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N,N-Dimesylimides and *N,N*-dinosylimides as new leaving groups for the stereoselective nucleophilic substitution of amines

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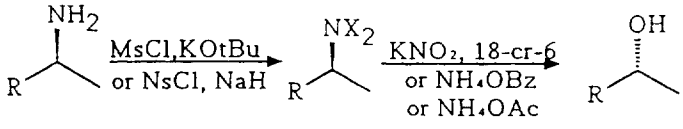
Abstract: The enantiospecific transformation of the optically active amines **1** and **2** via the nucleophilic substitution of the *N,N*-dimesylimides (**1Ms**, **2Ms**) and the *N,N*-dinosylimides (**1Ns**, **2Ns**) to the corresponding alcohols **3** and **4** is reported. Different oxygen nucleophiles were used and the alcohol products were enriched with 74–95% of the enantiomer formed by *inversion* of configuration. © 1997 Elsevier Science Ltd

For the preparation of homochiral substances it is important to have access to a set of stereospecific synthetic methods to make use of already existing stereogenic centres in available starting material. It is essential to develop transformation methods both for the inversion and the retention of stereochemistry. We have previously reported the use of the *N,N*-ditosylimide derivatives, -NTs_2, of primary aliphatic amines as suitable substrates for nucleophilic substitution. Starting with chiral primary amines both the preparation of the inverted amines[1,2] and the preparation of alcohols[3,4] with inverted stereochemistry have been carried out by this method. The corresponding alcohol products enriched with the enantiomer formed with retention of configuration have been prepared via the diazonium intermediate[4]. Based on our experience with the *N,N*-ditosylimides we wanted to try the corresponding method used on the *N,N*-dimesylimide, -NMs_2, and the *N,N*-dinosylimide, -NNs_2, intermediates. Both mesylate, -OMs, and nosylate, -ONs, derivatives of alcohols are known[5] as good leaving groups and useful intermediates for nucleophilic substitution of alcohols giving new products with inversion of configuration.

We hereby report the preparation of the new *N,N*-disulfonylimides derivatives, the *N,N*-dimesylimides, **1Ms** and **2Ms**, and the *N,N*-dinosylimides, **1Ns** and **2Ns**, from the chiral primary amines **1** and **2**. The stereoselectivity of the transformation reactions of the imides to the corresponding alcohol products **3** and **4** are investigated, see Scheme 1. Results from the *N,N*-disulfonylimide formations and the inversion degree in the nucleophilic substitution using respectively KNO_2/18-crown-6, NH_4OBz, and NH_4OAc are summarized in Table 1.



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

1Ms: R = Ph X = Ms
1Ns: R = Ph X = Ns
2Ms: R = $(CH_2)_2$Ph, X = Ms
2Ns: R = $(CH_2)_2$Ph X = Ns

3: R = Ph
4: R = $(CH_2)_2$Ph

Scheme 1.

Based on our previous experimental experience with the preparation of *N,N*-ditosylimides[1–4] using NaH as a suitable base, we wanted to use similar reaction conditions for the formation of the *N,N*-mesylimides **1Ms** and **2Ms** and the *N,N*-dinosylimides **1Ns** and **2Ns**. Because of the extensive formation of by-products and respectively low yields of the imide products in the preparation of

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Table 1. Results from the reactions shown in Scheme 1

Substrate, % ee, *R* or *S*	Product, % ee, *R* or *S*	Degree of inversion	Reagent, nucleophile
1Ms, >99 % ee, *S* (from **1** in 41 % yield)	**3**, 64 % ee, *R*	82 %	KNO_2, 18-crown-6
	3, 48 % ee, *R*	74 %	NH_4OBz
	3, 60 % ee, *R*	80 %	NH_4OAc
1Ns, >99 % ee, *S* (from **1** in 10 % yield)	**3**, 64 % ee, *R*	82 %	KNO_2, 18-crown-6
2Ms, >99 % ee, *R* (from **2** in 32 % yield)	**4**, 84 % ee, *S*	92 %	KNO_2, 18-crown-6
	4, 86 % ee, *S*	93 %	NH_4OBz
	4, 76 % ee, *S*	88 %	NH_4OAc
2Ns, >99 % ee, *R* (from **2** in 17 % yield)	**4**, 90 % ee, *S*	95 %	KNO_2, 18-crown-6
	4, 48 % ee, *S*	74 %	NH_4OBz
	4, 90 % ee, *S*	95 %	NH_4OAc

