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A new and general synthesis of chiral β-ketosulfoxides by reaction of (+)-(*R*)-methyl *p*-tolyl sulfoxide with nitriles

Robert Vleggaar * and Jacob G. Zeevaart

Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

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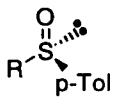
Abstract

The nitrile functional group is efficiently transformed into the β-ketosulfoxide moiety by reaction with the anion formed from (+)-(*R*)-methyl *p*-tolyl sulfoxide and aqueous acidic work-up of the reaction.

Keywords: nitriles; chiral sulfoxides; chiral β-ketosulfoxides; carbon–carbon bond formation.

Chiral β-ketosulfoxides have found wide application over the years in the asymmetric synthesis of natural products.[1,2] The synthesis of a great variety of enantiomerically pure acyclic β-ketosulfoxides is based[3] on the reaction of esters with the α-sulfinyl anion derived from a chiral sulfoxide such as (+)-(*R*)-methyl *p*-tolyl sulfoxide **1**.[4] In our synthetic studies[5] on the C_{20} backbone of the fumonisins, mycotoxins produced by cultures of *Fusarium moniliforme*,[6] we developed a strategy for the synthesis of the substituted *anti* 1-methyl-3-hydroxy group motif present in these compounds, based[1,7] on the stereoselective reduction of a chiral β-ketosulfoxide intermediate.



1 R = Me
8 R = Et

The strategy is outlined in Scheme 1 and involves a one-carbon chain extension of the protected alcohol **2** via the *O*-tosylate derivative to the nitrile **3.** Base hydrolysis of the nitrile **3** followed by esterification of the formed acid gives the ester **4** which is converted by established procedures,[8] to the β-ketosulfoxide **5** upon treatment with 2 equivalents of the α-anion derived from the chiral sulfoxide **1**.[9,10] In this letter we report that the synthetic sequence can be efficiently shortened by two steps through use of the nitrile **3** to prepare the β-ketosulfoxide **5**. The rationale for this reaction is that nucleophilic attack of the α-sulfinyl anion on the carbon atom of the nitrile group of **3** leads to carbon–carbon bond formation and an

* Corresponding author. Tel: +27 12 420-3095; fax: +27 12 362-5297; e-mail: vleggaar@scientia.up.ac.za

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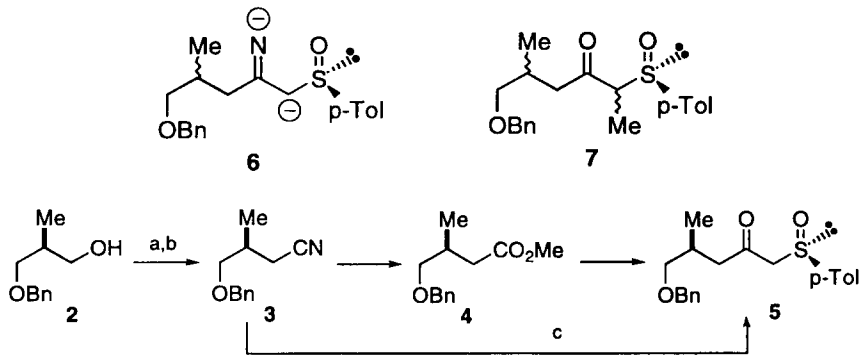
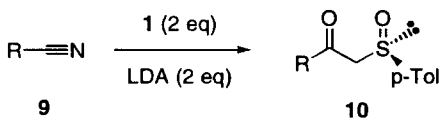
iminide intermediate **6**. Aqueous acidic work-up generates an imine which in turn is hydrolysed under the conditions to the β-ketosulfoxide **5**. The method was investigated using a variety of nitrile compounds (see Table 1) and is illustrated in Scheme 1 for the synthetic sequence using *rac*-**2**.[11]

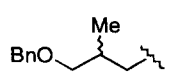
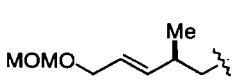


