Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 893–896

TETRAHEDRON: *ASYMMETRY*

Formation of chiral aryl ethers from enantiopure amine or alcohol substrates

Sadri A. Said and Anne Fiksdahl*

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7491 Trondheim, Norway

Received 22 February 2001; accepted 15 March 2001

Abstract—Three methods for the preparation of chiral aryl ethers are demonstrated. *N*,*N*-Disulfonylimide derivatives are used in the stereoselective formation of aryl ethers from chiral amines. Nucleophilic attack of aryloxide anions on the cyclic *N*,*N*-disulfonylimide derivative of (*S*)-1-phenylethylamine afforded the (*R*)-1-phenylethyl phenyl and 2-naphthyl ethers with 83–87 and 70–79% inversion of configuration, respectively. The results are compared with results from alternative methods for the preparation of homochiral aryl ethers from chiral alcohols with complete retention and inversion of configuration, respectively.
© 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have previously shown[1–7] that *N*,*N*-disulfonyl derivatives of primary amines (*N*,*N*-ditosylimides, *N*,*N*-dimesylimides, *N*,*N*-dinosylimides, *N*,*N*-1,2-benzenedisulfonylimides and *N*,*N*-1,2-naphthalenedisulfonylimides) are useful intermediates for the transformation of chiral amines into the corresponding alcohols or amines with inverted stereochemistry. We have also reported preliminary results for the preparation of chiral aryl ethers from disulfonylimides.[8]

Herein, we describe the preparation of chiral aryl ethers from amines via homochiral *N*,*N*-1,2-benzenedisulfonylimide or *N*,*N*-1,2-naphthalenedisulfonylimide derivatives. Application of two alternative methods for the preparation of homochiral (*R*)- or (*S*)-1-phenylethyl aryl ethers from (*R*)-1-phenylethanol, with either complete retention or inversion of configuration, are also presented.

2. Results and discussion

Cyclic (*S*)-*N*,*N*-1,2-benzenedisulfonylimide **2a** and (*S*)-*N*,*N*-1,2-naphthalenedisulfonylimide **2b** derivatives were prepared from (*S*)-phenylethylamine **1** and the respective benzene- and naphthalene-1,2-disulfonyl chlorides as previously described.[6,7] Nucleophilic substitution of imides **2a** and **2b** with aryloxide nucleophiles, prepared by sodium hydride deprotonation of phenol and 2-naphthol, respectively, afforded the corresponding phenyl and 2-naphthyl ethers **3a** and **3b** in 39–68% yield (see Scheme 1). Stereoselectivity data indicated a degree of inversion of 87 and 83% for the preparation of **3a** from **2a** and **2b**, respectively. In the preparation of **3b**, 79 and 70% inversion was observed from **2a** and **2b**, respectively (see Table 1).