the *N,N*-dimesylimides using NaH as a base, NaH was replaced by KO*t*Bu giving improved yields. For the formation of the *N,N*-dinosylimides the corresponding KO*t*Bu reactions gave complexed mixture of products and NaH was therefore used even if the yields were lower compared with both the ditosylimide and the dimesylimide reactions. For both the dimesylimides and the dinosylimides we observed an unwanted high tendency of hydrolysis of the *N,N*-disulfonylimides products back to the *N*-monomesyl/*N*-mononosylamides both in the quenching of the reactions and during the purification of the products by flash chromatography. Great improvements of the yields were obtained for the dimesylimides by rapid chromatographic elution on short and wide silica columns. For the dinosylimides recrystallization from acetone was concluded to be the best purification method.

Three different oxygen nucleophiles were used for the nucleophilic substitution of the *N,N*-disulfonylimides[3]. We have previously shown that the analogue nucleophilic attack by NH_4OBz, NH_4OAc[3] and KNO_2/18-crown-6[4] on the *N,N*-ditosylimides give the corresponding alcohol products directly as a result of an ester hydrolysis *in situ*. None of the ester intermediates (benzoate, acetate or nitrite ester) were observed. All the three methods afforded comparable high inversion degree of the chiral centre. Our present results (see Table 1) show that all three methods utilized on the *N,N*-dimesylimides (**1Ms**, **2Ms**) and the *N,N*-dinosylimides (**1Ns**, **2Ns**) afford the corresponding alcohol products **3** and **4** with 74–95% inversion of the stereochemistry. None of the three methods gave distinguished higher or lower stereoselectivity in the nucleophilic substitution reactions. The results indicate a higher inversion degree for the imide derivatives of substrate **2** compared with the corresponding derivatives of amine **1** in contrast to previous results for the corresponding *N,N*-ditosylimides[1–4]. Obtained yields were in general 20–40% (see Experimental) which is comparable with the yields reported previously for the respective ditosyl intermediates[3,4].

In conclusion the *N,N*-dimesylimides (**1Ms, 2Ms**) and the *N,N*-dinosylimides (**1Ns, 2Ns**) were prepared from the corresponding primary amines **1** and **2** in respectively 32–41% and 17–23% yield. Nucleophilic substitution of these *N,N*-disulfonylimides with different oxygen nucleophiles afforded the alcohol products (**3**, **4**) with 74–95% inversion of configuration. The results demonstrate that *N,N*-dinosylimides and especially the *N,N*-dimesylimides (because of their higher yields) are suitable intermediates for the stereoselective transformation of chiral amines to alcohols with inverted stereochemistry. As such these new dimesyl- and dinosyl-derivatives of primary amines can be recommended as supplementary substrates for the stereoselective transformation of optically active amines to alcohols with inverted stereochemistry in addition to the previously described *N,N*-ditosylimides[1–4].

Experimental

Chemicals: (*S*)-1-phenylethylamine (**1**), Hexel Chemical Products; (*R*)-1-cyclohexylethylamine (**2**), 18-crown-6, ammonium benzoate, ammonium acetate, methanesulfonyl chloride, Fluka (*purum*); 4-nitrobenzenesulfonyl chloride, potassium tert-butoxide, Fluka (*pract.*); sodium hydride, Aldrich (98%); potassium nitrite, Acros (>97%). 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.

N,N-*Dimesylimide formation*

*(S)-*N,N-*Di-(methanesulfonyl)-1-phenylethylamine (**1Ms**) from (S)-phenylethylamine (**1**)*

A solution of KO*t*Bu (3 eqv., 2.43 g, 21.6 mmol) in in dry THF (25 ml) was added **1** (0.87 g, 7.2 mmol) in dry THF (5 ml). Methanesulfonyl chloride, MsCl (2.2 eqv., 1.82 g, 15.8 mmol) in dry THF (5 ml) was added dropwise. The reaction was refluxed under nitrogen for 52 h. The reaction was followed at TLC. After cooling water was added and the product was extracted with chloroform to yield 0.92 g (46%) crude product and 0.82 g (41%) crystalline **1Ms** (one spot on TLC) after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (d, 3H), 3.0 (s, br., 6H), 5.83 (q, 1H), 7.3–7.6 (m, 5H). ^{13}C NMR (75.47 MHz, $CDCl_3$): 19.7, 45.1, 60.2, 128.9, 129.0, 137.9. MS [m/z (% rel. int.)]: 198 (M-Ms, 100%), 184 (7%), 120 (67%), 105 (51%), 104 (87%), 91 (9%).

