Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2627–2633

TETRAHEDRON: *ASYMMETRY*

Preparation and nucleophilic substitution of the *N*,*N*-1,2-naphthalenedisulfonylimide derivative of a chiral amine

Sadri A. Said and Anne Fiksdahl *

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7034 Trondheim, Norway

Received 27 May 1999; accepted 22 June 1999

Abstract

In our series of nucleophilic substitution reactions on *N*,*N*-disulfonylimides we hereby report the preparation and the nucleophilic substitution of the *N*,*N*-1,2-naphthalenedisulfonylimide derivative **1a** of the chiral amine **1**. The disulfonimide was prepared by using the disulfonyl chloride reagent. Nucleophilic substitution of **1a** by KNO_2 and azide afforded the corresponding alcohol **2** and the azide product **3** with, respectively, 63 and 70% inversion of configuration. The stereochemical results are compared with previously reported results for a series of *N*,*N*-disulfonylimides showing that the degree of inversion of **1a** is lower than for the other *N*,*N*-disulfonylimides.

1. Introduction

In our ongoing effort to develop stereoselective transformation reactions for chiral amines we have previously shown[1–6] that some *N*,*N*-disulfonyl derivatives of primary amines: *N*,*N*-ditosylimides, *N*,*N*-dimesylimides, *N*,*N*-dinosylimides and *N*,*N*-1,2-benzenedisulfonylimides, may be transformed by nucleophilic substitution reactions into the corresponding amines or alcohols with inversion of stereochemistry.

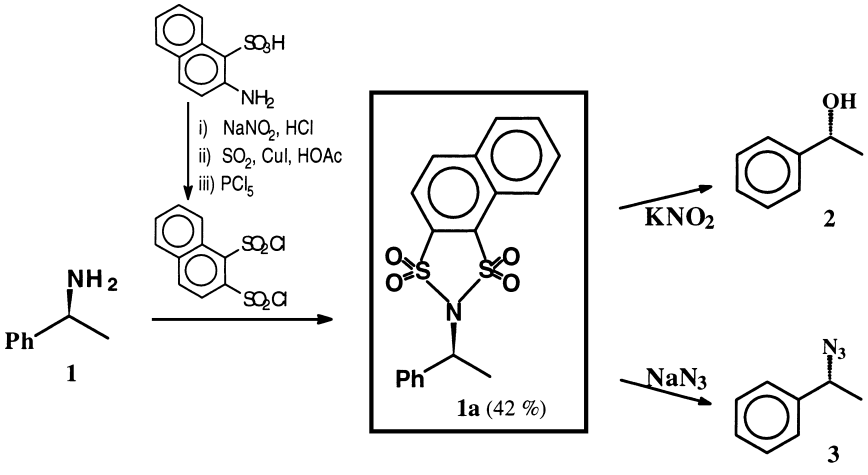
In the present study we report the preparation of the new cyclic *N*,*N*-1,2-naphthalenedisulfonylimide derivative **1a** of the primary amine **1** using naphthalene-1,2-disulfonyl chloride. The leaving group ability of the *N*,*N*-1,2-disulfonylimide moiety in this intermediate was studied in the nucleophilic attack by KNO_2 and azide. The corresponding alcohol **2** and azide **3** were formed. The stereochemistry of the substitution reactions are discussed and compared with our previously reported results for a series of *N*,*N*-disulfonylimides.[1–6]

* Corresponding author. Tel: +47 73 59 90 94; fax: +47 73 59 42 56; e-mail: anne.fiksdahl@chembio.ntnu.no