Scheme 1. Reagents and conditions (racemic compounds): (a) TsCl, DMAP, pyridine, CH_2Cl_2, 0°C, 5 h, 90%; (b) NaCN, DMF, 90°C, 16 h, 92%; (c) LDA, **1**, 0°C→rt, 1 h, 85%

Table 1
Data for the β-ketosulfoxides **10a–g** prepared from the nitriles **9a–g**



9 **10**

β-Ketosulfoxide 10	Yield	m.p. (Lit. m.p.)	$[\alpha]_D$ (Lit. $[\alpha]_D$)
a R = Me	78%	34–36°C (35–36°C)[12]	+ 247.5 (*c* 0.51)[a] (+ 246.9 (*c* 0.55))[a,12]
b R = Et	74%	68–69°C (69–70°C)[13]	+ 259.0 (*c* 0.62)[a] (+ 260.3 (*c* 1.0))[a,13,14]
c R = *n*-Pr	80%	58–59°C (58–59°C)[12]	+ 264.0 (*c* 1.47)[a] (+ 265.0)[a,14,15]
d R = *cyclo*-Hexyl	78%	110–112°C (—)	+ 191.4 (*c* 0.51)[b] (—)
e R = Ph	96%	88–89°C (82–83.5°C)[13]	+ 185.7 (*c* 0.95)[b] (+ 180.9 (*c* 1.0))[b,13]
f R = 	85%	oil	— (—)
g R = 	77%	oil	+167.1 (*c* 1.2)[b] (—)

[a] In acetone.
[b] In chloroform.

The reaction conditions were established using the nitrile, *rac*-**3**. The formation of the dianion intermediate **6** was confirmed by the isolation of **7** (a mixture of 4 diastereomers) (10% yield) and **8** when the reaction at –40°C was quenched with an excess of MeI. It must be pointed out that the reaction is sensitive to the acidity of the α-protons of the nitrile substrate. The pK_a of the chiral sulfoxide **1** is ca. 35 whereas the nitriles **9a–g** is ca. 31. In the case of phenylacetonitrile (pK_a ca. 22) the reaction failed and an intractable mixture formed.

A typical procedure for the transformation of the nitrile functionality to a β-ketosulfoxide moiety is as follows: *n*-Butyl lithium (1.60 M in hexane, 6.9 ml, 11.0 mmol) was added by syringe to a solution of diisopropylamine (1.11 g, 11.0 mmol) in dry THF (20 ml) at –40°C under a nitrogen atmosphere. After 30 min a solution of the sulfoxide **1** (1.54 g, 10.0 mmol) in dry THF (10 ml) was added to the solution at –40°C by syringe. After 30 min the reaction mixture was allowed to warm to 0°C and the nitrile **3** (0.95 g, 5.0 mmol) in dry THF was added by syringe and the reaction allowed to reach room temperature. After 1 h the reaction was quenched by addition of water (1 ml), the THF–hexane solvent evaporated and the residue diluted with water (20 ml). The aqueous solution was acidified (pH 2, 6 M HCl) and extracted with CH_2Cl_2. The product mixture was purified by column chromatography on silica gel using EtOAc:hexane (1:1) as eluent to give the β-ketosulfoxide **5** (1.46 g, 85%).

Acknowledgements

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9. Compound **1** was prepared by the procedure as reported in Ref. 4 and had mp 74.5–75.5°C and $[\alpha]_D$+192 (*c* 4.0, $CHCl_3$) in agreement with published values.
10. Satisfactory ^1H and ^{13}C NMR, and HR FAB-MS data were obtained for all compounds.
11. *rac*-**2** was prepared from (2*RS*)-2-methyl-1,3-propanediol in two steps: (a) PhCHO, TsOH, benzene (Dean–Starke), 98%; (b) $LiAlH_4$, $AlCl_3$, Et_2O, 92%.
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