157. Optically Active *t*-Butyl 2-(*p*-Tolylsulfinyl)propionate and -butyrate: Synthesis and Reactivity in Aldol-type Condensations

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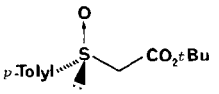
Summary

The syntheses of optically active *t*-butyl 2-(*p*-tolylsulfinyl)propionate and -butyrate (**2a** and **2b**, respectively) are described, and it is shown that aldol-type condensation of the corresponding enolates is limited by steric hindrance. Optically active (**2a**) reacted, however, in high yield with aliphatic aldehydes and lead to 80% of asymmetric induction.

(+)-(*R*)-*t*-Butyl (*p*-tolylsulfinyl)acetate (**1**), which can be considered as a chiral synthetic equivalent to the enolate anion of *t*-butyl acetate, was shown to be a very powerful chiral synthon in asymmetric aldol type condensations [1] [2], and several synthetic applications have already appeared [3] [4].

We report now synthesis and reactivity studies of chiral substituted α-sulfinyl esters of type **2** which represent chiral synthetic equivalents to the enolate anions of *t*-butyl propionate and butyrate.



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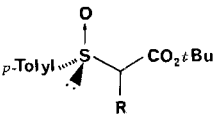

2

a R = CH_3
b R = C_2H_5
c R = $C_6H_5CH_2$

We first studied the methylation of (+)-(*R*)-*t*-butyl (*p*-tolylsulfinyl)acetate (**1**) under several conditions *(Table)*. The results showed that formation of **2a** occurred only with lithium bases such as butyl lithium or *t*-butyl lithium at 0° and only with methyl iodide as alkylating agent. However the stereoselectivity of the methylation was very poor; the best ratio of the two diastereoisomers of **2a** was 42 : 58, as determined by 250 MHz – ^{1}H-NMR. (two quadruplets at 3.42 and 3.70 ppm arising from H–C(2)).

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Table. *Alkylation of* t-*butyl* (p-*tolylsulfinyl*)*acetate* (**1**)

Alkylation agent	Base	Solvent	Temp. [°C]	Chemical yield [%]	Ratio of diastereo-isomers
	BuLi	THF	−78	0	
	BuLi	THF	−40	0	
	BuLi	THF	0	80	50:50
	t-BuLi	THF	0	84	42:58
MeI	Et_2NLi	THF/HMPT	25	64	47:53
	t-BuMgBr	THF	25	0	
	$(i\text{-Pr})_2NMgBr$	THF	reflux	0	
$(MeO)_3PO$	*t*-BuLi	THF	25	0	
TsOMe	*t*-BuLi	THF	25	0	
$C_6H_5CH_2Br$	*t*-BuLi	THF	0	80	46:54
i-PrBr	*t*-BuLi	THF	0	0	
EtI	BuLi	THF	25	89	40:60

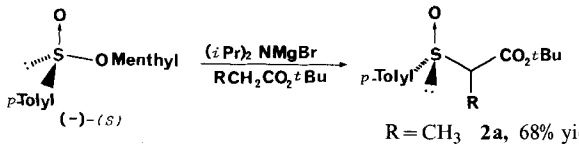
This poor selectivity is in sharp contrast with the highly stereoselective methylation of carbanions in α-position to a chiral sulfoxide group [2] as well as the stereospecific alkylation of the dianions derived from chiral β-hydroxy esters [5] [6]. Such a difference can be attributed to the fast exchange at 0° between two metalated structures derived from ester **1** as shown by a ^{13}C-NMR. study [7].

We also investigated several other alkylating agents such as trimethyl phosphate and methyl *p*-toluenesulfonate, but we did not observe any methylation.