2.1. Chiral analysis and syntheses of reference compounds

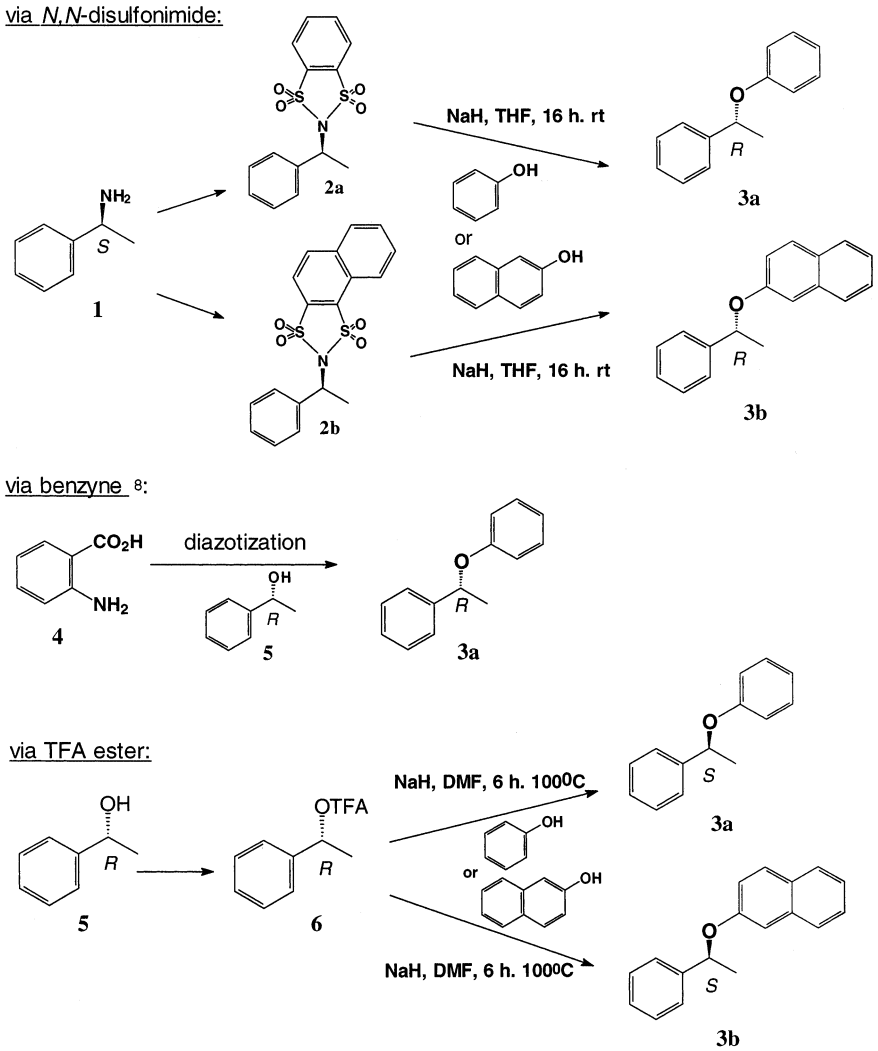
The enantiomeric purity of aryl ether **3a** was determined by chiral GLC. Confirmation of the absolute configuration of **3a** was based on comparison of the specific rotation data for the homochiral reference compound (*R*)-phenyl-1-phenylethyl ether **3a**, which was synthesised by a recently developed benzyne route[8] from anthranilic acid **4** via diazotisation with *tert*-butylnitrite and thermal decomposition to benzyne followed by nucleophilic attack by (*R*)-1-phenylethanol. Complete retention of configuration is observed in this method (see Scheme 1 and Table 1). The present stereoselectivity results, based on chiral GLC, are higher than our previously reported results,[8] which were based on the less accurate method of establishing enantiomeric purity of comparing the specific rotation of two samples.

The degree of inversion in the formation of **3b** could not be determined by chiral GLC or NMR/shift reagents due to the lack of enantioseparation in both methods. Attempts to prepare the homochiral (*R*)-1-

* Corresponding author. Tel.: +47 73 59 40 94; fax: +47 73 59 42 56; e-mail: anne.fiksdahl@chembio.ntnu.no

0957-4166/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(01)00130-6

phenylethyl 2-naphthyl ether **3b** using the benzyne route[8] were also unsuccessful. However, the homochiral phenyl and 2-naphthyl ether reference compounds **3a** and **3b** could be prepared in 65–87% yield by nucleophilic substitution of the corresponding (*R*)-1-phenylethanol TFA ester[9] **6** (see Scheme 1 and Table 1). The nucleophile was prepared by treatment of phenol with NaH. Complete inversion of stereochemistry was observed in this reaction, as shown by chiral GLC analysis of the phenyl ether product **3a**. The optical purity of the 2-naphthyl ether products (**3b** from **2a** and **2b**) was established based on comparison of optical rotation data with the homochiral reference compound **3b**. However, as mentioned above, this method is less



Scheme 1.

Table 1. Results for reactions are shown in Scheme 1

Starting material	Substrate	Nucleophile	Product (yield %)	$[\alpha]_D$ ($CHCl_3$)	Stereoselectivity
2a, **2b**	(*S*)-**2a**	PhO^-	(*R*)-**3a** (39)	+4.8 (*c*=2)	87% inv.[a]
	(*S*)-**2a**	2-$NaphthO^-$	(*R*)-**3b** (44)	+98 (*c*=0.2)	79% inv.[b]
	(*S*)-**2b**	PhO^-	(*R*)-**3a** (57)	+4.05 (*c*=2)	83% inv.[a]
	(*S*)-**2b**	2-$NaphthO^-$	(*R*)-**3b** (68)	+87 (*c*=0.2)	70% inv.[b]
4	**4**	(*R*)-**5**	(*R*)-**3a** (42)	+5.55 (*c*=2)	100% ret.[a]
6	(*R*)-**6**	PhO^-	(*S*)-**3a** (65)	−5.6 (*c*=2)	100% inv.[a]
	(*R*)-**6**	2-$NaphthO^-$	(*S*)-**3b** (87)	−124 (*c*=0.2)	100% inv.[c]

[a] Enantiomeric purity of the phenyl ether products (*R*)- and (*S*)-**3a** is based on chiral GLC.

