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Stereoselective transformation of amines to alcohols enriched with the enantiomer formed by respectively inversion and retention of configuration

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Abstract: We hereby report the transformation of the chiral amines **1–3** to the corresponding alcohols **4–6** with 90–100% *inversion* of stereochemistry. KNO_2 and catalytic amounts of 18-crown-6 were used in the nucleophilic attack on the *N,N*-ditosylimide intermediates **1a–3a**. A diazotization reaction for the corresponding preparation of the alcohols **4–6** from the respective amines **1–3** with 65–90% *retention* of configuration is also discussed. © 1997 Elsevier Science Ltd

Introduction

The conversion of aliphatic amines into products with new functionality have not been extensively explored. For amine substrates having their primary amine function adjacent to an asymmetric centre, it is also important to study whether the transformation reaction proceeds stereoselectively, either by inversion of configuration or by retention of the stereochemistry. For many other functional groups there exist convenient chiral transformation methods for the stereospecific preparation of compounds with new functionality[1]. By development of new specific chiral transformation reactions for *amine* substrates such compounds can be converted to different functional groups with defined stereochemistry. Thus a number of target molecules can be synthesized. We have previously shown[2,3] that the stereochemistry of optically active amines can be completely inverted in an S_N2 type reaction of the *N,N*-ditosylimide, NTs_2, giving the original amine with the opposite configuration. We have also studied[4] the corresponding transformation of chiral amines into alcohols proceeding with 85–100% inversion of configuration using different oxygen-nucleophiles. Our results showed that the *N,N*-ditosylimides are promising intermediates for such transformations.

Of the methods available for the *inversion* of hydroxy functions, the reaction of tosylates of secondary optically active alcohols with potassium nitrite in DMSO or DMF is reported to afford the inverted alcohol as the main product[5,6]. A variety of triflate derivatives of sterically hindered chiral alcohols have also been converted to their enantiomers by treatment with KNO_2 in the presence of 18-crown-6 at room temperature[7] explained by a nitrite ester intermediate which hydrolyses *in situ*.

For the *retention* of configuration the diazotization reactions have successfully been used for the transformation of amino acids to α-hydroxy- or α-bromo-carboxylic acids[8–12]. In general diazotization reactions have previously not been recommended for conversion of aliphatic primary amines since they are reported to lead to a mixture of products[13,14]. However, aliphatic chiral amines are reported to give the acetate and the alcohol products in acceptable yields with varying stereoselectivity via the diazonium ions in acetic acid[15–17]. To give products with retention of configuration the loss of molecular nitrogen from diazonium ions has been interpreted as proceeding through carbocation or ion-pair intermediates in the product-forming step. Some retention data have been postulated to be consistent with a cyclic transition state or intermediate. To explain the formation of products with

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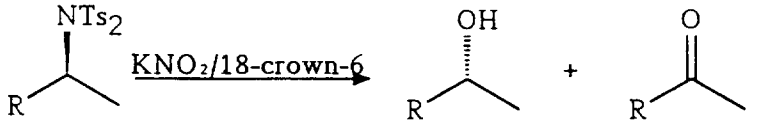
inversed stereochemistry a bimolecular substitution at carbon has also been proposed when a reasonably stable carbocation cannot form.

In the present study we report the results from the nucleophilic attack on the chiral *N,N*-ditosylimides **1a–3a** using KNO_2 and catalytic amounts of 18-crown-6 for the transformation of chiral amines to the corresponding alcohols with *inversion* of stereochemistry. We also present and discuss the product distribution and *retention* stereoselectivity obtained from diazonium ions generated from the chiral aliphatic primary amines **1–3**.

Results and discussion

Inversion

Starting with the *N,N*-ditosylimides, **1a–3a** prepared from the respective amines **1–3**[2,3], the alcohols **4–6** enriched with the enantiomer formed by inversion were obtained in 14–26% yield, see Scheme 1 and Table 1. (See Table 1 for the %ee, *R* or *S* of the substrates **1a–3a** and the products **4–6**.)



1a: R=Ph
2a: R=$(CH_2)_2$Ph
3a: R=cyclohexyl

4: R=Ph
5: R=$(CH_2)_2$Ph
6: R=cyclohexyl

7: R=Ph
8: R=$(CH_2)_2$Ph
9: R=cyclohexyl

Scheme 1.