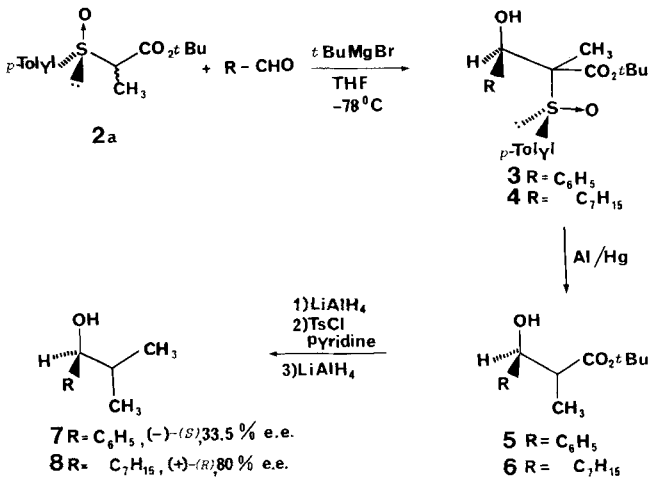
However, benzyl bromide reacted with **1** in the presence of *t*-butyl lithium yielding to 80% the corresponding phenyl(sulfinyl)propionate **2c** which was shown by ^1H-NMR. (from the two singlets of the *t*-butyl group) to be a mixture of the two diastereoisomers in the ratio: 46:54. Isopropyl bromide did not react at all, but ethyl iodide afforded the corresponding sulfinylbutyrate **2b** in high yield, the diastereoisomeric ratio being 40:60.

Another way to prepare compounds **2** was to displace the menthyl group of (−)-menthyl *p*-tolylsulfinate with the enolate anion of the corresponding ester, in analogy to the synthesis of *t*-butyl (*p*-tolylsulfinyl)acetate [1] [2]. This pure S_N2-process proceeded nicely with the magnesium enolate anion of *t*-butyl propionate (68% yield), but to a lesser extent (45%) with the one of *t*-butyl butyrate. The diastereoisomeric ratio was shown by ^1H-NMR. to be 1:1 in **2a** and 3:7 in **2b**.

In conclusion these results showed that *t*-butyl 2-(*p*-tolylsulfinyl)propionate (**2a**) can be obtained either by methylation of the parent ester **1** or from menthyl (*p*-tolyl)sulfinate, meanwhile *t*-butyl 2-(*p*-tolylsulfinyl)butyrate (**2b**) is best prepared by alkylation, probably because of the steric hindrance of the enolate anion of *t*-butyl butyrate in the displacement reaction.



R = CH_3 **2a**, 68% yield
R = C_2H_5 **2b**, 45% yield

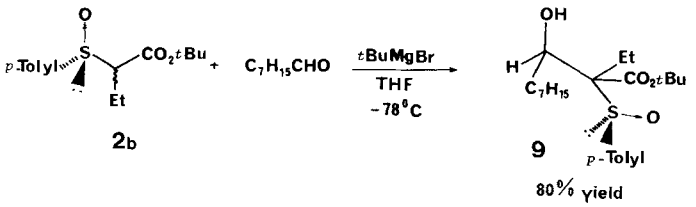


We next studied aldol-type condensations of the enolate anion of sulfinylpropionate **2a** which was prepared from **2a** as usual with the base *t*-BuMgBr [1] [2]. At $-78°$ we did not observe any addition to acetophenone but only to aldehydes such as benzaldehyde and octanal. The crude product **3** and **4** respectively was desulfurized with aluminium amalgam yielding the corresponding *β*-hydroxy esters **5** and **6**. Chemical yields were in both cases 90% for the two steps.

The amount of asymmetric induction was determined by transformation of the *β*-hydroxy esters to the corresponding isopropyl-substituted alcohols **7** and **8**. It is important to notice that the ratio of the diastereoisomers easily determined in **5** and **6** is not representative of the amount of asymmetric induction because of the unknown stereochemistry of the desulfuration step.

The alcohol **7** was shown to be 33.5% optically pure and to have the absolute configuration *(S)* by comparison with literature results [8] [9]. The 80% enantiomeric excess of the unknown alcohol **8** was determined by ^{1}H-NMR. in presence of a chiral europium complex, whereas its absolute configuration *(R)* was predicted by the use of *Brewster*'s rules [10].

We finally investigated the aldol-type condensation of the enolate anion of the sulfinylbutyrate **2b** which at $-78°$ did not react with acetophenone and benzaldehyde but only with octanal in 80% yield. Unfortunately, the desulfuration with aluminium amalgam of the adduct **9** failed in this case, and we could not determine neither the amount of asymmetric induction nor the absolute configuration of the product.



It can be concluded from this study that the reactivity of substituted (*p*-tolylsulfinyl)acetates towards carbonyl compounds is limited by steric hindrance. However, they react quite nicely with aliphatic aldehydes, and at least in the case of *t*-butyl 2-(*p*-tolylsulfinyl)propionate (**2a**), the amount of asymmetric induction is very high.

