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Short Communication

The Synthesis of (*S*)-1-Methyl-3-phenylpropylamine by Inversion of Amines

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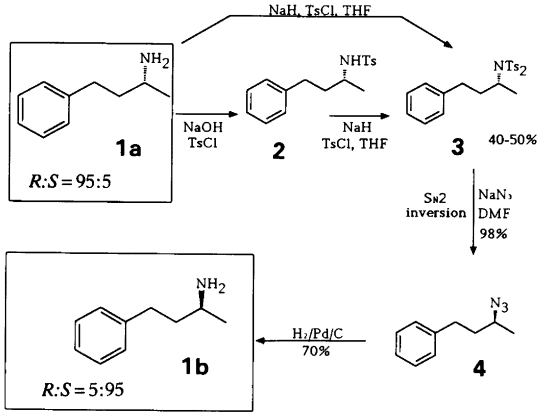
Interest in homochiral substances is rapidly increasing especially because of their importance as intermediates in the pharmaceutical industry. The development of suitable biotechnological methods and chiral syntheses for the preparation of pure enantiomers is impressive. However, processes based on optical resolution by selective crystallization of diastereomeric salts are still among the most important and profitable methods for the industrial production of optically active compounds. On the other hand the latter processes suffer from the disadvantage of low yields caused by the loss of at least 50% of an unwanted isomer when starting from a racemic mixture. More profitable optical resolution processes can be obtained by increasing the overall yields after inversion of the chiral centre of the unwanted isomer. This is particularly important for processes involving expensive racemic starting material.

Chiral intermediates used in the pharmaceutical industry often involve hydroxy- or amino-functions connected to the chiral centre. A variety of methods for the inversion of chiral alcohols by the S_N2 mechanism have been reported. However, the corresponding use of amine-substrates has received scant attention and the need for good methods for the inversion of chiral amines is therefore obvious. An important task is to develop efficient methods for inversion of the configuration of chiral amine-substrates in order to improve the overall yields in optical resolution processes involving amines.

Results and discussion

The leaving group ability of $-NH_2$ can be greatly improved by converting the primary amine into the ditosylimide, $-NTs_2$.[1] The $-NTs_2$ group has been successfully replaced by a number of nucleophiles with no regard for the stereochemistry.[2] It is reported that nucleophilic attack by azide ion gives inversion of configuration of sulfonates[3,4] (–OTs, –ONs, –OMs), halides[5,6] and epoxides.[7–10] Azides can be reduced to amines by a number of methods.

Herein we report the inversion of configuration of amines (**1a** → **1b**, Scheme 1) by nucleophilic attack of the azide ion on the *N*,*N*-ditosylimide **3**. (*R*)-1-Methyl-3-phenylpropylamine (**1a**, 90% ee) was used as a model substance in this work. We obtained the (*R*)-ditosyl-derivative (**3**) directly from the (*R*)-amine (**1**) with NaH in 40–50% yield, or via the (*R*)-tosylamide (**2**) in about 50% yield. The nucleophilic substitution reaction was carried out with NaN_3 in DMF (110–120°C, 20 h) catalysed by NaI. Quantitative yields of the azide (**4**) were obtained after chromatography. The optical purity of the inverted product could be measured after catalytic reduction of the azide (**4**) to the amine (**1b**). The overall yield of the total synthesis was about 35%, although no yield optimisation was carried out.



Scheme 1. Inversion of optically active amines. Synthetic route for the transformation of the *R*-amine (**1a**) into the *S*-amine (**1b**).

It was shown that the transformation of the ditosylimide into the azide occurred through an inversion of the

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chiral centre since the final product (**1b**) had an optical purity of 90% ee of the *S*-isomer. Chiral analysis of the starting material (**1a**) and the final amine product (**1b**) was carried out by GLC analysis of the diastereomeric derivatives. The derivatizing agent was (*S*)-α-methoxyphenylacetyl chloride. Our experience is that optical rotation measurement, $[\alpha]_D$, is a less reliable method of analysis of optical purity, particularly for non-crystalline products.

In conclusion, the configuration of the model substance, an optically active amine, can be inverted in a three-step synthesis. The inversion is carried out with an S_N2 type reaction of the *N,N*-ditosylimide by nucleophilic attack of the azide ion. The azide product is reduced by hydrogenolysis.