The imides **1a–3a** were treated with 5–20 equivalents of KNO_2 in DMF added 0.5 equivalents of 18-crown-6. It was shown that 5 equivalents of KNO_2 are sufficient for the reaction. Compared with the reported analogous inversion reaction for alcohol-sulphonate substrates, our reactions in general needed higher temperature (reflux DMF, 110°C) and prolonged reaction time (48–72 h). Other solvents were also tried for the reaction, showing that CH_3CN gave both poorer yields and stereoselectivity. However comparable results regarding both yield and degree of inversion were obtained using either DMSO or DMF as solvent. The alcohol products from a series of reactions showed completely inverted stereochemistry. However several different experiments performed with varying reaction conditions, showed that the degree of inversion for this reaction generally was between 91–100%. Compared with our previously reported transformation reactions[4] for the amine derivative **2a** to the corresponding alcohol **5** using KOH, NH_4OAc or NH_4OBz as reagents, our present stereoselectivity results are some better. However is the configuration completely inverted in the best experiments for both the KNO_2/18-crown-6- and the KOH-/NH_4OAc-/NH_4OBz-reactions indicating an S_N2 type reaction. The yields are slightly better for the latter reactions. Our study has focused on the degree of inversion for the reaction and no attempts to optimize the yields of the alcohols were made.

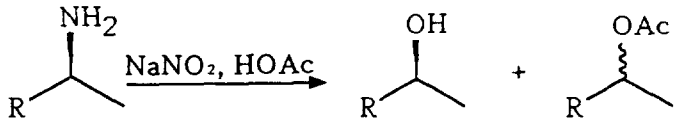
Table 1. Results for the reactions shown in Scheme 1

Substrate, % ee, *R* or *S*	**Product, % ee, *R* or *S***	**Degree of inversion** (general results from several experiments)	**Yield** Alcohol/Ketone
1a, >99 % ee, *R*	**4**, 80 - 92 % ee, *S*	**4**: 90 - 96 %	26 % / 10 %
2a, >99 % ee, *R* **2a**, 46 % ee, *S*	**5**, 88 % ee, *S* **5**, 46 % ee, *R*	**5**: 94 - 100 %	22 % / 7%
3a, >99 % ee, *R*	**6**, 82 % ee, *S*	**6**: 91 - 95 %	14 % / 3 %

The enantiomeric excess of the alcohol products **4–6** were analysed by GLC on a cyclodextrin chiral stationary phase. The identification of the respective *R*- and *S*-enantiomers by chiral GLC was based on comparison with specific rotation data and GLC results presented elsewhere[4]. The chromatographic separation parameters; the selectivity, and the resolution factors, R_S, were satisfactory for the *R/S* enantioseparations for the alcohols **4–6**, increasing going from **6**<**5**<**4** as expected[4]. However, the optimum analysis conditions were performing a sufficient but a marginal enantioseparation of **6**. See elsewhere for the discussion of chromatographic separation parameters for the analogous amine, alcohol and chloride compounds[4]. The alcohols **4–6** were otherwise characterized by ^{1}H NMR, IR and MS. We also isolated and characterized small amounts of the oxidized by-product, the corresponding ketones, **7–9**.

Retention

The chiral primary aliphatic amines **1**, **2** and **3** were used as substrates for the diazotization reaction as shown in Scheme 2. When the reaction of the amines **1** and **2** was carried out in acetic acid, both the alcohols (**4** and **5**) and the acetate products (**10** and **11**) were formed while standard diazotization conditions in sulphuric acid only afforded the alcohol products (**4** and **5**). These results were expected as the result of a substitution of the diazonium compounds by the present solvent in combination with the evolution of nitrogen. The results are given in Table 2. In general these diazotization experiments show that the acetate products (**10**, **11**) are the major product and the alcohols (**4**, **5**) are formed in lower yield when acetic acid is used as a solvent for the reaction. The optical activity of the acetate products is more or less lost (6–22% ee) during the reaction while the alcohol products (**4–6**) formed in the acetic acid diazotization reactions of the respective amines **1–3** are enriched with 65–90% of the enantiomer formed by retention of configuration. These results were obtained in several experiments with varying reaction conditions represented by different substrate and reagent concentrations and reduced reaction temperature. (See Table 2 for the %ee, *R* or *S* of the substrates **1–3** and the products **4–6**, **10** and **11**.)



