Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2825-2828, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00472-3

Asymmetric Synthesis of Chiral Sulfoxides and Sulfinimines by using *N*-Sulfinylsultam

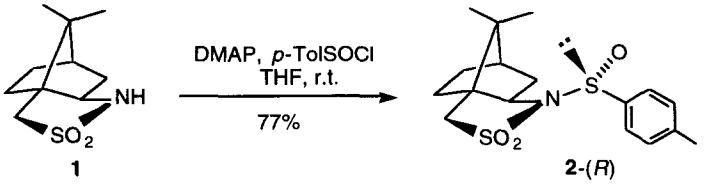
Wolfgang Oppolzer†, Olivier Froelich*[1], Chantal Wiaux-Zamar[2] and Gérald Bernardinelli

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract *:* Bornane-10,2-sultam **1** is stereoselectively converted by DMAP-assisted sulfinylation to diastereomerically pure (2*R*)-*N*-[(*R*)-*p*-tolylsulfinyl]-bornane-10,2-sultam **2** in 77% yield. The crystalline sulfinylating agent **2** reacts with a variety of nucleophiles to afford sulfoxides **3** and sulfinimines **5** in excellent yields and enantioselectivities. © 1997 Elsevier Science Ltd.

Over the last 20 years, chiral sulfoxides have received considerable attention as key intermediates in efficient asymmetric synthesis[3]. The synthesis of optically active sulfoxides, originally proposed by Gilman[4a] then developed by Andersen[4b,c] and Solladié[4d], is based on the reaction of the diastereomerically pure (-)-(*S*)-menthyl *p*-toluenesulfinate with Grignard reagents. Following the same strategy, other chiral auxiliaries have been later developed, *e.g.* 2-phenylcyclohexanol[5], diacetone-D-glucose[6] or oxazolidinones[7]. Double transfer of the sulfinyl moiety using chiral sulfites[8] or oxathiazolidine-*S*-oxide[9] has also been reported. Finally, asymmetric oxidation of sulfides with chiral oxidizing agents[10] or in a few cases with enzymes[3e,11] represents an attractive alternative.

We describe here a new chiral sulfinyl transfer agent derived from the versatile bornane-10,2-sultam **1**[12]. Thus, *N*-[*p*-tolylsulfinyl]-bornane-10,2-sultam **2** was readily synthesised on a gram scale *via* DMAP-assisted sulfinylation of sultam **1** as a 6.2:1 mixture of diastereomers. Crystallisation of the mixture from ether/hexane afforded pure and stable **2**-(*R*) in 77 % yield[13,14,15]. The absolute configuration (*R*) at the sulfur centre in the major diastereomer was established by X-ray crystallography (*Figure 1*)[16]. The diastereoselectivity was proved to be controlled by kinetic factors. Indeed, treating one equivalent of pure minor diastereomer **2**-(*S*) with a 1:1 mixture of sultam **1** and DMAP gave no epimerisation at the sulfur centre after 4 h at r.t.. In contrast, sulfinylation of sultam **1**, by using *n*-Buli (-78°C) instead of DMAP, led to a 1:1 mixture of diastereomers **2**. When diastereomerically pure **2**-(*R*) was submitted to 0.1 equivalent of *n*-BuLi and sultam **1** in THF at - 78°C, complete epimerisation at the sulfur chiral centre was observed in less than 5 min, indicating that the reaction is now under thermodynamic control.



1 **2**-(*R*)

† Deceased 15th March 1996

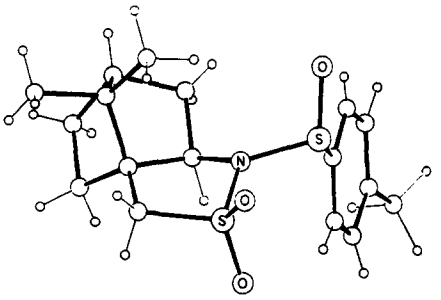


Figure 1 : X-ray of *N*-[(*R*)-*p*-tolylsulfinyl]-bornane-10,2-sultam **2**

The reagent **2**-(*R*) reacted rapidly at low temperature with a variety of Grignard or Reformatsky reagents giving high yields (>79%) of enantiomerically pure sulfoxides **3** (e.e. ≥96% , *Table 1*).

