Stereoselective Synthesis of Enantiopure Amino Compounds, *via* Mitsunobu Azidation of (2*S*,R_S)-1-(*p*-Tolylsulfinyl)butan-2-ol†

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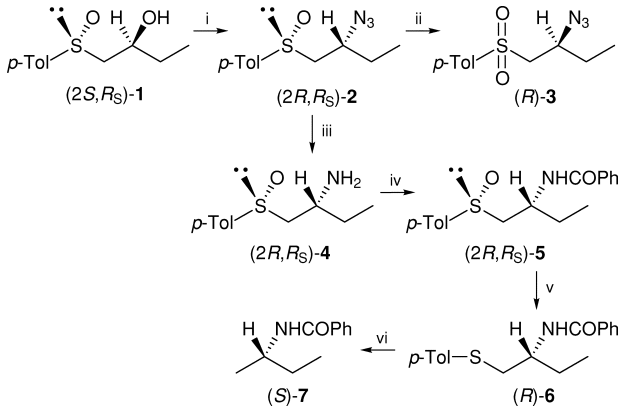
Azidation of (2*S*,R_S)-1–(*p*-tolysulfinyl)butan-2-ol under Mitsunobu conditions is the key step for a highly stereoselective preparation of enantiomerically pure amino compounds *via* chiral sulfoxide chemistry.

The stereocontrolled synthesis and the reactivity of chiral amines are topics of great interest in modern organic chemistry,[1] owing to the remarkable biological properties connected with this class of molecule. Our recent attention towards the development of new stereocontrolled approaches to chiral amines led us to investigate the azidation of fluorosubstituted β-sulfinyl alcohols under Mitsunobu conditions[2] as a new tool for preparing enantiomerically pure β-fluoro α-amino acids.[3] Since, to our knowledge, no reports dealing with Mitsunobu-type reactions of fluorine-free β-sulfinyl alcohols are extant in the literature, a further aim of this study was to investigate the compatibility of the stereogenic sulfinyl group with the Mitsunobu conditions, to extend this methodology to the synthesis of fluorine-free chiral amines. In this paper we describe the Mitsunobu azidation of enantiopure (2*S*,R_S)-1-(*p*-tolylsulfinyl)butan-2-ol **1**, and the transformation of the resulting azide (2*R*,R_S)-**2** into several amino compounds (**4**–**7**) (Scheme 1).

The starting β-sulfinyl alcohol (2*S*,R_S)-**1** was stereoselectively prepared by reduction with diisobutylaluminium hydride (DIBAH) of the corresponding (*R*)-1-(*p*-tolylsulfinyl)butan-2-one.[4] Transformation of (2*S*,R_S)-**1** into the β-sulfinyl azide (2*R*,R_S)-**2** was accomplished by treatment with NaN_3–PPh_3–CBr_4 (method A, 76%)[5] or, alternatively, with HN_3–PPh_3–DEAD (method B, 57%). As expected the desired product (2*R*,R_S)-**2** was formed with clean inversion of configuration at C-2, as a single diastereoisomer, isolated in pure form by flash chromatography on silica gel.



Scheme 1 *Reagents, conditions and yields*: i Method A: NaN_3, Ph_3P, CBr_4 (76%); Method B: HN_3, Ph_3P, DEAD (57%); ii, *m*-CPBA, 0 °C (96%); iii, $HS[CH_2]_3SH$–NEt_3 (97%); iv, $PhCO_2H$–DCC (72%); v, $(CF_3CO)_2O$–NaI (83%); Raney-Ni–H_2, 60 °C (94%)

The β-sulfinyl azide (2*R*,R_S)-**2** can be considered as a versatile synthetic intermediate. In fact its sulfinyl and azide moieties were submitted to several chemoselective elaborations, as described in Scheme 1. Oxidation of (2*R*,R_S)-**2** to the corresponding β-tosylazide (*R*)-**3** was achieved by reaction with *m*-chloroperbenzoic acid (*m*-CPBA) at 0 °C (96%). Furthermore, the azide function of (2*R*,R_S)-**2** could be reduced to amine by treatment with $HS[CH_2]_3SH$–triethylamine,[6] providing the β-sulfinyl amine (2*R*,R_S)-**4** in almost quantitative yield, without affecting the stereogenic sulfinyl centre.