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00258-X

2. Results and discussion

The cyclic *N*,*N*-1,2-naphthalenedisulfonylimide derivative **1a** was obtained from the primary amine **1** and naphthalene-1,2-disulfonyl chloride in comparable yields (42%) (Scheme 1) and by identical reaction conditions as previously reported for the *N*,*N*-1,2-benzenedisulfonylimides.[6] The *N*,*N*′-bis-byproduct, the disulfonamide, R-NH-SO_2-Ph-SO_2-NH-R, could be isolated as well and characterized. The reagent, naphthalene-1,2-disulfonyl chloride, was prepared in a three-step procedure via diazotization from 2-aminonaphthalenesulfonic acid essentially as previously described for benzene-1,2-disulfonyl chloride.[6] In contrast to what was observed in the preparation of the benzene reagent, the 2-OH- and the 2-Cl-naphthalenesulfonic acids could be isolated and identified as byproducts. This can be rationalized by a displacement of the diazonium group in 2-position both by hydroxyl and chloro substituents and indicates a higher reactivity of the 2-position in 1-naphthalenesulfonic acid than the corresponding benzene compound.



Scheme 1.

To reduce the amount of unwanted products, concentrated hydrochloric acid was replaced by glacial acetic acid in step two to dissolve the diazonium salt.

Nucleophilic attack on the *N*,*N*-1,2-naphthalenedisulfonylimide **1a** by KNO_2 and NaN_3 afforded the alcohol **2** and azide **3** with, respectively, 60–63% and 60–70% inversion of configuration (see Table 1). The stereoselectivity in the formation of **2** and **3** from the *N*,*N*-1,2-naphthalenedisulfonylimide **1a** is lower (60–70%) than for the analogous previously reported *N*,*N*-1,2-benzenedisulfonylimide[6] (see Table 2, **8b**, 84–94%). This might be explained by a higher contribution from an ionic or ion pair mechanism leading to partly racemized products because of the higher stability of the naphthalene relative to the benzenedisulfonylimide leaving group. The naphthalene leaving group is not expected to be a better nucleophile than the analogous benzene leaving group, and an explanation of the higher racemization for the former substrate would not be that the released disulfonylimide competes as a nucleophile on the starting material **1a**. As can be seen from Tables 1 and 2 the mildest reaction conditions for the substitution of the naphthalenedisulphonylimide substrate **1a** with both nitrite and azide are comparable with the previously reported reaction conditions for the analogous benzenedisulphonylimide **8b.** Both **1a** and **8b** are more easily substituted than the corresponding ditosyl- **5b**, dimesyl- **6b** and dinosyl-imides **7b**.[1–5] This is particularly apparent at lower reaction temperatures. However, in contrast to what was observed for the *N*,*N*-1,2-benzenedisulfonylimides **8a**,**b**,[6] the degree of inversion of the naphthalenedisulphonylimide **1a** could not be optimized by varying the temperature, the reaction time

Table 1
Results for the nucleophilic substitution of **1a** (>99% ee/*S*) shown in Scheme 1

	Substitution product, % ee/*R* (reaction conditions)	**Degree of Inversion**
	Alcohol 2[a]	
entry 1	20 % ee/*R* (KNO_2/18-cr-6, DMF, 0°C, 3 hrs)	60 %
entry 2	20 % ee/*R* (as above, 30% DMF/DMSO, 0°C,5 hrs)	60 %
entry 3	24 % ee/*R* (as above, DMF, 18°C, 24 hrs)	62 %
entry 4	20 % ee/*R* (as above, DMSO, 18°C, 24 hrs)	60 %
entry 5	24 % ee/*R* (KOH, DMF, 18°C, 24 hrs)	62 %
entry 6	26 % ee/*R* (NH_4OAc, DMF, 18°C, 24 hrs)	63 %
entry 7	26 % ee/*R* (NH_4OBz, DMF, 18°C, 24 hrs)	63 %
entry 8	20 % ee/*R* (KNO_2/18-cr-6, DMF, 80°C, 3 hrs)	60 %
entry 9	22 % ee/*R* (as above, DMSO, 80°C, 3 hrs)	61 %
	Azide 3[a]	
entry 10	40 % ee/*R* (NaN_3, 30 % DMF/DMSO, 0°C, 24 h)	70 %
entry 11	34 % ee/*R* (NaN_3, DMF, 18°C, 4 days)	67 %
entry 12	40 % ee/*R* (NaN_3, DMSO, 18°C, 24 h)	70 %
entry 13	20 % ee/*R* (NaN_3, DMF, 60°C, 24 h)	60 %
entry 14	36 % ee/*R* (NaN_3, DMSO, 60°C, 24 h)	68 %