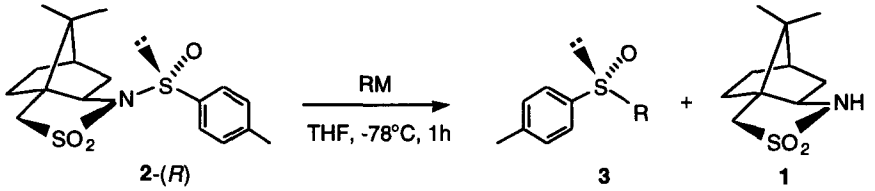


Table 1 : Synthesis of Optically Active *p*-tolylsulfoxides **3** from Sulfinamide **2**

RM	Sulfoxides **3**			Sultam **1**
	Yield [%]	$[\alpha]_D$ ($CHCl_3$)	e.e.[(a)] [%]	Yield [%]
MeMgBr	93	+155[(b)]	99 (*R*)	91
*i*PrMgCl	92	+182[(c)]	99 (*R*)	91
*n*BuMgCl	97	+180[(c)]	97 (*R*)	94
benzylMgCl	91	+238	>99 (*R*)	93
vinylMgCl	95	+455[(c)]	96 (*R*)	95
(*Z*)-1-propenylMgBr	80	+363	99 (*R*)	92
(*E*)-1-propenylMgBr	79	+55	96 (*R*)	95
2-propenylMgBr	90	+122	>99 (*R*)	92
allylMgCl	96	+198[(b)]	>99 (*R*)	98
2-thienylMgBr	89	+147	99 (*S*)	91
3-furylMgBr	89	+102	99 (*S*)	91
1-pentynylMgBr	85	+89	>98 (*R*)	93
$BrCH_2COOtBu$ / Zn	83	+142[(b)]	>99 (*R*)	93

(a) Determined by chiral HPLC (b) EtOH (c) Acetone

As expected, inversion occurred at the sulfur centre in agreement with a S_N2 type mechanism[3a,e,f] . In addition, the bornane-10,2-sultam **1** was easily recovered in high yield (≥91%) by chromatography or crystallisation.

In order to evaluate the potential of this new chiral sulfinylating reagent **2**, we examined its utility for preparing enantiopure sulfinimines **5**. The latter are, for example, useful precursors in the synthesis of enantiomerically pure amines and α- and β-amino acid derivatives[17]. To date, the method of choice for

obtaining chiral sulfinimines is based on the displacement of Andersen's sulfinate with lithium bis(trimethylsilyl)amide (LiHMDS) followed by condensation with aryl or α,β–unsaturated aldehydes (Davis method)[18]. Nevertheless, reactions with enolisable aldehydes afford only low yields of sulfinimines.

Our results (*Table 2*) show that this drawback can be circumvented by a modification of the Davis procedure. Indeed, extensive experimentation revealed that enolisable aldehydes could be converted into enantiomerically pure sulfinimines **5** (e.e. ≥99.5%) in good yields (65-73%), if one equivalent of water was added to the sulfinylated HMDS **4** prior to the addition of the aldehyde (Method A: *entries 1, 5, 6, 7*)[19]. Interestingly, if these conditions were used with benzaldehyde, sulfinimine could not be detected (*entry* 3). On the other hand, non-enolisable aldehydes are easily converted to sulfinimines according to Davis procedure (Method B : *entries 4, 8*)[18].

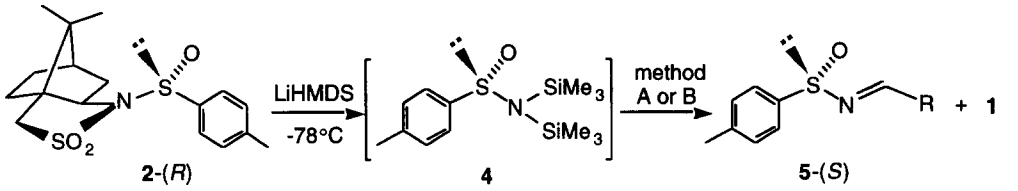


Table 2 : Synthesis of Optically Active (*S*)-Sulfinimines **5** from Sulfinamide **2**

Entry	Aldehydes	Method	Sulfinimines 5			Sultam 1
			Yield [%]	$[\alpha]_D$ ($CHCl_3$)	e.e.[(a)] [%]	Yield [%]
1	*n*-BuCHO	A	73	+302	>99.5	87
2	*n*-BuCHO	B	0			90
3	PhCHO	A	0			84
4	PhCHO	B	84	+112	>99.5	89
5	*i*-PrCHO	A	65	+299	>99.5	89
6	CyclohexylCHO	A	67	+221	>99.5	88
7	(*E*)-CH_3CH=CHCHO	A	70	+620	>99.5	86
8	(*E*)-PhCH=CHCHO	B	74	+350	98	85

Method A: i) 1 eq. H_2O in THF, - 78°C ii) 1.1 eq. RCHO, - 20°C to 5°C (a) Determined by chiral HPLC
Method B: i) 1.1 eq. RCHO, - 20°C ii) 2 eq. CsF, - 20°C to r.t.