Dr. *A. Solladié-Cavallo* is gratefully acknowledged for helpful comments.

Experimental Part

General remarks. IR. spectra: absorptions in cm^{-1}. – ^{1}H-NMR. spectra: chemical shifts in ppm relative to tetramethylsilane (= 0 ppm), coupling constants J in Hz; *s* = singulet, *d* = doublet, *t* = triplet, *qu* = quadruplet, *m* = multiplet, *br.* = broad.

*Alkylation of (+)-t-butyl (p-tolylsulfinyl)acetate (**1**). – General procedure.* At the required temp., 0.2 g (0.78 mmol) of (+)-(*R*)-**1** was dissolved in 30 ml of THF. Then 1 equiv. of base was added dropwise within 20 min. and the mixture stirred for 30 min. Two equiv. of alkylating agent, diluted in THF, were finally added, and stirring was continued for 30 min. The mixture was decomposed with 50 ml of sat. ammonium chloride solution. The aqueous layer was extracted with $CHCl_3$ (3 times 50 ml), the organic layer dried over Na_2SO_4 and the solvent evaporated. Chemical yield and diastereoisomeric ratios were determined on the crude product by ^{1}H-NMR., the chemical yield being obtained from a comparison of the signals of unreacted **1** and products. – 250-MHz-^{1}H-NMR. of (+)-**1** ($CDCl_3$): 1.4 (*s*, 9 H, *t*-Bu); 2.4 (*s*, 3 H, $CH_3C_6H_4$); 3.51 and 3.89 (*AB*-system, 2 H); 7.2–7.6 (*m*, $CH_3C_6H_4$).

In this way, *t-butyl 3-phenyl-2-(p-tolylsulfinyl)propionate* (**2c**) was obtained in 80% yield. – 250-MHz-^{1}H-NMR. ($CDCl_3$): 1.05 and 1.2 (2*s* in the ratio 46:54, 9 H, *t*-Bu); 2.35 (*s*, 3 H, $CH_3C_6H_4$); 2.6–4.0 (*m*, 1 H); 7.2–7.6 (*m*, 9 arom. H).

*Synthesis of (R)-t-butyl 2-(p-tolylsulfinyl)propionate (**2a**).* The reaction of 4.5 g (34,6 mmol) of *t*-butyl propionate and 5 g (17,0 mmol) of (–)-(*S*)-menthyl *p*-tolylsulfinate in presence of (diisopropylamino)-magnesium bromide was performed at –30° under the conditions already described [1] [2] for the synthesis of (+)-**1**. A 68%-yield (3.1 g) of **2a** as a 1:1 mixture of the 2 diastereoisomers was obtained, $[\alpha]_D^{25} = +148.3°$ (EtOH, $c = 0.3$). – IR. (CCl_4): 3020 (C–H), 1725 (C=O), 1050 (S→O). – 250-MHz-^{1}H-NMR. ($CDCl_3$): 1.25 and 1.48 (2*d*, 3 H, 3 H–C(3); 1.38 and 1.42 (2*d*, 9 H, *t*-Bu); 2.40 (1*s*, 3 H, $CH_3C_6H_4$); 3.42 and 3.70 (2*qa* in the ratio 1:1, 1 H, H–C(2)); 7.2–7.6 (*m*, 4 H, $CH_3C_6H_4$).

$C_{14}H_{20}O_3S$ Calc. C 62.55 H 7.51% Found C 62.77 H 7.42%

*Synthesis of (R)-t-butyl 2-(p-tolylsulfinyl)butyrate (**2b**).* The same procedure applied to 10 g 34,0 mmol) of (–)-(*S*)-menthyl *p*-tolylsulfinate, 7.5 g (52,0 mmol) of *t*-butyl butyrate afforded, in presence of (diisopropylamino)magnesium bromide at –35°, a 45%-yield (4.1 g) of **2b** as a 72:28 mixture of the two diastereoisomers, $[\alpha]_D^{20} = +147°$ (EtOH, $c = 2.0$). – IR. (CCl_4): 1721 (C=O), 1040 (S→O). – 250-MHz-^{1}H-NMR. ($CDCl_3$): 0.85–1.15 (*m*, 3 H, 3 H–C(4)); 1.17 and 1.27 (2*s* in the ratio 28:72, 9 H, *t*-Bu); 1.55–2.25 (*m*, 2 H, 2 H–C(3)); 2.41 (*s*, 3 H, $CH_3C_6H_4$); 3.25–3.55 (*m*, 1 H, H–C(2)); 7.2–7.6, (*m*, 4 H, $CH_3C_6H_4$).