The amino group of (2*R*,R_S)-**4** was subsequently protected upon treatment with DCC–benzoic acid (72%). The sulfinyl group of the resulting *N*-benzoyl derivative (2*R*,R_S)-**5** was deoxygenated with NaI–trifluoroacetic anhydride (TFAA), according to the Oae–Drabowicz protocol,[7] which delivered the *N*-benzoyl β-(*p*-tolylthio)amine (*R*)-**6** in 83% yield.

Finally, *N*-benzoyl *sec*-butylamine (*S*)-**7** was obtained by reductive desulfenylation of (*R*)-**6**, with Raney-Ni in ethanol at 60 °C (94%). Since the enantiomeric compound (*R*)-**7**, having $[\alpha]_D^{20}$ −21.5 (*c* 1.15, CH_2Cl_2), has been previously described in the literature,[8] polarimetric analysis of our sample, having $[\alpha]_D^{20}$ +24.7 (*c* 1.12, CH_2Cl_2), allowed us to confirm both its (*S*)-configuration, as well as the enantiomeric purity of all the precursor compounds **2**–**6**, represented in the Scheme 1.

In conclusion, we have reported a synthetically useful protocol for the synthesis of enantiomerically pure amino compounds from β-sulfinyl alcohols, which uses azidation under Mitsunobu conditions as the key step. This method features both high overall yields and stereoselectivity, and could therefore be successfully exploited for the preparation of many other biologically interesting, enantiopure amino compounds.

Experimental

General Procedure.—The instrumentation and general experimental and analytical procedures were recently described in detail.[9] The β-sulfinyl alcohol (2*S*,R_S)-**1** was prepared according to a literature procedure.[4]

β-Sulfinyl Azide (2*R*,R_S)-**2**.—*Method A*. To a stirred solution of (2*S*,R_S)-**1** (1.22 g, 5.75 mmol) in DMF (50 ml) cooled at 0 °C were added NaN_3 (5.61 g, 86.3 mmol), Ph_3P (5.53 g, 17.3 mmol) and finally CBr_4 (5.74 g 17.3 mmol). The mixture was stirred at r.t. for 4 h, then water and diethyl ether were added and the phases were separated. The organic phase was repeatedly washed with water in order to remove DMF, then dried over anhydrous Na_2SO_4, filtered and the solvent removed at reduced pressure. The crude mixture was submitted to flash chromatography (FC) (1:1 *n*-hexane–ethyl

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acetate), which afforded 1.02 g of the desired azide (2*R*,R_S)-**2** (76%), as a yellowish oil.

Method B. A solution of (2*S*,R_S)-**1** (212 mg, 1 mmol) and Ph_3P (524 mg, 2 mmol) in anhydrous benzene (11 mL) and HN_3 (4.0 mL of 1.0 M solution in anhydrous benzene, 4 mmol) was cooled with an ice–water bath under nitrogen. To the stirred solution DEAD (0.63 ml, 4 mmol) diluted with the same solvent (5 mL) was added dropwise. The bath was removed and, after *ca*. 15 min, TLC control revealed that all (2*S*,R_S)-**1** had been consumed. The reaction mixture was filtered, the solvent was removed *in vacuo*, and finally the crude was purified first by FC on silica gel, then on neutral alumina (4:6 *n*-hexane–ethyl acetate), providing 135 mg of the desired azide (2*R*,R_S)-**2** (57%).