[b] Enantiomeric purity of the 2-naphthyl ether product (*R*)-**3b** is based on $[\alpha]_D$ comparison with authentic enantiomerically pure synthetic standard of (*S*)-**3b** prepared via the TFA ester (*R*)-**6**.

[c] Enantiomeric purity of the 2-naphthyl ether product (*S*)-**3b** is based on the assumption that the stereoselectivity of this reaction is identical to that established by chiral GLC for the phenyl ether (*S*)-(**3a**) formation above.

accurate and gives lower results than the more precise GLC method.

Based on previous experience,[7] we have made the following observations regarding the effect of the leaving group, the substrate and the attacking nucleophile on the degree of inversion in nucleophilic substitution reactions of *N*,*N*-disulfonylimides:

1. Higher stereoselectivity was observed for the reported ether formation from the cyclic disulfonylimides relative to the corresponding azide and alcohol formation previously reported.[7] The 1,2-naphthalenedisulfonylimide leaving group affords only a slightly lower degree of inversion than the corresponding 1,2-benzene leaving group in the formation of aryl ethers **3a** and **3b**. This is in contrast to our previous observations for the formation of azide and alcohol products,[6,7] which showed 20–25% lower stereoselectivity for the 1,2-naphthalene intermediate.
2. In the formation of the azide and alcohol products, alkyl substrates generally afford 5–15% higher stereoselectivity than benzylic substrates,[7] caused by the carbocation stabilising effect of the latter. For aryl ether formation, higher stereoselectivity would, therefore, have been expected for non-benzylic substrates.
3. The reactions were carried out at ambient temperature overnight. As observed previously, both **2a** and **2b** were more easily substituted than the corresponding ditosyl-, dimesyl- and dinosylimides.[1–7] This is demonstrated by the lower reaction temperatures required for the formation of ethers from **2a** and **2b**. The ethers were formed in 39–68% yield, which is higher than in our previous nucleophilic substitution reactions of *N*,*N*-disulfonylimides.[1–7] All studies were focused on the degree of inversion for the reactions and no attempts were made to optimise the yields.
4. Two methods are presented for the formation of ethers **3a** and **3b** from amine and alcohol derivatives, respectively, by nucleophilic substitution with ArO^- to give inversion of configuration. Higher stereoselectivity is observed for the oxygen leaving group, -O-TFA (100% for substrate **6**), compared with the cyclic *N*,*N*-disulfonylimides (70–87% for substrates **2a** and **2b**). The O-TFA leaving group, having higher electron withdrawing character and lower nucleophilic power, therefore seems to favour an S_N2 reaction even when a less ionising solvent (THF versus DMF) and less vigorous reaction conditions (room temperature compared to 100°C) are used for the disulfonylimide reactions, which occur with partial racemisation.

3. Conclusion

Nucleophilic attack on *N*,*N*-1,2-benzenedisulfonylimides **2a** and *N*,*N*-1,2-naphthalenedisulfonylimides **2b** by aryloxide anions afforded (*R*)-1-phenylethyl phenyl ether **3a** and 2-naphthyl ether **3b** in 39–68% yield with 83–87 and 70–79% inversion of configuration, respectively. The homochiral phenyl and 2-naphthyl ethers **3a** and **3b** were prepared alternatively from the corresponding chiral alcohol via the TFA ester with 100% inversion of configuration. Phenyl ether **3a** has also been synthesised[8] via a benzyne route with complete retention of configuration.

4. Experimental

(*S*)-*N*,*N*-1,2-Benzenedisulfonyl-1-phenylethylamine **2a** and (*S*)-*N*,*N*-1,2-naphthalenedisulfonyl-1-phenylethylamine **2b** were prepared from (*S*)-phenylethylamine **1** and benzene 1,2-disulfonyl chloride and naphthalene 1,2-disulfonyl chloride, respectively, as described elsewhere.[6,7] Phenol and 2-napthol were obtained from Merck, (*R*)-phenylethanol from Acros, TFA anhydride from Fluka, and NaH (>95%) from Aldrich. THF was distilled (N_2) from the sodium ketyl of benzophenone and was used immediately, while DMF was dried over activated molecular sieve (4 Å). All solvents were pro analysi quality. Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 5–5.5 psi. $^1H/^{13}C$ NMR: Bruker Avance DPX 300/75.47 MHz spectrometer; chemical shifts are reported in ppm downfield from TMS. MS: MAT 95 XL. IR: Nicolet 20SXC FT-IR spectrometer.

