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1,3-Dipolar cycloadditions of prop-1-ene-1,3-sultone with nitrile oxides/nitrones

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Abstract—The scope and limitations of dipolar cycloaddition reactions between nitrile oxides/nitrones and prop-1-ene-1,3-sultone have been investigated. A remarkably high degree of regioselectivity and stereoselectivity was observed. The homochiral sultam **8e** was synthesized in a four-step reaction sequence starting from the substituted isoxazoline **4e** obtained from the cycloaddition. The absolute stereochemistry of this material was assigned by an X-ray crystallographic investigation of the intermediate **7e**.

1,3-Dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring carbocycles and heterocycles.[1] Nitrile oxides and nitrones have been shown to be effective 1,3-dipoles and they undergo smooth reactions with substituted olefins.[2] The 1,3-dipolar reaction of alkenes with nitrile oxides and nitrones give substituted isoxazolines and isoxazolidines, respectively. Both classes of heterocycle are versatile intermediates for the syntheses of natural products and biologically active compounds.[3]

To extend the scope of the 1,3-dipolar cycloaddition reactions, the development of new dipolarophiles has attracted the attention of many scientific investigators.[4] In this connection, α,β-unsaturated sultones exemplified by prop-1-ene-1,3-sultone were developed as effective dienophiles in Diels–Alder reactions.[5] Subsequent transformations of the δ-sultone moiety of the cycloadducts allowed the preparation of chiral non-racemic sultams, which were developed as chiral auxiliaries in promoting asymmetric synthesis.[6] To explore fully the synthetic utility of propene sultone in cycloaddition reactions, its reactions as a dipolarophile with nitrile oxides and nitrones have been investigated.

In this paper, we present highly regioselective and stereoselective 1,3-dipolar cycloaddition reactions of propene sultone **3** with nitrile oxides **1** and nitrones **2**. To set the stage for our investigation, the requisite 1,3-dipoles were prepared according to literature routes. Nitrile oxides **1a**–**f** were prepared efficiently from either the corresponding hydroximoyl chlorides or primary nitro compounds via base induced dehydrochlorination and the Mukaiyama reaction, respectively.[7,8]

The labile nitrile oxides generated in situ were allowed to react with propene sultone **3** in toluene at room temperature. Monitored by TLC, nitrile oxides **1a** and **1b** possessing a sterically undemanding alkyl substituent underwent a smooth reaction with the dipolarophile giving the corresponding cycloadducts **4a** and **4b** in high isolated yields (Table 1, entries 1 and 2). Equally good yields of adducts were formed between **1c**–**f** and **3** after a longer period of reaction time. Increased bulkiness of the alkyl or aryl substituents present in the 1,3-dipoles retarded the rate of the cycloaddition reaction. In all cases, only one regioisomeric substituted isoxazoline **4** was obtained, indicating high regioselectivity of the transformation.

The ^{1}H NMR spectra of the adducts are consistent with the structural assignments shown in Scheme 1, which are compatible with the direction of bond polarization of both reactants. The *cis* relationship of the two rings in all adducts is supported by the coupling constant of 8.8–9.6 Hz observable between H_1 and H_2. The relatively downfield shift observed for H_1 and H_4 of **4**

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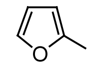
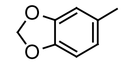
Table 1. Results of the 1,3-dipolar cycloaddition of prop-1-ene-1,3-sultone, nitrile oxides and nitrones

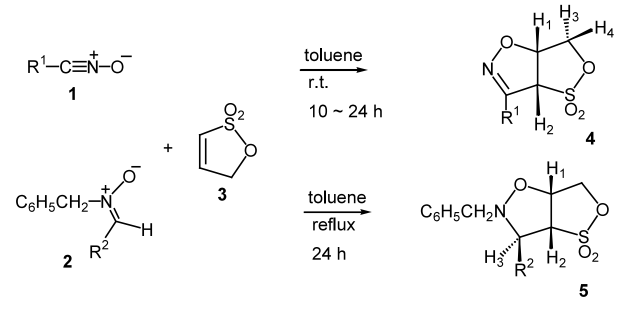
Entry	Dipole	R^1	R^2	Temp. (°C)	Time (h)	Product	Yield (%)[a]
1	**1a**	CH_3	–	22	10	**4a**	81
2	**1b**	C_2H_5	–	22	10	**4b**	83
3	**1c**	$(CH_3)_2CH$	–	22	24	**4c**	74
4	**1d**	$(CH_3)_3C$	–	22	24	**4d**	60
5	**1e**	C_6H_5	–	22	24	**4e**	81
6	**1f**	$CH_3OC_6H_4$	–	22	24	**4f**	78
7	**2a**	–	C_2H_5	120	24	**5a**	75
8	**2b**	–	$(CH_3)_3C$	120	24	**5b**	62
9	**2c**	–	C_6H_5	120	24	**5c**	86
10	**2d**	–		120	24	**5d**	78
11	**2e**	–		120	24	**5f**	72