1: R=Ph
2: R=$(CH_2)_2$Ph
3: R=cyclohexyl

4: R=Ph
5: R=$(CH_2)_2$Ph
6: R=cyclohexyl

10: R=Ph
11: R=$(CH_2)_2$Ph

Scheme 2

The stereochemical results can only be explained by the occurence of several competing modes of reaction. A number of parameters have to be considered to rationalize the possible competing deamination and solvolysis reaction mechanisms; the polarity of the solvent, the character of the substrate, the stability of a carbocation intermediate and the nature and the origin of the nucleophile[13–17]. The retention of configuration of the alcohol product formed in the acetic acid reaction can be explained by an ion-pair mechanism where the carbocation can hold the configuration and OH^- is postulated to be the counterion. The oxygen atom of the alcohol probably originates in the nitrite ion and in the diazotization intermediates **I** as shown:

[R-NH-N=O R-N=N-OH R-N=N^+ OH^- R^+ N_2 OH^-] **I**

A collapse of the 'hot' carbocation and the OH^- on the front side of the cation is proposed for the formation of the alcohol products **1–3** with retained stereochemistry in acetic acid. The formation of the corresponding racemic/slightly inverted acetate products **10** and **11** can be explained by an S_N1

Table 2. Results for the reactions shown in Scheme 2

Substrate, % ee, *R* or *S*	Alcohol product % ee, *R* or *S*	Yield	Acetate product % ee, *R* or *S*	Yield
1[a], >99 % ee, *S* **1**[b], >99 % ee, *S*	**4**, 66 % ee, *S* → 83 % Ret. **4**, 20 % ee, *R* → 60 % Inv.	23 %	**10**, 6 % ee, *R*	65 - 75 %
2[a], >99 % ee, *R* **2**[b], >99 % ee, *R*	**5**, 30 % ee, *R* → 65 % Ret. **5**, 26 % ee, *S* → 63 % Inv.	15 % 18 %	**11**, 22 % ee, *S*	20 - 40 %
3[a], >99 % ee, *S* **3**[b], >99 % ee, *R*	**6**, 80 % ee, *S* → 90 % Ret. **6**, 40 % ee, *R* → 70 % Ret.			

[a] The reaction was carried out in HOAc.

[b] The reaction was carried out in H_2SO_4/H_2O.

reaction mechanism via a planar carbocation combined with some bimolecular substitution where the acetate nucleophile attacks from the back side of the ion-pair to give some inverted acetate product. The corresponding diazotization reaction in 1 molar sulfuric acid afforded the alcohol products **4** and **5** slightly inverted (60–63%). In contrast to the acetic acid reactions the solvent of this reaction is water and most of the oxygen nucleophile may be derived from the solvent. Furthermore the environment is more acidic which will affect the diazonium equilibria and the degree of dissosiation of any ion-pair. An S_N1 reaction mechanism can account for the observed selectivity. Some backside attack of the nucleophile on the diazotization intermediate **I** can explain the more inversed product.

A similar inversion observation has been made by addition of pyridine to a 'retention' $SOCl_2$ reaction[18–20]. The corresponding explanation as above has been proposed. In general the opposite solvent effect is known from $SOCl_2$ reactions. In polar and unpolar organic solvents chiral alcohols react with $SOCl_2$ to give the chloride substitution products with respectively retention and inversion of stereochemistry explained by the S_Ni and the S_N2 mechanism. In these reactions, however, the solvent is not a nucleophile.

The alcohol product **6** from the sulphuric acid reaction was surprisingly formed with some retention (70%) of stereochemistry. This can possibly be rationalized by lower solubility of the cyclohexyl substrate in 1 molar sulfuric acid giving a more closely assosiated counter-ion and can as such explain the retention of configuration for this product.

In conclusion the alcohols **4–6** have been prepared both by nucleophilic substitution of the *N,N*-ditosylimides **1a–3a** using KNO_2/18-crown-6 and via the diazonium ion of the amines **1–3** giving respectively 91–100% inversion and 65–90% retention of configuration. Our present results represent a contribution in developing a series of methods for the stereoselective transformation of chiral amines.