(2*R*,R_S)-**2**: R_f (6:4 *n*-hexane–ethyl acetate) 0.31; $[\alpha]_D^{20}$+140.4 (*c* 0.88, $CHCl_3$); δ_H ($CDCl_3$) 7.56 (2 H, d, *J* 8.1 Hz), 7.36 (2 H, d, *J* 8.1 Hz), 3.6–3.4 (1 H, m), 3.08 (1 H, dd, *J* 13.1 and 7.0 Hz), 2.84 (1 H, dd, *J* 13.1 and 6.3 Hz), 2.42 (3 H, s), 2.0–1.5 (2 H, m), and 1.01 (3 H, t, *J* 7.3 Hz); δ_C ($CDCl_3$) 142.0, 139.9, 130.2, 124.1, 61.0, 58.3, 27.3, 21.5, 10.1 (Found: C, 55.3; H, 6.8; N, 17.4. $C_{11}H_{15}N_3OS$ requires C, 55.7; H, 6.4; N, 17.7%).

β-Tosyl Azide (*R*)-**3**.—To a solution of sulfinyl azide (2*R*,R_S)-**2** (44 mg, 0.18 mmol) in CH_2Cl_2 (2 ml), cooled at 0 °C, a solution of commercial *m*-CPBA (57–86%) (84 mg, 0.27–0.41 mmol) in CH_2Cl_2 (3 ml) was added dropwise. After 1 h at 0 °C (TLC monitoring) the reaction mixture was washed with aqueous 10% sodium sulfite, then with saturated aqueous $NaHCO_3$, finally with brine. The aqueous phases were washed with CH_2Cl_2, the collected organic phases were dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. FC of the crude (*n*-hexane–ethyl acetate 8:2) provided pure (*R*)-**3** as a yellowish oil (45 mg, 96%).

(*R*)-**3**. R_f 0.35 (4:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{20}$ + 40.1 (*c* 0.33, $CHCl_3$); δ_H ($CDCl_3$) 7.83 (2 H, d, *J* = 8.4 Hz), 7.37 (2 H, d, *J* 8.4 Hz), 3.87–3.78 (1 H, m), 3.26 (1 H, dd, *J* 14.5 and 8.2 Hz), 3.16 (1 H, dd, *J* 14.5 and 4.0 Hz), 2.47 (3 H, s), 1.8–1.5 (2 H, m), and 1.00 (3 H, t, *J* 7.3 Hz); δ_C ($CDCl_3$) 145.8, 137.3, 130.7, 128.7, 60.5, 59.3, 28.7, 22.4, 10.6; FT IR ν_{max}/cm^{-1} (KBr) 2972, 2121, 2070, 1598, 1319, 1303, 1146; *m*/*z* (EI, 70 eV) 226 (M^++1 − C_2H_5, 18), 211 ($M^+ - N_3$) (Found: C, 52.5; H, 6.4; N, 16.4. $C_{11}H_{15}N_3O_2S$ requires C, 52.2; H, 6.0; N, 16.6%).

β-Sulfinyl Amine (2*R*,R_S)-**4**.—To a solution of azide (2*R*,R_S)-**2** (200 mg, 0.84 mmol) in methanol (5 mL) at r.t. under nitrogen were added propane-1,3-dithiol (847 μL, 8.44 mmol) and triethylamine (1.17 mL, 8.44 mmol). After *ca* 4 h (TLC monitoring) the mixture was submitted to prolonged evaporation *in vacuo*, then the residue was purified by FC (ethyl acetate–isopropanol 95:5 to 5:95). The desired amine (2*R*,R_S)-**4** was obtained as a yellowish oil (172 mg, 97%).

(2*R*,R_S)-**4**. R_f 0.30 (5:95 ethyl acetate–isopropanol); $[\alpha]_D^{20}$+166.5 (*c* 1.02, $CHCl_3$); δ_H ($CDCl_3$) 7.56 (2 H, d, *J* 8.0 Hz), 7.33 (2 H, d, *J* 8.0 Hz), 3.24 (1 H, m), 2.88 (1 H, dd, *J* 8.3 and 13.2 Hz), 2.73 (1 H, dd, *J* 4.2 and 13.2 Hz), 2.41 (3 H, s), 1.71 (2 H, s), 1.61 (1 H, m), 1.47 (1 H, m), 0.95 (3 H, t, *J* 7.3 Hz); *m*/*z* (EI, 70 eV) 212 (M^++1, 85), 148 (46), 91 (25), 72 (100); FT IR ν_{max}/cm^{-1} (KBr) 3365 (br), 3270, 1597, 1495, 1459, 1399, 1087, 1034.

