Practical Synthesis of Chiral Sultam Auxiliaries: 3-Substituted-1,2-benzisothiazoline 1,1-Dioxides

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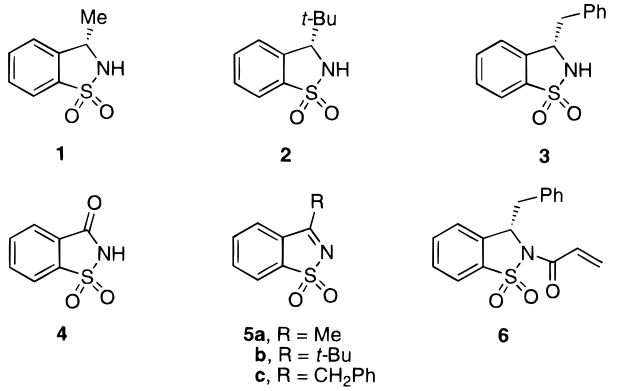
The sultam compounds **1** and **2** are an important class of chiral auxiliaries, developed by Oppolzer and coworkers.[1] They are structurally simpler than the well-known Oppolzer's camphorsultam auxiliary[2] and have a benzene chromophore which makes their detection easier. Sultam **1** has been shown to be a highly selective chiral auxiliary in asymmetric alkylations, acylations, aldolizations, and Diels−Alder reactions.[1b,c] Both enantiomers of sultam **1** are synthesized from an inexpensive starting material, saccharin (**4**), in two steps:[1a] (1) methyllithium addition to saccharin to give the corresponding *N*-sulfonylimine **5a**; (2) asymmetric hydrogenation of the sulfonylimine with a Ru-BINAP catalyst. Sultam **2** is also an excellent chiral auxiliary, particularly for the 1,3-dipolar cycloaddition of nitrile oxides, for which moderate stereoselectivities were observed with sultam **1**.[1d] In spite of the excellent stereofacial discrimination of sultam auxiliary **2**, its usefulness as a chiral auxiliary has not been explored fully, probably owing to its multistep preparation. Each enantiomer of sultam **2** was prepared by chemical resolution of the racemic mixture via *N*-(*S*)-camphorsulfonylated sultams.[1d] Sultam **3** has been briefly tested as an auxiliary in a racemic form in the Diels−Alder reaction.[1b] Because it has a phenyl group which could possibly participate in π-π interactions during the cycloaddition stage, it would be of interest to study it and its analogs as chiral auxiliaries further. As a continuing project toward the development and utilization of chiral auxiliaries in asymmetric reactions,[3] we have studied a more efficient synthesis of chiral 3-substituted sultam compounds. Here we report a practical synthesis of the sultam auxiliaries **2** and **3** in high enantiomeric excess which is also applicable to the synthesis of other structural analogs.

We studied the asymmetric reduction of *N*-sulfonylimine **5b** using several ruthenium-BINAP catalysts such as (*R*)-$RuCl_4(BINAP)_2Et_3N$,[1a] (*R*)-$Ru(OAc)_2$(BINAP),[4] and (*R*)-$RuCl_2$(BINAP)[5] under ca. 5 atm of hydrogen pressure but failed to reduce the imine bond. However, we were pleased to find that the transfer hydrogenation



with Noyori's RuCl(TsDPEN)(benzene) catalyst[6] produced desired sultams in high enantioselectivity. Thus, the transfer hydrogenation of **5b**[1d] in the presence of 0.5 mol % (*S,S*)-RuCl(TsDPEN)(benzene) afforded (*S*)-**2**[7] in 91% ee. The crude extracted product was crystallized, providing optically pure compound in 75% isolated yield. The enantiopurity was determined by ^{19}F NMR and GC analyses of the corresponding *N*-acylated derivative prepared using (*R*)-Mosher's acid chloride.[8] For the practical synthesis of chiral sultam **3**, it was necessary to improve the synthetic yield of *N*-sulfonylimine **5c** from saccharin. Addition of benzylmagnesium chloride to saccharin in degassed THF at −78 to 25 °C gave **5c** in low yields (20−30%), as precedented in the literature.[1b] However, by changing the solvent from THF to Et_2O, the yield could be increased to 67%.[9] Then, subsequent ruthenium-catalyzed transfer hydrogenation of **5c** as above gave (*S*)-**3** in 93% ee. Recrystallization of the extracted product gave essentially optically pure product. The absolute configuration of (*S*)-**3** was unambiguously determined from the X-ray crystal structure of its *N*-acryloylsultam derivative **6**.[10] Our results indicate that the transfer hydrogenation method, which has been demonstrated to be highly effective in the asymmetric reduction of imines, can be equally extended to *N*-sulfonylimines.[11]