Experimental

Chemicals

N,N-Di-(*p*-toluenesulfonyl)-1-phenylethylamine **1a**, *N,N*-di-(*p*-toluenesulfonyl)-1-methyl-3-phenylpropylamine (**2a**) and *N,N*-di-(*p*-toluenesulfonyl)-1-cyclohexylamine **3a** were prepared from the primary amines **1–3** as described elsewhere[2–4]. Potassium nitrite (Acros, >97%), sodium nitrite (Merck, >99%), 18-crown-6 (Fluka *purum*), Solvents: *p.a.* quality. TLC: DC-Fertigplatten Kieselgel 60 F_{254} (0.25 mm). Detection: UV light at 254 nm or preferentially by 5% alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230–400 mesh) Merck. GLC: Carlo Erba Model 8130; injector: split (100 ml/min, T=300°C), hydrogen, detector: FID (T=270°C), column: Chrompack CP-SIL 5CB fused silica WCOT (25 m). Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 4–5.5 p.s.i. ^{1}H NMR: Bruker Avance DPX 300 MHz and 400 MHz NMR spectrometer, chemical shifts are reported in ppm downfield from TMS. MS: AEI MS-902. IR: Nicolet 20SXC FT-IR spectrometer.

Inversion *reactions*

(S)-1-Phenylethanol ***4*** *from* (R)-N,N-*di* (p-*toluenesulfonyl*)-*1-phenylethylamine* ***1a***

A solution of the *N,N*-ditosylimide **1a** (1 g, 2.33 mmol), potassium nitrite (4 g, 46.6 mmol, 20 eqv.) and 18-crown-6 (0.29 g, 1.1 mmol, 0.5 eqv.) in DMF (30 ml) was refluxed for 72 h. The reaction was followed by TLC. The product was extracted with ether after the addition of water. Purification of the crude product by flash chromatography afforded 73 mg (26%) of **4**. MS [m/z (% rel. int.)]: 122 (53%), 121 (7%), 120 (5%), 107 (100%), 105 (19%), 104 (59%), 103 (26%), 91 (2%), 79 (68%), 78 (29%), 77 (51%). ^{1}H NMR ($CDCl_3$): 1.50 (d, 3H), 1.85 (br, 1H), 4.90 (q, 1H), 7.26–7.39 (m, 5H). IR (film, cm^{-1}): 3348 (br, s), 3029 (w), 2973 (s), 2926 (w), 2873 (w), 1603 (w), 1493 (m), 1451 (s), 1369 (w), 761 (m), 700 (s). $[\alpha]_D$: +42.2 (c=0.3, $CHCl_3$), 92% ee, *R*, see below; lit.[21], *S*-isomer: $[\alpha]_D$: −53.5 ($CHCl_3$, c=2.6). The alcohol product coeluted with an authentic commercial racemic standard (Fluka) both on the unpolar methylsilicone and the chiral cyclodextrin GLC column. Chiral GLC analysis of the product showed a *R*:*S* ratio of 94:6%. The results from several experiments showed that the stereoselectivity for this reaction generally was 90–96%. The oxidation by-product phenylmethylketone (**7**, 27 mg, 10%) was also isolated from this reaction: MS [m/z (% rel. int.)]: 120 (M, 55%), 105 (100%), 77 (70%), 51 (24%). ^{1}H NMR ($CDCl_3$): 2.61 (s, 3H), 7.44–7.98 (m, 5H). IR (film, cm^{-1}): 2956 (w), 2919 (m), 2849 (w), 1724 (m), 1677 (s), 1582 (w), 1450 (w), 1359 (m), 1267 (s), 760 (m), 690 (m).

(S)-4-Phenyl-2-butanol ***5*** *from* (R)-N,N-*di*(p-*toluenesulfonyl*)-*1-methyl-3-phenylpropylamine* ***2a***