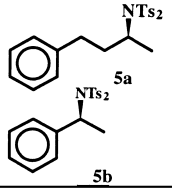
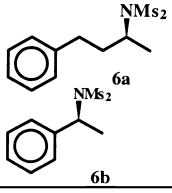
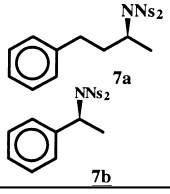
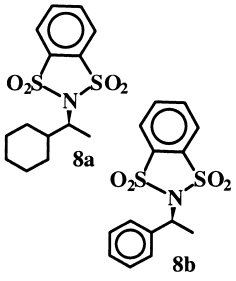
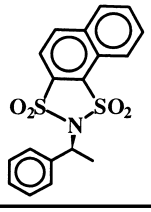
[a] The % enantiomeric excess of the alcohol product **2** and the azide product **3** is based on the direct chiral GLC analysis.

or the solvent. Thus, the stereoselectivity in the formation of **2** and **3** from **1a** was not dependent on the reaction conditions (see Table 1). Other oxygen nucleophiles such as hydroxide, acetate and benzoate[3] were used in addition to nitrite for the preparation of the alcohol **2** (see Table 1, entry 5–7) giving no specific change in stereoselectivity. A comparison of the *N,N*-disulfonylimides **1a**, **5**–**8** listed in Table 2 shows that only the ditosylimides (-NTs_2, **5a**,**b**) give complete inversion of configuration by nucleophilic substitution independent of benzylic or aliphatic substrates. As expected, caused by the carbocation stabilizing effect, the benzylic substrates **6b**–**8b** in general give a lower degree of inversion than the corresponding aliphatic substrates **6a**–**8a**. All these studies have focused on the degrees of inversion for the reactions and no attempts to optimize the yields were made.

3. Conclusion

In conclusion, nucleophilic attack on the *N,N*-1,2-naphthalenedisulfonylimides **1a** by KNO_2 and NaN_3 afforded the alcohol **2** and azide **3** with, respectively, 60–63% and 60–70% inversion of configuration.

Table 2
Comparison between nucleophilic substitution reactions of different *N,N*-disulfonylimides[1–6]

Nucleophilic Substitution of *N,N*-disulfonylimides	**Degree of inversion, (optimal reaction conditions)**	
	Alcohol product 	**Azide product** 
 **5a** **5b**	**100 %** (KNO_2,DMF, 120^{0}C, 72h) **100 %** (as above)	**100 %** (NaN_3, DMF,135^{0}C, 2h) **100 %** (as above)
 **6a** **6b**	**93 %** (as above) **82 %** (as above)	- -
 **7a** **7b**	**95 %** (as above) **82 %** (as above)	- -
 **8a** **8b**	**90 %** (KNO_2,DMF, 90^{0}C, 3d) **84 %** (KNO_2,30%DMF/DMSO, 0^{0}C, 24h)	**98 %** (NaN_3, DMSO,80^{0}C,4d) **94 %** (NaN_3,30%DMF/DMSO, 0^{0}C,24h)
 **1a**	**60-63 %** (Independent of reaction conditions, see Table 1)	**70 %** (Independent of reaction conditions, see Table 1)

This is lower than for the previously reported analogous *N*,*N*-1,2-benzenedisulfonylimides[6] (**8a**–**b**, 84–98%). The degree of inversion by nucleophilic substitution of *N*,*N*-1,2-naphthalenedisulfonylimide **1a** does not vary with reaction conditions in contrast to what has been observed for the previously reported *N*,*N*-1,2-benzenedisulfonylimides.[6] Among the so far prepared *N*,*N*-disulfonylimides, the *N*,*N*-ditosylimides **5a**,**b**, -NTs_2, give the best and complete inversion of configuration independent of benzylic or aliphatic substrates.