$C_{15}H_{22}O_3S$ Calc. C 63.83 H 7.85% Found C 63.71 H 7.71%

*Synthesis of t-butyl 3-hydroxy-2-methyl-3-phenylpropionate (**5**).* To 1.5 g (5,6 mmol) of **2a** in 400 ml of THF at –78°, 40 ml of a *t*-butylmagnesium bromide solution (prepared from 3 g of magnesium, 20 g of *t*-butyl bromide and 50 ml of ether) were added dropwise within 20 min. After stirring the mixture at –78° for 30 min., 2 g (18,9 mmol) of benzaldehyde in 30 ml of THF were added dropwise. Then stirring was continued for 15 min and the mixture hydrolyzed with 50 ml of sat. ammonium chloride solution. Extraction with $CHCl_3$ (2 times 100 ml) gave, after drying over Na_2SO_4 and evaporation, the crude product **3** which was rapidly purified by column chromatography on silicagel with ether/petroleum ether 1:1 to remove the excess of benzaldehyde. – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.9 and 1.20 (2*s*, 3 H, H_3C–C(2)); 1.38 (*s*, 9 H, *t*-Bu); 2.35 (*s*, 3 H, $CH_3C_6H_4$); 4.35 and 4.45 (2*s*, 1 H, H–C(3)); 7–7.8 (*m*, 9 arom. H).

The crude **3** was desulfurized, after dilution with 440 ml of THF/water 10:1, by adding 12 g of aluminium amalgam (6 times 2 g) and keeping the temp. between 15° and 20°. The mixture was stirred vigorously overnight. After filtration and washing with 50 ml of $CHCl_3$, the solvent was evaporated and the residue purified by column chromatography on silica gel with ether/petroleum ether 1:4, giving 95% (with respect to **2a**) of **5**. – IR. (CCl_4): 3400 (OH), 1700 (C=O). – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.95 and 1.20 (2*d*, 3 H, H_3C–C(2)); 1.35 and 1.40 (2*s*, in the ratio 2: 10.2, 9 H, *t*-Bu); 2.40–2.90 (2*qa*, 1 H); 4.62 and 4.95 (2*d*, 1 H, H–C(3)); 7.25 (br. *s*, 5 arom. H).

Synthesis of (–)-(S)-α-isopropylbenzyl alcohol (7). a) In the usual way 1.04 g (4.6 mmol) of **5** were reduced by 0.5 g of $LiAlH_4$ in refluxing ether. Workup yielded 0.6 g (86%) of *1-benzyl-2-methyl-1,3-propanediol*. – IR. (CCl_4): 3360 (OH). – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.65 and 0.75 (2*d*, 3 H, H_3C–C(2)); 2.90–3.80 (*m*, 3 H, 2 H–C(3) and HO); 3.42 and 3.82 (2*d*, 1 H, H–C(1)); 7.25 (br. *s*, 5 arom. H).

b) Tosylation of the primary OH of 1-benzyl-2-methyl-1,3-propanediol was performed as usual in pyridine at 0°: 91% yield. – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.72 and 0.82 (2*d*, 3 H, H_3C–C(2)); 2.25 and 2.45 (2*s*, $CH_3C_6H_4$); 0.3–3.8 (*m*, 2 H); 4.58 and 4.92 (2*d*, 1 H); 7.25 (br. *s*, 5 arom. H); 7.52 (*AB*-system, $J = 13.4$, $CH_3C_6H_4$).

c) The crude (*p*-toluenesulfonate was then reduced by $LiAlH_4$ in refluxing ether and the crude **7** purified by flash chromatography with ether/petroleum ether 1:3. Yield = 98%, $[\alpha]_D^{20} = -15.9°$ (Et_2O, $c = 4.16$) ([8] [9]: $[\alpha]_D^{20} = +47.7°$ (Et_2O)). – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.82 and 0.95 (2*d*, 3 H, CH_3); 1.02–2.42 (*m*, 3 H); 4.02 (*d*, 1 H); 7.28 (br. *s*, 5 arom. H).