4.1. Preparation of (*R*)-1-phenylethyl phenyl ether 3a from (*S*)-*N*,*N*-1,2-naphtalenedisulfonyl-1-phenylethylamine 2b

The preparation of (*R*)-**3a** from (*S*)-**2b** and the characterisation of (*R*)-**3a** has been published elsewhere.[8] HRMS calcd for $C_{14}H_{14}O$: 198.1045; obsvd: 198.1042. Chiral GLC indicated a degree of inversion of 83% (*R*:*S* ratio 83:17).

4.2. Preparation of (*R*)-1-phenylethyl 2-naphthyl ether 3b from (*S*)-*N*,*N*-1,2-naphthalenedisulfonyl-1-phenylethylamine 2b

The reaction was carried out as described elsewhere[8] for (*R*)-**3a** using 2-naphthol (33 mg, 0.23 mmol), NaH (16.5 mg, 0.69 mmol, 3 equiv.) in dry THF (5 mL) and (*S*)-*N*,*N*-1,2-naphthalenedisulfonyl-1-phenylethylamine (**2b**, 85 mg, 0.20 mmol) in dry THF (5 mL). The oily product (38.6 mg, 68% yield) was obtained after flash chromatography. ^1H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, $J=6.4$ Hz, 3H), 5.46 (q, $J=6.4$ Hz, 1H), 6.9 (d, $J=2$ Hz, 1H), 7.18 (dd, $J=8.1$ and 2 Hz, 1H), 7.30 (m, 5H), 7.42 (m, 2H), 7.58 (d, $J=8.1$ Hz, 1H), 7.71 (dd, $J=8$ and 1.8 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 24.6, 76.2, 109.0, 119.7, 123.7, 125.8, 126.1, 126.4, 127.0, 127.6, 127.7, 128.9, 129.5, 134.6, 143.2, 156.5; MS [*m*/*z* (% rel. int.)]: 248 (M, 6%), 145 (9%), 144 (100%), 127 (3%), 105 (57%), 104 (33%), 77 (15%); IR (neat film, cm^{-1}): 3058 (w), 3028 (w), 2972 (w), 2869 (w), 1628 (s), 1600 (s), 1510 (m), 1485 (s), 1386 (m), 1258 (s), 1217 (s), 1181 (m), 1103 (m), 837 (m), 747 (m), 700 (s). HRMS calcd for $C_{18}H_{16}O$: 248.1201; obsvd: 248.1203. $[\alpha]_D$ +87 ($c=0.2$, $CHCl_3$). Comparison of

specific rotation $[\alpha]_D$ with an authentic homochiral standard of (*S*)-**3b** (see below) indicated a degree of inversion of 70% (*R*:*S* ratio 70:30).

4.3. Preparation of (*R*)-1-phenylethyl phenyl ether 3a from (*S*)-*N*,*N*-1,2-benzenedisulfonyl-1-phenylethylamine 2a

The preparation of (*R*)-**3a** from (*S*)-**2a** and phenol was carried out using a similar procedure to that described above and elsewhere.[8] The oily product (39% yield) obtained after flash chromatography was characterised giving data in accordance with (*R*)-**3a** obtained from (*S*)-**2b** above. $[\alpha]_D$ +4.8 ($c=2$, $CHCl_3$). Chiral GLC indicated a degree of inversion of 87% (*R*:*S* ratio 87:13).

4.4. Preparation of (*R*)-1-phenylethyl 2-naphthyl ether 3b from (*S*)-*N*,*N*-1,2-benzenedisulfonyl-1-phenylethylamine 2a

The preparation of (*R*)-**3b** from (*S*)-**2a** and 2-naphthol was carried out using a similar procedure to that described above and elsewhere.[8] The oily product (44% yield) obtained after flash chromatography was characterised giving data in accordance with (*R*)-**3b** obtained from (*S*)-**2b** above. $[\alpha]_D$ +98 ($c=0.2$, $CHCl_3$). Comparison of the specific rotation $[\alpha]_D$ with an authentic homochiral standard of (*S*)-**3b** (see below) indicated a degree of inversion of 79% (*R*:*S* ratio 79:21).