The nucleophilic substitution of ditosylimides with azide represents a convenient method for the inversion of configuration of the unwanted amine-isomer in optical resolution processes, and, as such, may help to increase the overall yields in these processes to make them more profitable.

Experimental

Reagents: *p*-toluenesulfonyl chloride, Fluka (*purum*); NaH, Aldrich (98%); NaN_3, Merck (reinst), (*S*)-α-methoxyphenylacetyl chloride from (*S*)-α-methoxyphenylacetic acid (Fluka, *purum*). Solvents: *pa* quality. THF was purified by being refluxed with $LiAlH_4$ and distilled, and was stored over molecular sieves, Merck (4 Å). M.p.s are uncorrected, and were measured on a Büchi apparatus. TLC: DC-Fertigplatten Kieselgel 60 F_{254} (0.25 mm). Detection: UV light at 254 nm or, better, with 5% alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230–400 mesh) Merck. GLC: Carlo Erba Model 8130, split-injection, hydrogen, detector: FID, column: Chrompack CP-SIL 5CB (25 m). ^{1}H NMR: Jeol FX-100 100 MHz NMR spectrometer, chemical shifts are reported in ppm downfield from TMS. MS: AEI MS-902. IR: Nicolet 20SXC FT-IR spectrometer. $[\alpha]_D$: Perkin Elmer 241 polarimeter (10 cm cell with a total volume of 1 ml). Hydrogenolysis: C. Gerhardt GmbH, Parr apparatus.

(R)-*1-Methyl-3-phenylpropylamine* (**1a**) was obtained by optical resolution using diastereoselective crystallization with (*S*)-*N*-acetylcysteine.[11] Typical procedure: from a solution of racemic amine (**1**, BASF, 120 g, 0.81 mol) and (*S*)-*N*-acetylcysteine (120 g, 0.81 mol) in ethanol (610 ml) was obtained about 50% yield (60 g) of a crystalline salt, m.p. 146–149°C, *R*:*S* ratio of the amine; 85:15 (GLC of the diastereomeric amides after extraction and derivatization with (*S*)-α-methoxyphenylacetyl chloride). Recrystallization from ethanol (200 ml) afforded 75% yield (45 g) of crystals, m.p. 154–157°C, *R*:*S* ratio 95:5. The amine was extracted from a NaOH-solution (pH > 13) to give 21 g (93%) of **1a**. MS [*m/z* (% rel int.)]: 149 (*M*, 6), 132 (16), 117 (8), 91 (17), 44 (100). IR (KBr, cm^{-1}): 2924 (s), 1584 (m), 1495 (m), 1454 (s), 748 (m), 699 (s). ^{1}H NMR ($CDCl_3$): δ 1.11 (d, 3 H), 1.4 (br, 2 H), 1.7 (m, 2 H), 2.7 (m, 2 H), 2.9 (m, 1 H), 7.24 (m, 5 H). $[\alpha]_D$ −4.3° (*c* = 1, $CHCl_3$).

(R)-N-*(p-Toluenesulfonyl)-1-methyl-3-phenylpropylamine* (**2**) *from* (R)-*1-methyl-3-phenylpropylamine* (**1a**). To NaOH (1.26 g, 32 mmol) in water (8 ml) was added **1a** (4.5 g, 30 mmol). *p*-Toluenesulfonyl chloride (5.7 g, 30 mmol) dissolved in ether (20 ml) and MeOH (25 ml) was added dropwise and the reaction was refluxed for 1 h. The reaction was followed by TLC. A crystalline product was obtained from the cooled mixture identified as **2**; 8.6 g (95% yield); m.p. 70–74°C. MS [*m/z* (% rel. int.)]: 303 (*M*, 2), 198 (33), 155 (43), 132 (100), 117 (15), 105 (7), 91 (88). IR (KBr, cm^{-1}): 3246 (s), 1599 (m), 1494 (m), 1306 (m), 1165 (s). ^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3 H), 1.7 (m, 2 H), 2.42 (s, 3 H), 2.6 (dt, 2 H), 3.4 (m, 1 H), 4.6 (br d, 1 H), 7.1 (m, 7 H), 7.77 (d, 2 H). $[\alpha]_D$ +23.7° (c = 1, $CHCl_3$).