N-Benzoyl β-sulfinyl amine (2*R*,R_S)-**5**.—A mixture of β-sulfinyl amine (2*R*,R_S)-**4** (130 mg, 0.62 mmol), benzoic acid (144 mg, 1.18 mmol), DCC (243 mg, 1.18 mmol) and *p*-dimethylaminopyridine (13 mg, 0.11 mmol) in CH_2Cl_2 (6 ml) was stirred at r.t. for 90 min (TLC monitoring). The mixture was diluted with 10 ml of diethyl ether, filtered, and the solvent was removed *in vacuo*. FC (*n*-hexane–ethyl acetate 1:1) provided the desired *N*-benzoyl amine (2*R*,R_S)-**5** as a white solid (202 mg, 72%).

(2*R*,R_S)-**5**. R_f 0.30 (1:1 *n*-hexane–ethyl acetate); mp 151.5–153.0 °C (ethyl acetate); $[\alpha]_D^{20}$+79.1 (*c* 0.61, $CHCl_3$); δ_H ($CDCl_3$) 7.82 (2 H, d, *J* 8.0 Hz), 7.58 (2 H, d, *J* 8.0 Hz), 7.50–7.27 (5 H, m), 7.23 (1 H, br d, *J* 7.4 Hz), 4.32 (1 H, m), 3.23 (1 H, dd, *J* 8.7 and 13.4 Hz), 3.12 (1 H, dd, *J* 4.8 and 13.4 Hz), 2.40 (3 H, s), 1.94–1.50 (2 H, m), 0.92 (3 H, t, *J* 7.3 Hz); δ_C ($CDCl_3$) 167.4, 141.8, 140.3, 134.2, 131.5, 130.1, 128.4, 127.1, 124.2, 61.9, 48.3, 27.8, 21.4, 10.2; *m*/*z* (EI, 70 eV) 316 (M^++1, 10), 176 (100), 105 (70), 77 (32); FT IR ν_{max}/cm^1 (KBr) 3303, 1634, 1530, 1029 (Found: C, 68.0; H, 7.1; N, 4.9, $C_{18}H_{21}NO_2S$ requires C, 68.4; H, 6.7; N, 4.5%).

N-Benzoyl p-Tolylthioamine (*R*)-**6**.—To a mixture of *N*-benzoyl β-sulfinyl amine (2*R*,R_S)-**5** (107 mg, 0.32 mmol) and NaI (145 mg, 0.97 mmol) in acetone (2 ml) at −20 °C, a solution of TFAA (0.23 ml, 1.62 mmol) in acetone (1 ml) was added dropwise. The mixture immediately became dark green. After 5 min at −20 °C (TLC monitoring) the reaction was quenched with a saturated aqueous sodium sulfite solution, then a saturated aqueous $NaHCO_3$ solution was added until neutral pH was reached. The mixture was allowed to warm at room temperature, then the mixture was extracted with ethyl acetate, the collected organic phases were dried over anhydrous sodium sulfate and filtered and the solvent was removed *in vacuo*. FC (*n*-hexane–ethyl acetate 7:3) provided the desired *N*-benzoyl amine (*R*)-**6** (80 mg, 83%).

(*R*)-**6**. R_f 0.45 (7:3 *n*-hexane–ethyl acetate); δ_H ($CDCl_3$) 7.59 (2 H, m), 7.52–7.29 (5 H, m), 7.06 (2 H, d, *J* 7.8 Hz), 6.12 (1 H, brd, *J* 8.1 Hz), 4.30 (1 H, m), 3.21 (2 H, br signal), 2.28 (3 H, s), 1.88–1.58 (2 H, m), 0.96 (3 H, t, *J* 7.3 Hz); *m*/*z* (EI, 70 eV) 299 (M^+, 68%), 178 (46), 105 (100), 77 (67). FT IR ν_{max}/cm^{-1} (KBr) 3308, 1639, 1535, 1490 (Found: C, 71.2; H, 7.2; N, 4.6. $C_{18}H_{21}NOS$ requires C,72.2; H, 7.1; N, 4.7%).

