Tetrahedron Letters,Vol.30,No.49,pp 6919-6922,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

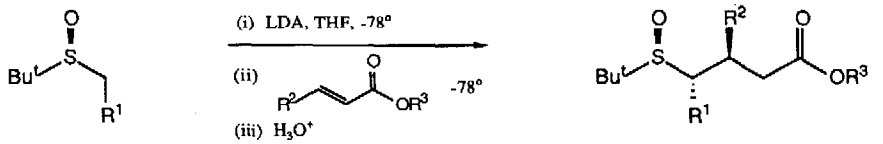
STEREOSELECTIVE CONJUGATE ADDITIONS OF BENZYL SULPHOXIDES TO α,β-UNSATURATED ESTERS

Mike Casey * and Ajith C. Manage
Department of Chemistry and Applied Chemistry, University of Salford, Salford. M5 4WT

Ray S. Gairns
ICI Colours & Fine Chemicals, PO Box 42, Hexagon House, Blackley, Manchester M9 3DA

Summary : Lithiated benzyl sulphoxides react with α,β-unsaturated esters to give the conjugate addition products with excellent stereoselectivity.

We recently reported the first examples of conjugate additions of alkyl sulphoxides to unsaturated esters.[1] These reactions proceed with good selectivity and provide a promising new method for carrying out

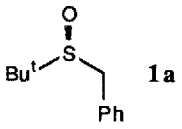
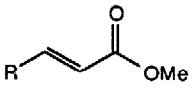
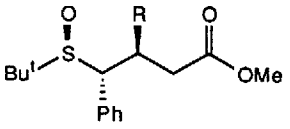
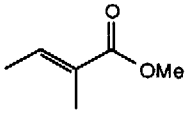
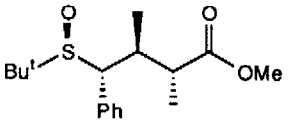
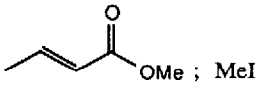
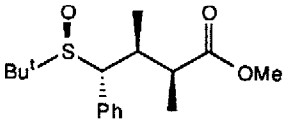
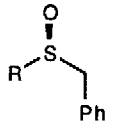
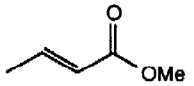
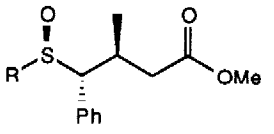
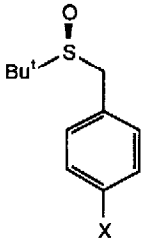
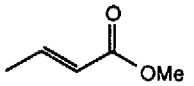
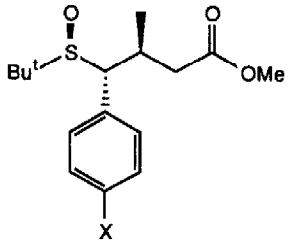
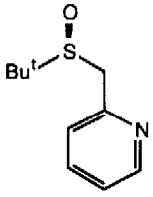
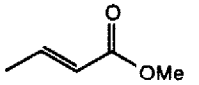
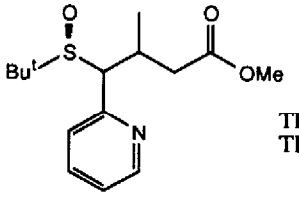


asymmetric conjugate additions. This method is complementary to most existing techniques in that the chiral auxiliary is attached to the nucleophile rather than the electrophile, and is attached to a carbon atom of the product, thus facilitating purification, and providing a site for further reactions. We are continuing to study the use of sulphoxide stabilised carbanions[2] as chiral nucleophiles and now present our work on the addition of benzyl sulphoxides to α,β-unsaturated esters.

Conjugate addition of lithiated benzyl sulphoxides to unsaturated esters and ketones was used as the first step in an annelation method developed by Hauser and Rhee, but the final products were aromatic and no mention was made of the stereoselectivity of the initial addition.[3] The only other example appears to be the addition of a pyridylmethyl sulphoxide to ethyl γ-bromocrotonate to give a cyclopropane, which was stereochemically homogeneous.[4] There are also reports of additions of benzyl sulphoxides to cyclic enones which resulted in 1,2-addition, [5] and destruction of the enone.[6]

We now find that lithiated benzyl sulphoxides, like their alkyl counterparts, undergo highly regio-selective and stereoselective 1,4-additions to acyclic α,β-unsaturated esters. Deprotonation of benzyl *t*-butyl sulphoxide using LDA, followed by addition of various esters at low temperatures, gave the adducts in excellent yield, as shown in Table 1. Reaction with methyl acrylate, methyl crotonate, and methyl cinnamate gave the conjugate addition products in good yields, and the products were essentially stereochemically pure. Although traces of stereoisomers may have been present in some cases, they were not isolated, and unless otherwise noted the yields in the Table refer to isomerically pure materials. Addition to methyl tiglate was quite selective