In conclusion, we have developed a new crystalline chiral sulfinylating agent **2** which reacts with Grignard or Reformatsky reagents giving high yields of enantiomerically pure sulfoxides **3**. Furthermore, the reagent **2** reacts with both enolisable or non-enolisable aldehydes, under specific conditions, to afford aryl and alkyl sulfinimines **5** in good yields and enantioselectivities.

Financial support of this work by the *Swiss National Science Foundation* is gratefully acknowledged. We thank Mr. *J.P. Saulnier*, Mr. *A. Pinto* and Mrs. *D. Klink* for NMR and MS measurements.

References and Notes

1. Present address: Novartis Products Inc, Animal Health Sector, CH-4002 Basel, Switzerland.
2. Present address: Firmenich S.A, P.O.B. 329, CH-1211 Genève 8, Switzerland
3. (a) In "*The Chemistry of Sulfones and Sulfoxides*"; S. Pataï, Z. Rappoport, C.J.M. Stirling, Eds. John Wiley & Sons, Ldt. **1988**, Chapter 3 by K.K. Andersen; Chapter 8 by J. Drabowicz, P. Kielbasinski, M. Mikolajczyk; Chapter 16 by G.H. Posner. (b) G. Solladié, *Pure and Appl. Chem.* **1988**, *60*, 1699 (c) A.J. Walker, *Tetrahedron: Asym.* **1992**, *3*, 961. (d) *In "Comprehensive Organic Synthesis"*; B.M. Trost, I. Fleming, Eds. Pergamon Press, Oxford **1991**, Vol. 6, Chapter 3 by G. Solladié. (e) M. C.

Carreno, *Chem. Rev.* **1995**, *95*, 1717. (f) G. Solladié, M.C. Carreno, *Organosulfur Chemistry, Synthetic Aspects*, Eds. Academic Press Ldt. **1995**, Chapter 1.