In summary, we have developed an efficient synthesis of chiral 3-substituted-1,2-benzisothiazoline 1,1-dioxides **2** and **3** which involves no chromatographic separation. Because these sultam derivatives are excellent chiral auxiliaries, their application in asymmetric syntheses now becomes more feasible. An extension of the transfer hydrogenation method to other *N*-sulfonylimine com-

(1) (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117. (b) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. (c) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. (d) Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893. An attempted asymmetric hydrogenation of **5b** under the same conditions that were used for the synthesis of **1** gave only traces of racemic sultam **2**.

(2) (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

(3) (a) Ahn, K. H.; Lee, S.; Lim, A. *J. Org. Chem.* **1992**, *57*, 5065. (b) Ahn, K. H.; Yoo, D. J.; Kim, J. S. *Tetrahedron Lett.* **1992**, *33*, 6661.

(4) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053.

(5) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.

(6) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.

(7) *R*-Description for this (−)-**2** in the literature should be corrected to *S* according to the sequence rule: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 101−112.

(8) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(9) The solvent must be degassed by flushing with an inert gas; otherwise, the dimerization of benzyl Grignard reagent significantly reduces the addition yield. For the addition of Grignard reagents to saccharin, see: Abramovitch, R. A.; Smith, E. M.; Humber, M.; Purtschert, B.; Srinivasan, P. C.; Singer, G. M. *J. Chem. Soc., Perkin Trans. I* **1974**, 2589.

(10) The authors have deposited atomic coordinates for **6** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(11) After completion of our work, asymmetric hydrogenation of *N*-tosylimines, with low to moderate enantioselectivities, by Ru^{II}-BINAP complexes under high-H_2 pressure has been reported; see: Charette, A. B.; Giroux, A. *Tetrahedron Lett.* **1996**, *37*, 6669.

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pounds and application of resulting sultams in asymmetric syntheses are under investigation.

Experimental Section

General Methods. The *tert*-butyllithium and benzylmagnesium chloride used were from fresh bottles of commercial products. THF and Et_2O were purified from sodium−benzophenone ketyl under nitrogen and degassed by flushing with an inert atmosphere (Ar, N_2) for the addition reaction of benzylmagnesium chloride to saccharine. GC analysis was carried out using a capillary column (HP-1, cross-linked methyl silicone gum phase, 25 m × 0.2 mm × 0.33 μm) under the conditions given below. Melting points are uncorrected. All purification of reaction products was done by crystallization of the extracted products, but purification by SiO_2 column chromatography can be also used if necessary. HRMS data were obtained from the Korea Basic Science Center, Seoul.

3-(Phenylmethyl)-1,2-benzisothiazole 1,1-Dioxide (5c). To a degassed diethyl ether (70 mL) solution of saccharin (5.21 g, 28.4 mmol) at 25 °C was added fresh benzylmagnesium chloride (1.0 M in Et_2O, 62.5 mL) dropwise. The resulting mixture was further stirred at the same temperature for 6 h before quenching with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted further with Et_2O (60 + 30 mL); then the combined organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent and crystallization from EtOAc−Et_2O gave the desired sulfonylimine **5c** in 67% yield (first crop, 4.16 g; second crop, 0.73 g): R_f = 0.36 (ethyl acetate/hexanes = 2/3, v/v); mp 142.7−143.5 °C (lit.[1b] mp 129−131 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.28 (m, 9 H), 4.32 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.5, 134.3, 133.9, 133.3, 131.3, 129.6, 128.8, 128.3, 125.3, 122.9, 38.2; HRMS for $C_{14}H_{11}NO_2S$ (M^+) calcd 257.0511, found 257.0512.