Table 1

Sulphoxide	α,β-Unsaturated Ester	Product[a]	Yield[b]
 **1a**			R=H, **2a**, 78%[c] R=Me, **2b**, 80%[c] R=Ph, **2c**, 86%
			**2d**, (+ **2e**) 74%[d]
	 ; MeI		**2e**, 81%[c]
 R=Bu^t, **1a** R=Me, **1b** R=p-Tol, **1c**			R=Bu^t, **2b**, 80%[c] R=Me, **2f**, 79%[e] R=p-Tol, **2g**, 62%[f]
 X=Cl, **1d** X=OMe, **1e**			X=Cl, **2h**, 95% X=OMe, **2i**, 91%
			**2j** THF ; 65% (1:1 mixt.) THF, HMPA : 84%

a. The n.m.r. (^{1}H and ^{13}C), i.r., and mass spectra of the products were fully consistent with the structures shown.

b. Yields refer to stereoisomerically pure products, unless otherwise noted.

c. The reaction was carried out at -100°C.

d. The product was a 7:1 mixture of **2d** and **2e**.

e. The product was a 84:7:5:4 mixture of stereoisomers.

f. The base used was BuLi, at -100°C.

also, giving a 7:1 mixture of diastereoisomeric products **2d** and **2e**. The structure of the major product **2d** was established by *X*-ray crystallography (Figure 1).[7] The relative stereochemistry of this product is the same as was found for the additions of alkyl t-butyl sulphoxides,[1] and the configuration of the extra chiral centre is consistent with the standard model for the protonation of chiral enolates.[8] The stereochemistry of the minor product **2e** could not be unequivocally assigned, because although attempted epimerisation of **2e**, using various bases, did give some **2d**, the reactions were slow and irreproducible. However, the stereochemistry of **2e** and the other adducts can be assigned by analogy with the three compounds whose crystal structures have been determined (**2d**, **2f**, and the adduct reported previously[1]), reinforced by the consistent presence of distinctive features in the high field ^{1}H n.m.r. spectra of the products.[9] Addition to methyl crotonate followed by *in situ* trapping with methyl iodide gave the methylated product **2e**. Reaction with methyl methacrylate gave a mixture of stereoisomers which were not characterised. The only enoate which failed to give a conjugate addition product was dihydropyranone, a poor yield of acylation product being obtained instead. Addition of a benzyl sulphoxide to dihydrofuranone was reported to give poor results,[10] and we have failed to achieve conjugate additions of alkyl or benzyl sulphoxides to cyclic electrophiles.[1]

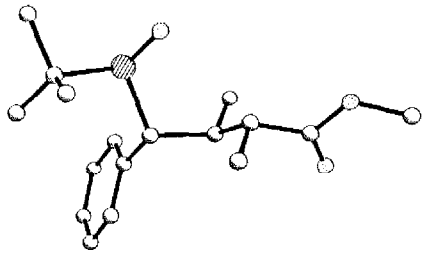


Figure 1 X-Ray structure of **2d**

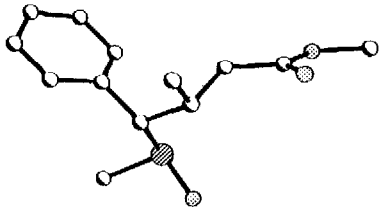


Figure 2 X-Ray structure of **2f**

The earlier work on alkyl sulphoxides had shown that the choice of the unreacting group of the sulphoxide was important, *t*-butyl sulphoxides giving much better stereoselectivity than the corresponding p-tolyl derivatives. In the present series the unreacting group has relatively little influence on the stereoselectivity, the *t*-butyl and p-tolyl benzyl sulphoxides, **1a** and **1c**, both giving high selectivity and the methyl derivative giving only slightly inferior results. *X*-Ray crystallography (Figure 2) established that the major diastereomer derived from benzyl methyl sulphoxide had the same relative stereochemistry as the benzyl *t*-butyl adduct **2d** (Figure 1).[7] However, the p-tolyl sulphoxide **1c** gave relatively poor yields of crotonate adduct **2g** because the reaction was incomplete. The addition was carried out under a variety of conditions but some unreacted sulphoxide was invariably recovered, the best results being obtained when BuLi, rather than LDA, was used as the base. The unreactivity of the p-tolyl benzyl sulphoxide is presumably a consequence of the extra stability of the anion. It is notable that those conjugate additions of benzyl sulphoxides which were reported previously,[3,4] involved even more stabilised anions, and they may only have been observed because the initially formed enolates were trapped by subsequent cyclisation reactions.

Electron poor and electron rich benzyl sulphoxides, **1d** and **1e** respectively, gave excellent yields of adducts. However the 2-pyridylmethyl derivative **1f** gave a mixture of stereoisomeric products. This anomaly may result from the anion adopting a different structure in this case, because of coordination of the pyridyl nitrogen to the lithium. Changes in stereoselectivity when the lithiated sulphoxide contained a coordinating group have been noted previously.[11] Addition of an excess of HMPA to the anion prior to the addition of the crotonate might be expected to disrupt the internal coordination, and indeed it did give a much more stereo-

selective reaction. However, the n.m.r. spectra of the product did not conform to the patterns found in the spectra of the other adducts and the interpretation of these results must await an unambiguous structure assignment. Addition of HMPA to the other sulphoxide anions did not change the stereochemical outcome.