*(R)-*N,N-*Di-(methanesulfonyl)-1-methyl-3-phenylpropylamine (**2Ms**) from (R)-1-methyl-3-phenyl-propylamine (**2**)*

The same procedure as described for the preparation of **1Ms** above starting with 1.95 g (13.1 mmol) of **2** in dry THF (20 ml), 4 eqv. of KO*t*Bu in dry THF (50 ml) and 3 eqv. of MsCl afforded 1.9 g (48%) crude product and 1.28 g (32%) crystalline **2Ms** (one spot on TLC) after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): 1.6 (d, 3H), 2.25 (m, 2H), 2.72 (m, 2H), 3.28 (s, br., 6H), 4.51 (m, 1H), 7.18–7.36 (m, 5H). MS [m/z (% rel. int.)]: 305 (M, 8%), 200 (12%), 132 (100%), 122 (71%), 117 (48%), 105 (13%), 91 (46%).

N,N-*Dinosylimide formation*

*(S)-*N,N-*Di-(*p*-nitrobenzenesulfonyl)-1-phenylethylamine (**1Ns**) from (S)-phenylethylamine (**1**)*

NaH (7 eqv. 0.68 g, 28.5 mmol) in in dry THF (25 ml) was added **1** (0.49 g, 4.1 mmol) in dry THF (5 ml). *p*-Nitrobenzenesulfonyl chloride, NsCl (2.2 eqv., 1.8 g, 8.1 mmol) in dry THF (5 ml) was added dropwise. The reaction was refluxed under nitrogen for 57 h. The reaction was followed at TLC. After cooling the solution was decanted, filtered under nitrogen, cooled, added water and extracted with chloroform to give 1.03 g (51%) crude product and 0.46 g (23%) crystalline **1Ns** (one spot on TLC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.9 (d, 3H), 5.0 (q, 1H), 7.8–8.2 (m, 13 H). MS [m/z (% rel. int.)]: 305 (M-Ns, 4%), 291 (1%), 276 (1%), 272 (1%), 223 (7%), 149 (1%), 122 (2%), 119 (2%), 105 (100%), 91 (2%), 77 (10%).

*(R)-*N,N-*Di-(*p*-nitrobenzenesulfonyl)-1-methyl-3-phenylpropylamine (**2Ns**) from (R)-1-methyl-3-phenylpropylamine (**2**)*

The same procedure as described for the preparation of **1Ns** above starting with 0.5 g (3.35 mmol) of **2** in dry THF (5 ml), 7 eqv. of NaH (1.7 g, 70.3 mmol) in THF (30 ml) and 3 eqv. of NsCl (2.23 g, 10.1 mmol) afforded 0.54 g (31%) crude product and 0.29 g (17%) crystalline **2Ms** (one spot on TLC) after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): 1.52 (d, 3H), 2.02 (m, 2H), 2.40 (m,

2H), 4.29 (m, 1H), 7.0–8.4 (m, 13H). MS [m/z (% rel. int.)]: 519 (M, 1%), 414 (2%), 333 (1%), 229 (91%), 186 (42%), 146 (7%), 132 (100%), 117 (45%), 105 (32%), 91 (53%).

The nucleophilic substitution reactions for the preparation of (*R*)-phenylethanol (**3**) from (*S*)-*N,N*-di-(methanesulfonyl)-1-phenylethylamine (**1Ms**), (*R*)-phenylethanol (**3**) from (*S*)-*N,N*-di-(*p*-nitrobenzenesulfonyl)-1-phenylethylamine (**1Ns**), (*S*)-4-phenyl-2-butanol (**4**) from (*R*)-*N,N*-di-(methanesulfonyl)-1-methyl-3-phenylpropylamine (**2Ms**), (*S*)-4-phenyl-2-butanol (**4**) from (*R*)-*N,N*-di-(*p*-nitrobenzenesulfonyl)-1-methyl-3-phenylpropylamine (**2Ns**) were carried out using KNO_2/18-crown-6, NH_4OBz and NH_4OAc as described elsewhere[3,4].

The alcohol products **3** and **4** coeluted on GLC (using both an unpolar methylsilicone and a chiral cyclodextrin stationary phase) with the respective alcohols prepared previously and characterized elsewhere[4]. Data for the optical purity of the alcohols **3** and **4** obtained by chiral GLC analysis are given in Table 1. Some of the transformation reactions were carried out in an analytical scale for chiral analysis, others in a preparative scale for additional full product characterization. For the latter the obtained yields were 20–40%.

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