[a] Isolated yield after flash column chromatographic purification.

favored the regiochemical assignment shown against the alternative structure. An unambiguous structural assignment of the products exemplified by **4e** was established by the X-ray crystallographic analysis as shown in Figure 1.

To exploit further the synthetic utility of our 'house-reagent', **3** was allowed to react in refluxing toluene with nitrones **2a**–**e** which are accessible from benzyl hydroxylamine and the corresponding aldehyde (Scheme 1).[9] Good to excellent yields of the substituted isoxazolidines **5** were obtained after purification by flash column chromatography (Table 1, entries 7–11). In principle, four isomeric products can be formed between nitrones and an unsymmetrical dipolarophile. Thus, it was gratifying to observe that the excellent stereoselectivity and regioselectivity of the 1,3-dipolar cycloaddition led to the formation of only one product. A coupling constant of 2.8 Hz observed between H_2 and H_3 of **5b** is compatible with the H *cis* assignment for H_1, H_2 and R^2. Again, the structural assignment was confirmed by X-ray crystallographic analysis as exemplified by **5c** (Fig. 2).

To demonstrate the synthetic utility of the 1,3-dipolar cycloadducts **4**, their transformations into multifunctional racemic and chiral nonracemic materials were explored (Scheme 2). For instance, under neutral conditions, the β-hydroxyketone **6f** was obtained from Raney nickel reduction of **4f**.[10] Adopting the synthetic protocol previously established in our laboratory for transforming racemic γ-sultones to optically pure γ-sultams, using (*S*)-(−)-α-phenylethylamine as the chiral resolving agent, a 1:1 diastereomeric mixture of **7e** and **7e′** was prepared in a two-step sequence from **4e**.[6a] Careful column chromatography resulted in a clear separation of these two diastereomers. The absolute configuration of the chiral centers in one of the diastereomers, **7e**, was confirmed by X-ray analysis (Fig. 3). Debenzylation of **7e** in refluxing formic acid followed by alkali treatment afforded the chiral sultam **8e** in an overall yield of 68% from **7e**. Evidently, the isoxazoline moiety survived intact under the mild debenzylation conditions. Accord-



Scheme 1. Formation of isoxazolines and isoxazolidines from 1,3-dipolar cycloaddition.

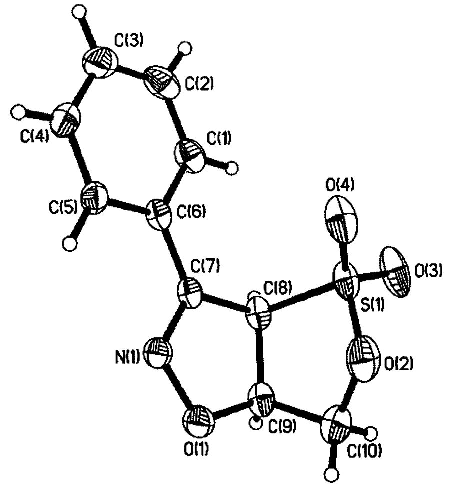


Figure 1. Crystal structure of **4e**.