3(*S*)-*tert*-Butyl-1,2-benzisothiazoline 1,1-Dioxide (2). To a CH_2Cl_2 solution (30 mL) of the catalyst RuCl(TsDPEN)(benzene), prepared *in situ* by heating an acetonitrile solution (10 mL) of $[RuCl_2(benzene)]_2$ (20 mg, 0.040 mmol) and (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN; 59 mg, 0.160 mmol) at 80 °C for 20 min according to the literature procedure[6b] followed by solvent exchange (evaporation of acetonitrile *in vacuo*, then addition of dichloromethane), were added sequentially *N*-sulfonylimine **5b**[1d] (3.57 g, 16.0 mmol) in CH_2Cl_2 (30 mL), formic acid (3.7 mL, 96.0 mmol), and triethylamine (5.6 mL, 40.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at 25 °C for 17 h before quenching with brine. After extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give sultam (−)-**2**.[7] The enantiopurity of this crude product was determined by ^{19}F NMR analysis of its *N*-acylated derivative obtained with (*R*)-Mosher's acid chloride: ^{19}F NMR ($CDCl_3$) δ 10.37 (4.2%), 8.67 (95.6%); 91% ee. After a single crystallization from $CHCl_3$−hexanes, enantiopure (*S*)-(−)-**2** was obtained in 75% yield (2.71 g). The enantiopurity was confirmed by GC analysis of its (*R*)-Mosher's ester [conditions: flow rate, 1 mL/min; oven temperature, 225 °C; injector temperature, 250 °C; detector temperature, 280 °C; t_R = 31.1 min (for comparison, an authentic sample of the Mosher's ester was synthesized from the racemic mixture of **2** which was prepared by the reduction of **5b** with $NaBH_4$; thus, the corresponding (*R*)-Mosher's ester of (*R*)-**2** has t_R = 30.0 min; this compound could not be detected in the once-crystallized sample of (*S*)-(−)-**2**)]: R_f = 0.23 (ethyl acetate/hexanes = 1/2, v/v); mp 128.5−129.5 °C (lit.[1d] mp 129−130 °C); $[\alpha]^{18}_D$ −54.0 (*c* 1.0, $CHCl_3$) [lit.[1d] $[\alpha]^{20}_D$ −53.9 (*c* 1.0, $CHCl_3$)]; IR (NaCl, cm^{-1}) 2953, 2352, 1545, 1474, 1336; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.68 (m, 4 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 141.5, 133.8, 133.3, 130.2, 127.0, 123.1, 38.9, 28.7; HRMS for $C_{11}H_{16}NO_2S$ $(M + H)^+$ calcd 226.0902, found 226.0900.

3(*S*)-(Phenylmethyl)-1,2-benzisothiazoline 1,1-Dioxide (3). This compound was prepared from **5c** (3.09 g) by a route similar to that for **2**. The enantiopurity of this product was determined by ^{19}F NMR analysis of its Mosher's ester: ($CDCl_3$) δ 10.54 (96.7%), 8.35 (3.3%); 93% ee. One crystallization of the extracted product from CH_2Cl_2 gave (−)-**3** (1.82 g, 59%) with 95.8% ee. Recrystallization of the first crop from ethyl acetate gave essentially optically pure compound (1.37 g, overall 44% yield), whose optical purity was determined by GC analysis of its (*R*)-Mosher's ester [conditions: flow rate, 1 mL/min; oven temperature, 250 → 290 °C (4 °C/min); injector temperature, 290 °C; detector temperature, 310 °C; t_R = 15.9 min ((*R*)-Mosher's ester of (*S*)-sultam **3**), 15.5 min (authentic (*R*)-Mosher's ester of (*R*)-sultam **3**): R_f = 0.25 (ethyl acetate/hexanes = 2/3, v/v); mp 146.7−147.6 °C; $[\alpha]^{23}_D$ −64.4 (*c* 1.0, $CHCl_3$); IR (NaCl, cm^{-1}) 3271, 3029, 1596, 1495, 1453, 1387, 1292, 1162, 1130, 1056; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79−7.28 (m, 9 H), 4.92 (dd, 1 H, *J* = 4.7, 13.7 Hz), 4.83 (s, 1 H), 3.29 (dd, 1 H, *J* = 4.7, 13.7 Hz), 3.06 (dd, 1 H, *J* = 9.2, 13.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 136.8, 133.4, 129.9, 129.8, 129.4, 127.8, 126.3, 124.8, 121.9, 59.2, 42.8; HRMS for $C_{14}H_{13}NO_2S$ (M^+) calcd 259.0667, found 259.0663.

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