In summary the conjugate addition of lithiated sulphoxides to α,β-unsaturated esters gives high regioselectivity and stereoselectivity and tolerates considerable structural variation. The stereochemical outcome is the same as that observed previously for the reaction of alkyl sulphoxides. The factors controlling the stereoselectivity will be discussed elsewhere,[12] but whatever its origins, the reliable selectivity of this novel asymmetric conjugate addition suggests that it will have considerable synthetic potential. Applications to natural product synthesis will be reported in due course.

Acknowledgements

We gratefully acknowledge generous financial support from ICI Colours and Fine Chemicals, Blackley, and we would like to thank Dr. A. Redhouse and Mr. Robin Thompson, of this Department, for carrying out the *X*-ray crystal structure determinations.

Representative Procedure

A precooled solution of t-butyl 4-chlorophenyl sulphoxide **1d** (1g, 4.34 mmol) in THF (5 ml) was added dropwise via a cannula to a solution of LDA (5.21 mmol) in THF (15 ml) at -78°C. After 10 minutes a solution of methyl crotonate (0.64 ml, 6.07 mmol, 1.40 equiv.) in THF (6 ml) at -78° was added dropwise, with stirring, via a cannula. After 3 minutes saturated aqueous ammonium chloride (10 ml) was added and the reaction mixture was allowed to warm to room temperature. The suspension was poured into water (30 ml) and extracted with dichloromethane (3 x 30 ml) and the combined extracts were dried over magnesium sulphate. The solvent was removed and the crude product was subjected to flash chromatography on silica gel, using a 1:1 mixture of light petroleum ether and ethyl acetate, to give the pure product **2h**; 1.36g, 95%, m.p. 125-125.5°C; Found: C, 58.20; H, 7.23; $C_{16}H_{23}ClSO_3$ requires C, 58.08; H, 7.01; δ(300MHz, $CDCl_3$) 1.00(3H, d, J 6.9Hz), 1.04(9H, s), 1.91(1H, dd, J 15.1, 10.4Hz), 2.83(1H, dd, J 15.1, 3.7Hz), 2.93(1H, m), 3.62(3H, s), 3.80(1H, d, J 3.9Hz), 7.15 (2H, d, J 8.5Hz), 7.30(2H, d, J 8.5Hz). $\delta^{13}C$(75MHz, $CDCl_3$) 17.9, 23.7, 31.0, 37.0, 51.5, 55.9, 64.5, 128.9, 131.1, 133.5, 134.1, 172.5.

References

1. M. Casey, A.C. Manage and L. Nezhat, *Tetrahedron Lett.*, 1988, **29**, 5821.
2. J. Drabowicz, P. Kielbasinski and M. Mikolajczyk in "The Chemistry of Sulphones and Sulphoxides", Ed. S. Patai, Z. Rappapoport, and C. Stirling, Wiley, Chichester, 1988, p. 233.
   S. Oae and Y. Uchida in "The Chemistry of Sulphones and Sulphoxides", Ed. S. Patai, Z. Rappaport, and C. Stirling, Wiley, Chichester, 1988, p. 583.
3. F.M. Hauser and R.P. Rhee, *J. Org. Chem.*, 1978, **43**, 178.
   F.M. Hauser and R.P. Rhee, *J. Org. Chem.*, 1980, **45**, 3061.
4. E. Ghera and Y. Ben-David, *Tetrahedron Lett.*, 1979, 4603.
5. M.R. Binns, O.L. Chai, R.K. Haynes, A.A. Katsifis, P.A.Schober and S.C.Vonwiller, *Tetrahedron Lett.*, 1985, **26**, 1569.
6. J.H. Dodd, R.S. Garigipati and S.M. Weinreb, *J. Org. Chem.*, 1982, **47**, 4045.
7. The *X*-Ray crystal structure determinations were carried out by Dr. A. Redhouse and Mr. R Thompson of this Department and full details will be published elsewhere.
8. T. Hayashi, Y. Matsumoto and Y. Ito, *J. Am. Chem. Soc.*, 1988, **110**, 5579.
9. The two protons alpha to the carbonyl invariably had very different chemical shifts ($\Delta\delta \approx 0.8$), and the beta proton always had an unusually low chemical shift ($\delta \approx 2.9$ for the crotonate adducts).
10. F.E. Ziegler and J.A. Schwartz, *J. Org. Chem.*, 1978, **43**, 985.
11. G. Demailly, C. Greck and G. Solladie, *Tetrahedron Lett.*, 1984, **25**, 4113.
    D.R. Williams, J.G. Phillips, F.H. White and J.C. Huffman, *Tetrahedron*, 1986, **42**, 3003.
12. See S.G. Pyne and G. Boche, *J. Org. Chem.*, 1989, **54**, 2663 for a discussion of related results.

(Received in UK 2 October 1989)