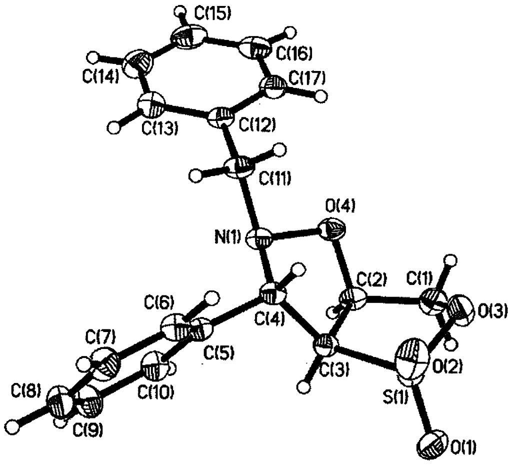
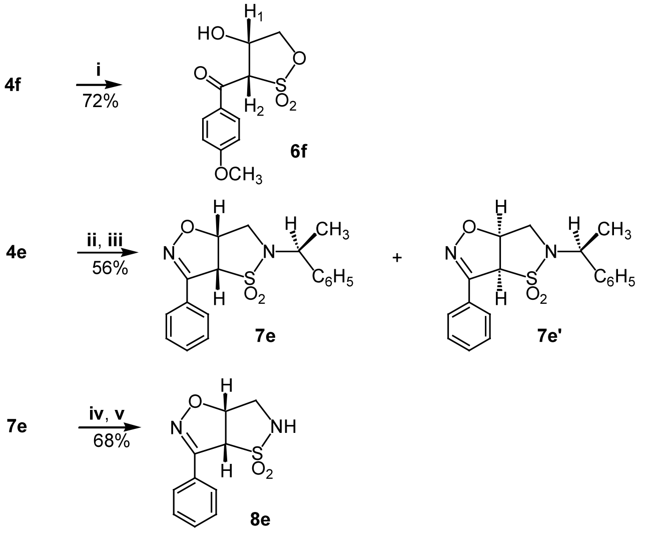


Figure 2. Crystal structure of **5c**.



Scheme 2. Further transformations of cycloadducts: (i) Raney Ni, H_2, 1 atm; (ii) (*S*)-(−)-α-methylbenzylamine, THF, reflux, 24 h; (iii) $POCl_3$, THF, reflux, 48 h; (iv) HCOOH, rt, 2 h; (v) KOH/EtOH, rt, 2 h.

ing to our synthetic protocol, in principle, a variety of multifunctional chiral sultams can be assembled. Their uses as chiral auxiliaries and chiral catalysts in asymmetric synthesis are under investigation.

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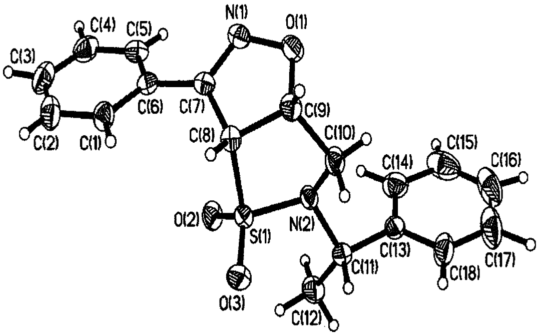

Figure 3. Crystal structure of **7e**.

References

1. (a) Huisgen, R. In *1,3,-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1; (b) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.
2. Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.
3. (a) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048; (b) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1983**, *66*, 1241; (c) Baggiolini, E. G.; Iacobeli, J. A.; Hennesy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098; (d) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 2225.
4. (a) deBlas, J.; Carretero, J. C.; Dominguez, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1035; (b) Louis, C.; Hootele, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2149; (c) Alguacil, R.; Farina, F.; Martin, M. V. *Tetrahedron* **1996**, *52*, 3457.
5. (a) Lee, A. W. M.; Chan, W. H.; Jiang, L.; Poon, K. W. *J. Chem. Soc., Chem. Commun.* **1997**, 611; (b) Jiang, L. S.; Chan, W. H.; Lee, A. W. M. *Tetrahedron* **1999**, *55*, 2245.
6. (a) Chan, W. H.; Lee, A. W. M.; Jiang, L. S.; Mak, T. C. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2501; (b) Lin, J.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y. *Tetrahedron* **1999**, *55*, 13983; (c) Lin, J.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y.; Huang, P. Q. *Tetrahedron Lett.* **2000**, *41*, 2949.
7. Larsen, K. E.; Torssel, K. B. G. *Tetrahedron* **1984**, *40*, 2985.
8. Makaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
9. (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; (b) Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299; (c) Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453.
10. Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.