Synthesis of t-*butyl 3-hydroxy-2-methyldecanoate (6).* The condensation of **2a** with octanal was conducted as described for the synthesis of **5**. – 60-MHz-^{1}H-NMR. of **4** ($CDCl_3$): 0.7–1.6 (*m*, 27 H); 2.36 (*s*, 3 H, $CH_3C_6H_4$); 4.5 and 4.6 (2*s*, 1 H); 7–7.8 (*m*, $CH_3C_6H_4$).

The adduct **4** was desulfurized with aluminium amalgam giving a 90% total yield of **6**. – IR. (CCl_4): 3500 (OH), 1710 (C=O). – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.7–1 (*m*, 3 H, 3 H–C(10); 1.20 and 1.5 (2*d*, 3 H, H_3C–C(2); 1.30 (*m*, 12 H); 1.45 and 1.5 (2*s*, in the ratio 18.7:4.2 9 H, *t*-Bu); 2.10–2.6 (*m*, 1 H).

Synthesis of (+)-(R)-2-methyl-3-decanol (8). a) Reduction of **6** with $LiAlH_4$ gave the corresponding diol in 90% yield. – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.7–1 (*m*, 6 H, 2 CH_3); 1–1.90 (*m*, 12 H); 3.3–3.9 (*m*, 4 H).

b) Tosylation of the diol at 0° gave the *p*-toluenesulfonate in 83% yield. – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.7–1.90 (*m*, 19 H); 2.42 and 2.80 (2*s*, $CH_3C_6H_4$); 3.20–4.2 (*m*, 3 H); 7.55 (*AB*-system, $J = 13$, $CH_3C_6H_4$).

c) Reduction of the tosyl group with $LiAlH_4$ afforded **8** in 95% yield. $[\alpha]_D^{20} = +8{,}6°$ (EtOH, $c = 1.4$). – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.7–1.0 (*m*, 9 H, 3 CH_3); 1.10–1.80 (*m*, 13 H); 3.35 (*m*, 1 H); 3.5–3.80 (*m*, 1 H). The optical purity of **8** was determined by ^{1}H-NMR. in presence of Eu(camphorato)$_3$. The diastereotopic methyl groups at C(2) gave under these conditions two separate signals ($\Delta\delta = 0.3$ Hz) in the ratio 9:1.

Synthesis of t-*butyl 3-hydroxy-2-(*p-*tolylsulfinyl)decanoate (9).* The condensation of **2b** and octanal was conducted as described for the synthesis of **5**. After purification by flash chromatography with ether/hexane 1:1 the yield of **9** was 80%. – 60-MHz-^{1}H-NMR. ($CDCl_3$): 0.7–1.7 (*m*, 29 H); 2.4 and 2.5 (2*s*, 3 H, $CH_3C_6H_4$); 3.1–3.4 (*m*, 1 H); 4.4–4.7 (*m*, 1 H); 7.1–7.8 (*m*, $CH_3C_6H_4$).

REFERENCES

[1] *C. Mioskowski & G. Solladié*, Tetrahedron *36*, 227 (1980).
[2] *G. Solladié*, Synthesis *1981*, 185.
[3] *E.J. Corey, L.O. Weigel, A.R. Chamberlin, H. Cho & D.H. Hua*, J. Am. Chem. Soc. *102*, 6613 (1980).
[4] *G. Solladié & F. Matloubi-Mogadham*, J. Org. Chem. *47*, 91 (1982).
[5] *G. Frater*, Helv. Chim. Acta *62*, 2825 (1979).
[6] *G. Frater*, Helv. Chim. Acta *62*, 2829 (1979).
[7] *A. Solladié-Cavallo & C. Mioskowski*, Org. Magn. Reson. *16*, 273 (1981).
[8] *R. Macleod, F.J. Welsh & H.S. Mosher*, J. Am. Chem. Soc. *82*, 876 (1960).
[9] *D.R. Clark & H.S. Mosher*, J. Org. Chem. *35*, 1114 (1970).
[10] *J.H. Brewster*, J. Am. Chem. Soc. *81*, 5475, 5483 and 5493 (1959); idem Tetrahedron *13*, 106 (1961).