N-Benzoyl sec-Butylamine (*S*)-**7**.—To a stirred solution of the thioamine (*R*)-**6** (72 mg, 0.24 mmol) in absolute ethanol (5.0 ml) Raney-Ni (*ca*. 0.4 g) was added and the slurry was vigorously stirred for 3 h at 80 °C under a hydrogen atmosphere. The Raney-Ni was removed by filtration on a Celite pad and the solvent was removed under reduced pressure. FC (*n*-hexane–ethyl acetate 4:1 to 7.3) provided the desired *N*-benzoyl amine (*S*)-**7** (40 mg, 94%) as a white solid.

(*S*)-**7**. R_f 0.40 (75:25 *n*-hexane–ethyl acetate); $[\alpha]_D^{20}$+24.7 (*c* 1.12, CH_2Cl_2); in the literature the enantiomer (*R*)-**7** is reported to have $[\alpha]_D^{20}$ − 21.5 (*c* 1.15, CH_2Cl_2)[8]; δ_H ($CDCl_3$) 7.81–7.78 (2 H, m), 7.52–7.36 (3 H, m), 6.10 (1 H, br signal), 4.20–4.03 (1 H, m), 1.57 (2 H, dq, *J ca*. 7.3 Hz both), 1.22 (3 H, d, *J* 6.8 Hz), 0.96 (3 H, t, *J* 7.3 Hz); δ_C ($CDCl_3$) 166.9, 135.0, 131.2, 128.4, 126.8, 47.0, 29.7, 20.5, 10.4.

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References

1 (*a*) J. Klein, in *The Chemistry of Double-Bonded Functional Groups: Supplement A*, ed. S. Patai, Wiley, Chichester, 1989, Vol. 2, Part 1, ch. 10; (*b*) *Methods of Organic Chemistry (Houben-Weyl): Stereoselective Synthesis*, eds. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Georg Thieme, Verlag: Stuttgart, 1995, Vol. E 21b.
2 (*a*) O. Mitsunobu, *Synthesis*, 1981, 1; (*b*) D. L. Hughes, *Organic Reactions*, 1992, Vol. 42, ch. 2; (*c*) E. Fabiano, B. T. Golding and M. M. Sadeghi, *Synthesis*, 1987, 190.
3 P. Bravo, G. Cavicchio, M. Crucianelli, A. Poggiali and M. Zanda, *Tetrahedron: Asymmetry*, 1997, **8**, 2811.
4 (*a*) G. Solladié, C. Greck, G. Demailly and A. Solladié-Cavallo, *Tetrahedron Lett*., 1982, **23**, 5047; (*b*) G. Solladié, G. Dmailly and C. Greck, *Tetrahedron Lett*., 1985, **26**, 435.
5 (*a*) I. Yamamoto, M. Sekine and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, 1980, 306; (*b*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama, H. Takada, K. Yamashita and A. Matsuda, *J. Org. Chem*., 1996, **61**, 915.
6 H. Bayley, D. N. Standring and J. R. Knowles, *Tetrahedron Lett*., 1978, **19**, 3633.
7 J. Drabowicz and S. Oae, *Synthesis*, 1977, 404.
8 (*a*) F. Foubelo and M. Yus, *Tetrahedron Lett*., 1994, **35**, 4831; (*b*) F. Foubelo and M. Yus, *Tetrahedron: Asymmetry*, 1996, **7** 2911.
9 A. Volonterio, M. Zanda, P. Bravo, G. Gronza, G. Cavicchio and M. Crucianelli, *J. Org. Chem*., 1997, **62**, 8031.