4.5. Preparation of (*R*)-1-phenylethyl trifluoroacetate 6 from (*R*)-1-phenylethanol 5

To a solution of (*R*)-1-phenylethanol (**5**, 0.5 g, 4.1 mmol) and triethylamine (0.68 mL, 4.9 mmol, 1.2 equiv.) in dichloromethane (10 mL) was carefully added trifluoroacetic anhydride (0.68 mL, 4.9 mmol, 1.2 equiv.) at 0°C and the solution was stirred for 30 min. The yellowish oily crude product (0.8 g, 90%), which was obtained after evaporation of the solvent, was purified by flash chromatography to give (*R*)-**6** as an oil (0.68 g, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (d, $J=6.6$ Hz, 3H), 6.04 (q, $J=6.6$ Hz, 1H), 7.36 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 22.0, 77.4, 114.7 (q, $J=286$ Hz), 126.3, 129.0, 129.1, 139.3, 157.3 (q, $J=42$ Hz); MS [*m*/*z* (% rel. int.)]: 218 (M, 18%), 203 (3%), 122 (15%), 107 (44%), 105 (45%), 104 (100%), 91 (15%), 77 (53%). $[\alpha]_D$ +111.8 ($c=2$, $CHCl_3$).

4.6. (*S*)-1-Phenylethyl phenyl ether 3a from (*R*)-1-phenylethyl trifluoroacetate 6[9]

A solution of phenol (97 mg, 1.03 mmol) and NaH (37 mg, 1.54 mmol, 1.5 equiv.) in DMF (10 mL) was stirred at rt until gas evolution ceased. (*R*)-**6** (150 mg, 0.7 mmol) in DMF (2 mL) was added and the mixture was heated for 6 h at 100°C. Water (25 mL) was added after cooling, and (*S*)-**3a** was obtained after extraction and flash chromatography (89 mg, 65% yield). The spectroscopic properties and GLC retention times were in agreement with those of (*R*)-**3a** prepared from the *N*,*N*-disulfonylimides **2a** and **2b**. $[\alpha]_D$ −5.6 ($c=2$, $CHCl_3$). Chiral GLC indicated a degree of inversion of 100% (>99% ee (*S*)-enantiomer).

4.7. Preparation of (*S*)-1-phenylethyl 2-naphthyl ether 3b from (*R*)-1-phenylethyl trifluoroacetate 6

The reaction was carried out as described above (for the preparation of (*S*)-**3a**) from 2-naphthol (317 mg, 2.2 mmol), NaH (79 mg, 3.3 mmol, 1.5 equiv.) and (*R*)-**6** (320 mg, 1.47 mmol) to give (*S*)-**3b** (317 mg, 87% yield). The spectroscopic properties and GLC retention times were in agreement with those of (*R*)-**3b** prepared from the *N*,*N*-disulfonylimides (*S*)-**2a** and (*S*)-**2b**. $[\alpha]_D$ −124 ($c=0.2$, $CHCl_3$). Complete inversion for the 2-naphthyl ether (*S*)-**3b** formation is based on the assumption that the stereoselectivity of this reaction is identical to that established by chiral GLC for the phenyl ether (*S*)-**3a** formation above.

4.8. Preparation of (*R*)-1-phenylethyl phenyl ether 3a from anthranilic acid 4 and (*R*)-1-phenylethanol 5

This method, via the benzyne intermediate, has been published elsewhere.[8]

References

1. Seljestokken, B; Fiksdahl, A. *Acta Chem. Scand.* **1993**, *47*, 1050–1052.
2. Johansen, C.; Fiksdahl, A. *Chirality* **1994**, *6*, 161–164.
3. Oppedal, H.; Tveit, I. C.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1994**, *5*, 895–902.
4. Ileby, N.; Kuzma, M.; Heggvik, L. R.; Sørbye, K.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2193–2198.
5. Heggvik, L. R.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2189–2192.
6. Sørbye, K.; Tautermann, C.; Carlsen, P. H.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1998**, *9*, 681–689.
7. Said, S. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2627–2633.
8. Said, S. A.; Fiksdahl, A.; Carlsen, P. H. *Tetrahedron Lett.* **2000**, *41*, 5593–5596.
9. Okamoto, K.; Kinoshita, T.; Takemura, Y.; Yoneda, H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1426–1433.