(R)-N,N-*Di-(p-toluenesulfonyl)-1-methyl-3-phenylpropyl amine* (**3**) *from* (R)-*1-methyl-3-phenylpropylamine* (**1a**). A solution of (*R*)-1-methyl-3-phenylpropylamine (**1a**, 5 g, 34 mmol) in dry THF (40 ml) was added to a suspension of NaH (4.9 g, 204 mmol, 6 equiv.) in dry THF (40 ml). *p*-Toluenesulfonyl chloride (13 g, 68 mmol) in dry THF (25 ml) was added after which the reaction was refluxed for 6–8 h. When TLC showed complete conversion into the ditosyl derivative the reaction was quenched with water (80 ml) after first being cooled to room temperature. The product was extracted with chloroform to yield 15.2 g of an oily product (98 %). Crystals (7 g, 45%) were obtained from ether, m.p. 116–118°C. MS [*m/z* (% rel. int.)]: 457 (*M*, 0.2), 442 (0.1), 352 (6), 308 (10), 198 (86), 155 (68), 146 (3), 139 (8), 132 (64), 117 (9), 105 (13), 91 (100). IR (KBr, cm^{-1}): 1597 (m), 1360 (s), 1163 (s), 1084 (m), 1049 (m). ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3 H), 2.20 (m, 4 H), 2.46 (s, 6 H), 4.15 (m, 1 H), 7.2 (m, 9 H), 7.88 (d, 4 H). $[\alpha]_D$ + 30.2° (*c* = 1, CH_3OH).

(R)-N,N-*Di-(p-toluenesulfonyl)-1-methyl-3-phenylpropyl-amine* (**3**) *from* N-*(p-toluenesulfonyl)-1-methyl-3-phenyl-propylamine* (**2**). The same procedure, as described for the preparation of the ditosyl derivative (**3**), directly from the amine (**1a**) was used (above). Only 5 equivalents of NaH were necessary and the yield of the crystalline product (**3**) after 2 h reflux and work-up was about 50%. Characterization of the product **3** was in accordance with the data above.

(S)-*1-Methyl-3-phenylpropyl azide* (**4**) *from* (R)-N,N-*di-(p-toluenesulfonyl)-1-methyl-3-phenylpropylamine* (**3**). To a solution of **3** (0.8 g, 1.8 mmol) and catalytic amounts of NaI (30 mg) in DMF (7 ml) was added NaN_3 (0.23 g, 3.6 mmol, 2 equiv.) and the reaction was heated (120°C) until complete conversion into the azide had accurred

(TLC, 20 h). The product was extracted with ether after addition of water. Purification of the crude product by chromatography afforded 0.31 g (98%) of **4** as a light yellow oil. MS [*m/z* (% rel. int.)]: 175 (*M*, 0.2), 147 (20), 132 (16), 126 (3), 117 (12), 104 (70), 91 (100). IR (film, cm^{-1}): 2928 (s), 2100 (br s), 1454 (s), 1250 (br s), 7.47 (m), 699 (s). ^1H NMR ($CDCl_3$): δ 1.28 (d, 3 H), 1.8 (m, 2 H), 2.7 (dt, 2 H), 3.4 (m, 1 H), 7.3 (m, 5 H). $[\alpha]_D + 75.3°$ ($c = 1$, $CHCl_3$).

(S)-*1-Methyl-3-phenylpropylamine* (**1b**) *from* (S)-*1-methyl-3-phenylpropylazide* (**4**). The azide (**4**, 0.5 g, 2.9 mmol) in methanol (100 ml) was hydrogenated over 10% palladium-on-charcoal for 12 h at a hydrogen pressure of 3.5 bar. The obtained product was isolated by chromatography to give 0.35 g (70%) of the inverted amine **1b**. Spectroscopic characterization (MS, IR, ^1H NMR) of the product was in accordance with the data for the *R*-amine (**1a**, above). The inverted product had an optical purity of 90% ee of the *S*-isomer [GLC of the diastereomeric amides after derivatization with (*S*)-α-methoxyphenylacetyl chloride]. $[\alpha]_D + 7.0°$ ($c = 1$, $CHCl_3$).

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