduct detected by ^{1}H-NMR (*anti:syn* >15:1[8]). It is also observed that the cycloadditions from benzonitrile oxide are less stereoselective than those from acetonitrile oxide (compare entries 3/4 and 5/6).

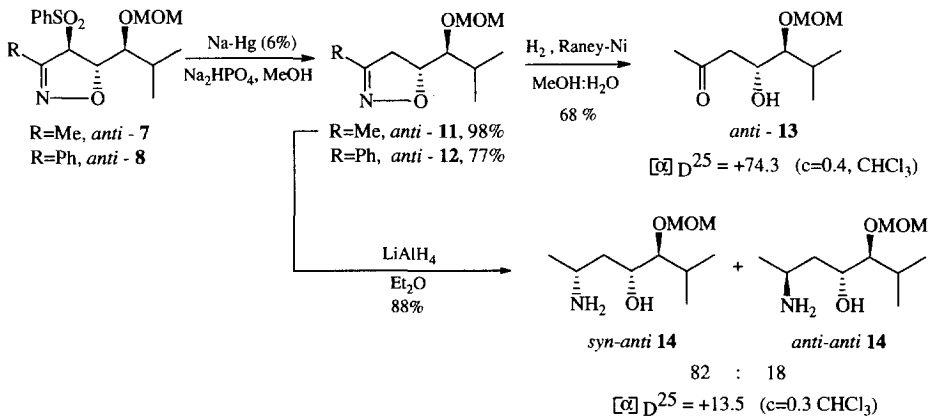
The formation of the major *anti* adducts is in agreement with the Houk's model for the most favourable transition state of the 1,3-dipolar cycloaddition[9] of nitrile oxides to allylic alcohol derivatives (see figure).



On the other hand, in order to check that the enantiomerically pure substrates **1-4** were configurationally stable under the reaction conditions, the enantiomerical purity of one of the adducts was measured. The enantiomeric excess of *anti*-**7** was very high (ee> 98%, determined by ^{1}H-NMR in the presence of 0.4 eq. of $Pr(hfc)_3$), demonstrating that there is no epimerization of (*S*)-**3** before cycloaddition.[10] Accordingly, the optical rotation of the recovered substrates (*S*)-**1** to (*S*)-**4**, obtained after purification of the crude cycloaddition mixtures, remained unaltered.

Transformation of the adducts: Interestingly, the phenylsulfonyl group of the isoxazolines can be reductively eliminated without breaking the N-O bond by reaction with Na-Hg. Treatment of *anti*-**7** and *anti*-**8** with excess of Na-Hg (6%, MeOH, Na_2HPO_4, rt or 0°C, 1h) afforded *anti*-**11** and *anti*-**12** in 98% and 77% yields respectively. Further hydrolytic reduction of *anti*-**11** with H_2/Raney nickel[11] (MeOH-H_2O, H_3BO_3, rt, 4h) provided the corresponding acyclic enantiomerically pure β-hydroxyketone *anti*-**13** (68% yield).

Additionally, the reduction of *anti*-**11** with $LiAlH_4$[12] (Et_2O, rt, 3h) gave a 82:18 mixture of the *syn-anti*/*anti-anti* isomers[13] **14** in 88% yield (see scheme).



In summary, the 1,3-dipolar cycloaddition of enantiomerically pure γ-alkoxyvinylsulfones with acetonitrile oxide and benzonitrile oxide occurred with moderate conversions (good yields in transformed product), complete regioselectivity in favour of isoxazolines with the phenylsulfonyl group at C-4 and moderate or high *anti*-stereoselectivity depending on substrates. The phenylsulfonyl group of the isoxazolines can be readily removed by reduction with Na-Hg and the products can be transformed following the usual methods into enantiomerically pure β-hydroxyketones or 1,3-aminoalcohols.

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References and Notes

† In memory of Prof. Francisco Fariña.

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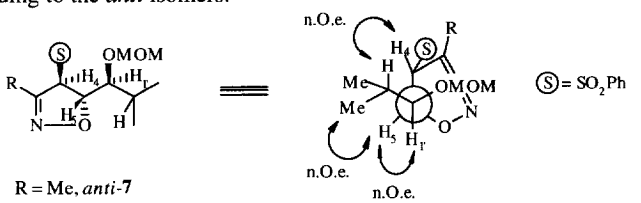
5. Generated *in situ* from nitroethane and phenyl isocyanate in the presence of a catalytic amount of Et_3N (in toluene) according to the Mukaiyama procedure (Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339).
6. Generated *in situ* by dehydrochlorination with NaOCl of benzohydroximinoyl chloride in CH_2Cl_2 (Huisgen method, Huisgen.R; Hack, W; Annseser, E. *Angew. Chem.* **1961**, *73*, 616). See for instance: Armstrong, S. K.; Collington, E. W.; Knight, J. G.; Naylor, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 443.
7. To minimize the effect of the dipole dimerization, the best yields (those given in table) were obtained by sequential addition of 1 equivalent of nitrile oxide precursors during the reaction period.
8. The stereochemical assignment as *anti* isomers of the major cycloadducts was proposed by ^{1}H-NMR, specially from the value of the coupling constant $^3J_{5,1'}$ and NOESY experiments. Thus, in the major adducts **7** and **8**, the value of $^3J_{5,1'}$ and the presence of strong n.O.e effects between the pairs of hydrogens $H_5/H_{1'}$, H_5/CH_3 (of *i*-Pr group), and H_4/CH (of *i*-Pr group) is indicative of the conformation indicated below, corresponding to the *anti* isomers.



R = Me, *anti*-**7**
R = Ph, *anti*-**8**

anti-**7**: $J_{5,1'}$ = 3.8 Hz
anti-**8**: $J_{5,1'}$ = 4.5 Hz

Moreover, the value of $^3J_{5,1'}$ (between 3.2 and 4.5 Hz) for adducts *anti*-**6** - *anti*-**10** agree with the values reported in the literature for related *anti*-adducts obtained in the cycloaddition of nitrile oxides with allylic alcohol derivatives. See for instance: a) Zhang, J.; Curran, D.P. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2627. b) Jäger, V; Schöter, D. *Synthesis* **1990**, 556. See also ref. 1a and 11d.

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13. The configurational assignment of the 1,3-amino alcohols *syn/anti*-**14** and *anti/anti*-**14** has been established by ^{1}H-NMR according to the criteria reported by Jäger et al.: see ref. 12 b.

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