The same procedure as described for the preparation of the alcohol **4** above starting with respectively 1 g (2.19 mmol) of substrate **2a** (*R*: *S*=27: 73), 20 eqv. (3.7 g, 43.8 mmol) of KNO_2 and 0.5 eqv. (0.29 g, 1.1 mmol) of 18-crown-6 yielded 72 mg (22%) of **5**. Characterization data (MS, ^{1}H NMR, IR) of **5** were in accordance with data presented elsewhere[4]. $[\alpha]_D$: −25.4 (c=0.3, $CHCl_3$), 46% ee, *R*, see below. The alcohol product coeluted with a reference standard from previous work[4] both on the unpolar methylsilicone and on the chiral cyclodextrin GLC column. Chiral GLC analysis of the product showed a *R*:*S* ratio of 73: 27% indicating a degree of inversion of 100%. The results from several experiments showed that the stereoselectivity for this reaction generally was 94–100%. The oxidation by-product 1-phenyl-3-butanone (**8**, 25 mg, 7%) was also isolated from this reaction: ^{1}H NMR ($CDCl_3$): 2.14 (d, 3H), 2.76 (m, 2H), 2.89 (m, 2H), 7.26–7.77 (m, 5H). IR (film, cm^{-1}): 3027 (w), 2927 (w), 1717 (s), 1604 (m), 1580 (w), 1497 (m), 1471 (m), 1453 (m), 1407 (m), 1359 (m), 1267 (m), 1162 (m), 769 (m), 750 (m), 698 (s).

(S)-1-Cyclohexylethanol ***6*** *from* (R)-N,N-*di*-(p-*toluenesulfonyl*)-*1-cyclohexylethylamine* ***3a***

The same procedure as described for the preparation of the alcohol **4** above starting with respectively 1 g (2.30 mmol) substrate and 20 eqv. (3.9 g, 46 mmol) of KNO_2 and 0.5 eqv. (0.29 g, 1.1 mmol) of 18-crown-6 yielded 40 mg (14%) of **6**. MS [m/z (% rel. int.)]: 128 (M, 0.5%), 127 (0.4%), 126 (1.2%), 113 (8.6%), 110 (33%), 95 (20%), 82 (69%), 67 (27%), 45 (100%). ^{1}H NMR ($CDCl_3$): 1.15 (d, 3H), 0.90–1.87 (m, 11H), 3.55 (m, 1H). IR (film, cm^{-1}): 3377 (br, m), 2969 (w), 2924 (s), 2852 (s), 1672 (m), 1450 (m). $[\alpha]_D$: −3.3 (c=0.4, $CHCl_3$), 80% ee, *R*, see below; lit.[22], *S*-isomer: $[\alpha]_D$: +5.4 (neat). The alcohol product coeluted with an authentic racemic standard made by $LiAlH_4$ reduction of cyclohexyl methyl ketone (Fluka) both on the unpolar methylsilicone and on the chiral cyclodextrin GLC column. Chiral GLC analysis of the product showed a *R*:*S* ratio of 90:10%. The results from several experiments showed that the stereoselectivity of this reaction generally was 70–90%. The oxidation product cyclohexylmethylketone (**9**, 9 mg, 3%) was also isolated from this reaction. ^{1}H NMR ($CDCl_3$): 0.92–2.34 (11H), 2.13 (s, 3H). Experiments using only 5 eqv. of KNO_2 gave comparable results.

Retention/*diazotization reactions*

Typical procedure: $NaNO_2$ (4.2 eqv.) was added in portions to a stirred solution of the amine substrate **1–3** (1.9 mmol) in acetic acid (16 ml/g amine substrate). After 18 h at room temperature the reaction was added water (2.5 ml/g amine substrate), stirred for 1 h and poured over a cooled NaOH (20%) solution. The product was extracted with ether and purified by flash chromatography. The alcohol products **4–6** formed in the diazotization reactions were in addition to GLC analysis characterized by ^1H NMR. Both ^1H NMR and GLC (chiral and unpolar methylsilicone columns) retention data were in accordance with the corresponding data for the identical products obtained in the inversion reactions above. The results from the chiral GLC analyses of the alcohols and the acetate products as well as the yields obtained are given in Table 2. 1-Phenyl-1-ethylacetate (**10**): ^1H NMR ($CDCl_3$): 1.55 (d, 3H), 2.10 (s, 3H), 5.90 (m, 1H), 7.38 (m, 5H). 1-Phenyl-3-butylacetate (**11**): ^1H NMR ($CDCl_3$): 1.29 (d, 3H), 1.90 (m, 2H), 2.05 (s, 3H), 2.65 (m, 2H), 4.95 (m, 1H), 7.26 (m, 5H). Diazotization in sulfuric acid, typical procedure: A mixture of the amine **1** (1 g, 8.25 mmol) in H_2SO_4 (1 M, 6 ml) was cooled to 0°C and dropwise added a solution of $NaNO_2$ (0.91 g, 13.2 mmol, 1.6 eqv.) in water (11 ml). The reaction was followed by TLC and worked up as described above.

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