4. Experimental

4.1. Chemicals

(*S*)-1-Phenylethylamine **1**, Hexel Chemical Products; NaH, Aldrich (>95%); phosphorus pentachloride, 18-crown-6, Fluka (*purum*); 2-aminonaphthalenesulfonic acid, Fluka (*pract*); sodium azide, Merck (*reinst*); sodium nitrite, Merck (>99%); potassium nitrite, Acros (>97%). Solvents: *pro analysi* quality. DMF and DMSO were dried over activated molecular sieve (4A). 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 5–5.5 psi. Mps are uncorrected, and were measured on a Büchi apparatus. ^{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.

4.2. Naphthalene-1,2-disulfonyl chloride from 2-aminonaphthalenesulfonic acid

Preparation of the title compound was carried out by a three step procedure from 2-aminonaphthalenesulfonic acid mainly as described elsewhere.[6] 2-Aminonaphthalenesulfonic acid (12 g, 53.8 mmol) and sodium carbonate (3.36 g, 31.7 mmol) were dissolved in water (100 ml) by stirring and heating. The solution was cooled to 10°C and sodium nitrite (3.70 g, 53.8 mmol) in water (10 ml) was added dropwise. The resulting brown solution was poured onto a mixture of concentrated hydrochloric acid (10.5 ml) and crushed ice (60 g). After cooling for 1 hour the brown crystals were filtered off and immediately dissolved in concentrated acetic acid (50 ml). A suspension of cuprous(I) chloride (1 g, 10 mmol) in sulfur dioxide/acetic acid (75 ml, 30% SO_2 solution) was added with stirring and the temperature was slowly raised to 40°C. After 5 hours the solvent was stripped off. The resulting solid was stirred and heated with saturated sodium chloride (10 ml) to yield a green porridge which was cooled, filtered, washed with cold methanol and dried to give the disodium salt of 1,2-naphthalene disulfonic acid (14.87 g, 44.8 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 2H), 7.93 (d, J=9.2 Hz, 1H), 8.06 (d, J=8.8 Hz, 1H), 8.19 (d, J=8.8 Hz, 1H), 8.92 (d, J=8.0 Hz, 1H). The disodium salt was heated overnight with phosphorus pentachloride (27.98 g, 134 mmol, 3 equiv.). Excess phosphorus pentachloride and the formed phosphorus oxychloride ($POCl_3$) were distilled off under vacuum. The yellowish solid was added ice water (100 ml) and the mixture was extracted with chloroform (3×50 ml). The solvent was evaporated and naphthalene-1,2-disulfonyl chloride (1.71 g, 5.3 mmol, 10% overall yield from 2-aminonaphthalenesulfonic acid) was obtained as a yellowish oil after flash chromatography

(silica gel, 15% acetone/heptane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (m, 2H), 8.05 (d, J=9.0 Hz, 1H), 8.42 (s, 2H), 9.06 (d, J=8.8 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 124.6, 126.6, 129.0, 129.1, 130.7, 131.0, 137.0, 137.1, 138.5, 142.5. The identity of the product was confirmed by HH/HC COSY and DEPT. MS [m/z (% rel. int.)]: 328/326/324 (M, 3.3/9.5/13.0%), 291 (36%), 289 (88%), 260 (30%), 226 (12%), 225 (12%), 198 (22%), 196 (30%), 177 (12%), 161 (87%), 127 (31%), 126 (100%). IR (KBr, cm^{-1}): 3100 (w), 3076 (w), 1372 (s), 1185 (s), 822 (m), 780 (m), 740 (m), 634 (s), 570 (s), 537 (m), 509 (s), 487 (m).