4. (a) H. Gilman, J. Robinson, N.H. Beaber, *J. Am. Chem. Soc.* **1926**, *48*, 2715. (b) K.K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93. (c) K.K. Andersen, *J. Org. Chem.* **1964**, *29*, 1953. (d) G. Solladié, *Synthesis* **1981**, 185.
5. (a) J.K. Whitesell, M.-S. Wong, *J. Org. Chem.* **1991**, *56*, 4552. (b) J.K. Whitesell, M.-S. Wong, *J. Org. Chem.* **1994**, *59*, 597.
6. (a) I. Fernández, N. Khiar, J.M. Llera, F. Alcudia, *J. Org. Chem.* **1992**, *57*, 6789. (b) N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1994**, *35*, 5719.
7. D.A. Evans, M.M. Faul, L. Colombo, J.J. Bisaha, J. Clardy, D. Cherry, *J. Am. Chem. Soc.* **1992**, *114*, 5977.
8. (a) F. Rebiere, H.B. Kagan, Tetrahedron Lett. **1989**, *30*, 3659. (b) F. Rebiere, O. Samuel, L. Ricard, H.B. Kagan, *J. Org. Chem.* **1991**, *56*, 5991.
9. S.C. Benson, J.K. Snyder, *Tetrahedron Lett.* **1991**, 32, 5885.
10. (a) J.-M. Brunel, P. Diter, M.D. Duetsch, H.B. Kagan, *J. Org. Chem.* **1995**, *60*, 8086. (b) J.-M. Brunel, H.B. Kagan, *Synlett* **1996**, 404. (c) Y. Watanabe, Y. Ono, S. Hayashi, Y. Ueno, T. Toru, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1879.
11. S. Colonna, N. Gaggero, P. Pasta, G. Ottolina, *Chem. Commun.*, **1996**, 2303.
12. W. Oppolzer, *Pure and Appl. Chem.* **1990**, *62* , 1241
13. All attempts to prepare **2** by oxidation of the *N*-(p-tolylthio)bornane-10,2-sultam showed poor diastereoselectivity.
14. The reagent **2**-(*R*) has exhibited a shelf life of at least 2 years at -20°C with no sign of decomposition.
15. General procedure for **2**-(*R*): To a solution of distilled *p*-tolylsulfinyl chloride (1.95 ml, 15.11 mmol) in THF (30 ml) was added *via cannula* a clear solution of (2*R*)-bornane-10,2-sultam (2.16g, 10.07 mmol) and 4-dimethylaminopyridine (DMAP) (1.35 g, 11.08 mmol) in THF (20 ml) at r.t.. A white precipitate was formed during the addition and the reaction was slightly exothermic. The mixture was stirred at r.t. for 2.5 h. After filtration on celite and evaporation under reduced pressure the HPLC analysis of the crude reaction mixture indicated a 6.2:1 ratio of **2**-(*R*) to **2**-(*S*). Crystallisation from ether afforded a mixture of **2**-(*R*) and **2**-(*S*) (2.30 g, 64.7%) in 61.3:1 ratio. Purification by FC of the remaining residue provided **2**-(*R*) (520 mg) and **2**-(*S*) as a colorless oil (410mg). Recrystallisation (Et_2O/hexane 8:1) at 0°C of both **2**-(*R*) fractions provided pure **2**-(*R*) (2.74g, 77.2%): M.p. = 124°C; $[\alpha]_D$ = -180.2 (c = 1.2, in $CHCl_3$). IR: 3034, 2962, 1460, 1393, 1338, 1314, 1228, 1169, 1136, 1072. ^{1}H-NMR (400MHz, C_6D_6): 0.39 (s, 3 H); 0.48 (m, 1 H); 0.61 (td, J = 8.8, 2.9, 1 H); 1.03 (dd, J = 13.6, 8.5, 1 H); 1.09 (td, J = 12.1, 4.4, 1 H); 1.22 (m, 1 H); 1.29 (s, 3 H); 1.33 (m, 1 H); 1.95 (s, 3 H); 2.57 (d, J = 14.0, 1 H); 2.80 (d, J = 14.0, 1 H); 2.87 (m, 1 H); 3.06 (dd, J = 8.1, 4.4, 1 H); 6.94 (d, J = 8.1, 2 H); 7.83 (d, J = 8.1, 2 H). ^{13}C-NMR: 142.20, 138.69, 130.10, 125.91, 65.11, 50.94, 50.81, 48.46, 44.96, 35.81, 31.67, 26.54, 21.10, 19.99, 19.79. MS: 354 (13, [$C_{17}H_{24}NO_3S_2^+$.]), 337 (4), 246 (3), 214 (51), 150 (25), 139 (100). HR-MS 337.1158 ($C_{17}H_{23}NO_2S_2^+$, calc. 337.1170). Microanalysis found for $C_{17}H_{23}NO_2S_2$: C: 57.68% H: 6.51% N: 4.08%, calc: C: 57.76% H: 6.56% N: 3.96%.
16. Crystallographic data for **2**-(*R*) have been deposited at the Cambridge Data Center. Structure factors may be obtained from one of us (G.B). The crystals of **2**-(*R*) are orthorhombic, space group $P2_12_12_1$, a = 10.078 (3), b = 13.154 (2), c = 13.250 (4) Å; $F(000)$ = 752. R=0.052 (ωR = 0.023; $\omega = 1/\sigma^2(F)$) for 1998 observed reflections [$|Fo| \geq 4\sigma(Fo)$]
17. (a) F.A. Davis, J.M. Szewczyk, R.E. Reddy, *J. Org. Chem.* **1996**, *61*, 2222. (b) F.A. Davis, P. S. Portonovo, R.E. Reddy, Y.-H. Chiu, *J. Org. Chem.* **1996**, *61*, 440. (c) D.H. Hua, N. Lagneau, H. Wang, J. Chen, *Tetrahedron: Asym.* **1995**, *6*, 349. (d) D.R.J. Hose, M.F. Mahon, K.C. Molloy, T. Raynham, M. Wills, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 691.(e) M. Mikolajczyk, P. Lyzwa, J. Drabowicz, M.W. Wieczorek, J. Blaszczyk, *Chem. Commun.* **1996**, 1503. (f) T. Fujisawa, Y. Kooriyama, M. Shimizu, *Tetrahedron Lett.* **1996**, *37*, 3881.
18. F.A. Davis, R.E. Reddy, J.M. Szewczyk, P.S. Portonovo, *Tetrahedron Lett.* **1993**, *34*, 6229.
19. General procedure for the preparation of sulfinimines starting from enolisable aldehydes (Method A)
To a solution of **2**-(*R*) (50 mg, 0.142 mmol) in THF (1.5 mL) at -78°C was slowly added a 1 M hexane solution of LiHMDS (156ml, 0.156 mmol). The clear solution was stirred at -78°C for 1 h and 1 equiv. of water was added (solution of 100 µl water in 1 ml of THF). The temperature was raised to -20°C, the mixture was stirred for 10 min and 1.1 equiv. of the freshly distilled aldehyde was added. The reaction was stirred for 2-3 h and the temperature slowly raised to 5°C. The mixture was filtered on celite, concentrated *in vacuo* and the resultant oil was purified by FC on silica gel.

(*Received in Germany* 18 *February* 1997; *accepted* 3 *March* 1997)