4.3. N,N-*1,2-Naphthalenedisulfonylimide formation*

*4.3.1. (*S*)-*N,N-*1,2-Naphthalenedisulfonyl-1-phenylethylamine **1a***

The preparation of the title compound from (*S*)-phenylethylamine **1** was carried out as described elsewhere.[6] Naphthalene 1,2-disulfonyl chloride (260 mg, 0.78 mmol) was dissolved in methylene chloride (30 ml) and brought to reflux. A solution of (*S*)-(+)-1-phenylethylamine (0.10 ml, 0.78 mmol) and triethylamine (0.239 ml, 1.72 mmol) in methylene chloride (10 ml) was added slowly over 12 hours. The reaction was allowed to reflux for another two hours. The solvent was evaporated in vacuo to yield 0.52 g of the crude product. The mixture was dissolved in hot acetone (10 ml), cooled to room temperature and triethylamine hydrochloride was filtered off. Compound **1a** was isolated and separated from the *N,N′′*-bis((*S*)-1-phenylethyl)-1,2-naphthalenedisulfonamide byproduct by flash chromatography (silica gel, 10% acetone/heptane) to yield 0.119 g (42%) of **1a**. Mp 131–133°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (d, J=7.08 Hz, 3H), 5.50 (q, J=7.08 Hz, 1H), 7.38 (m, 3H), 7.65 (m, 2H), 7.80 (m, 3H), 8.02 (m, 1H), 8.25 (m, 1H), 8.41 (m, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 19.9, 57.5, 115.8, 124.5, 125.2, 128.6, 129.0, 129.3, 129.6, 130.9, 131.2, 131.8, 134.0, 135.9, 136.5, 137.6. MS [m/z (% rel. int.)]: 373 (M, 0.4%), 358 (0.9%), 269 (30%), 244 (1.2%), 142 (11%), 126 (12%), 114 (24%), 105 (77%), 104 (100%). IR (KBr, cm^{-1}): 3075 (w), 1502 (w), 1454 (w), 1349 (s), 1326 (s), 1201 (m), 1169 (s), 1143 (s), 1056 (s), 984 (m), 895 (m), 817 (m), 772 (s), 696 (s), 524 (s). $[\alpha]_D^{20}$ −6.7 (c=1, $CHCl_3$). HRMS: calcd for $C_{18}H_{15}NO_4S_2$, 373.0443; observed, 373.0457.

4.3.2. N,N′-*Bis((*S*)-1-phenylethyl)-1,2-naphthalenedisulfonamide*

Yield 17%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (d, J=6.7, 6H), 4.71 (m, 2H), 6.76 (NH, 2H), 6.87 (m, 6H), 7.04 (m, 4H), 7.52 (m, 2H), 7.63 (m, 2H), 7.72 (d, J=6.6, 1H), 9.19 (d, J=6.6, 1H).

*4.4. 1-Phenylethanol **2** and 1-phenylethylazide **3** from (*S*)-*N,N-*1,2-naphthalenedisulfonyl-1-phenylethylamine **1a***

The nucleophilic substitution reactions for the preparation of the title compound were carried out using KNO_2/18-crown-6 and NaN_3 mainly as described elsewhere.[1–5] Specific reaction conditions are listed in Table 1, including the degree of inversion. The alcohol **2** and the azide product **3** were characterized by ^{1}H NMR and MS giving data in accordance with data for these substances published previously.[3–5] The products **2** and **3** coeluted on GLC (both on an unpolar methylsilicone and a chiral cyclodextrin stationary phase) with the respective compounds prepared previously and characterized elsewhere.[3–5] The percentage enantiomeric excess for **2** and **3** was based on chiral GLC analysis.

References

1. Seljestokken, B.; Fiksdahl, A. *Acta Chem. Scand.* **1993**, *47*, 1050.
2. Johansen, C.; Fiksdahl, A. *Chirality* **1994**, *6*, 161.
3. Oppedal, H., Tveit, I. C.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1994**, *5*, 895.
4. Ileby, N.; Kuzma, M.; Heggvik, L. R.; Sørbye, K.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2193.
5. Heggvik, L. R.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2189.
6. Sørbye, K.; Tautermann, C.; Carlsen, P. H.; Fiksdahl, A. *Tetrahedron: Asymmetry* **1998**, *9*, 681.