# 228. Conversion of Amines into Phenylsulfides and Phenylselenides *via* Ditosylamides

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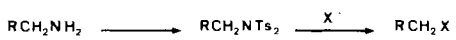
(29.X.80)

*Summary*

Amines are converted in good to excellent yields to phenylsulfides or phenylselenides *via* nucleophilic displacement on the corresponding ditosylamides. The conversion of (−)-(*S*)-1-phenylethylamine to the chiral phenylsulfide **6** was found to proceed with inversion of configuration. A simple one-pot procedure for the preparation of ditosylamides is reported.

**Introduction.** – The conversion of amino groups into another functionality is a problem of current synthetic interest. Recent approaches involve transformation of the amines into pyridinium salts, which in turn transfer the *N*-substituent to a wide range of nucleophiles [1] and the ruthenium-catalyzed reaction of phenyl selenolate with tertiary or silylated primary and secondary amines [2]. An additional method originally developed by *Baumgarten* [3] uses activation of the amino function by transformation to disulfonamides which are susceptible of undergoing displacement at the C-atom with soft nucleophiles [4].

*Scheme 1*




None of these methods has been used for reactions with control of stereochemistry. Transformations *via* pyridinium salts and ditosylamides were carried out mainly with primary amines. In the few cases where secondary amines were investigated [5] [6] the stereochemical course of the reaction was not controlled. The only alleged example reported concerns transfer of a chiral methyl group of *N*-methylditosylamide to homocysteine anion in HMPA [7], which is believed to proceed with inversion of configuration, although under the reaction condition a double displacement leading to formal retention [8] could also intervene. In the case of the ruthenium-catalyzed reactions [2], control of stereochemistry is impossible since an intermediate planar iminium ion complex is involved.

Displacement of amino groups with control of stereochemistry at the adjacent C-atom would allow the use of the chirality of naturally occurring amino compounds such as amino acids for preparation of chiral synthons. With this objective we have extended our study on ditosylamides to amines with secondary substituents.

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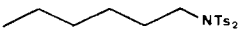
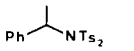
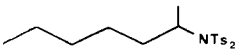
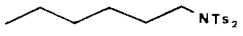
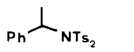
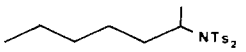
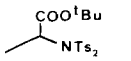
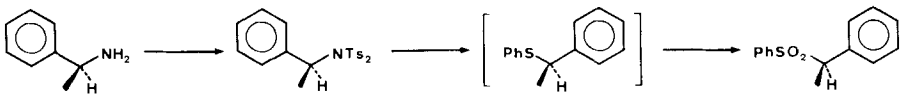
Table 1. *Displacement of ditosylamides with thiophenolate and phenylselenolate anions in DMF*

| Substrate | No | $X^{(-)}$ | Conditions | Yield %[a]) |
|---|---|---|---|---|
| $PhCH_2NTs_2$ | 1 | $PhS^{(-)}$ | 150°/15 min | 94[b]) |
|  | 2 | $PhS^{(-)}$ | 150°/90 min | 68[b]) |
|  | 3 | $PhS^{(-)}$ | 80°/30 min | 70 |
|  | 4 | $PhS^{(-)}$ | 120°/120 min | 60 |
| $PhCH_2NTs_2$ | 1 | $PhSe^{(-)}$ | 150°/15 min | 84 |
|  | 2 | $PhSe^{(-)}$ | 150°/60 min | 96[b]) |
|  | 3 | $PhSe^{(-)}$ | 80°/15 min | 80 |
|  | 4 | $PhSe^{(-)}$ | 150°/45 min | 77 |
|  | 5 | $PhS^{(-)}$ or $PhSe^{(-)}$ | | 0[c]) |

[a]) Products were identified by means of their spectral data and yields determined by GC. using independently prepared samples for instrument calibration. [b]) Ref. [4]. [c]) Partial N-S bond cleavage.

**Results and discussion.** – The ditosylamides of 1-phenylethyl- and 2-heptylamines were treated with thiophenolate and phenylselenolate anions in hot DMF (s. [9] and [10], resp.). Conditions and yields of the reaction are given in *Table 1*, which also contains previously published data for the purpose of comparison. With primary substrates reactions were carried out at 150°; the temperature was lowered with the secondary ones, in particular with the ditosylamide of 1-phenylethylamine (**3**) in order to avoid thermal decomposition of the compound. As *Table 1* shows, there is a decrease in yield for reaction of the thiophenolate ion in going from primary to secondary amine derivatives. For reactions with the phenyl selenolate ion however, the variation in yield for all substrates appears to be insignificant. It was expected that a carbonyl group adjacent to the reacting C-atom of ditosylamides would facilitate the displacement [11], but this was not the case. Reaction of the ditosylamide of alanine-*t*-butylester (**5**) with both nucleophiles afforded no substitution product, but rather the corresponding monotosyl-

*Scheme 2*




(−)-(*S*)-1-Phenylethylamine (+)-(*S*)-**3** (*R*)-**6** (+)-(*R*)-**7**

amide, presumably by nucleophilic attack at the S-atom [4]. The stereochemistry of the reaction of thiophenoxide anion with the ditosylamide (*S*)-**3** of (−)-(*S*)-1-phenylethylamine was investigated according to the sequence outlined in *Scheme 2.*

The commercially available amine was converted to (*S*)-**3** by the two-step procedure of *Baumgarten* [6] [12]. Displacement with thiophenolate ion was carried out in DMF at 80°. The crude sulfide (*R*)-**6** was oxidized without isolation by addition of acetic acid/$H_2O_2$ [13] to the sulfone **7** ($[\alpha]_D^{23} = +103°$ ($c = 1.5$, MeOH)) in 60% yield. Since the absolute configuration of (+)-**7** is known to be *R* (Lit. $[\alpha]_D^{30} = +94°$ [15]) our product also must have (*R*)-configuration. It follows that reaction of (*S*)-**3** with thiophenolate ion proceeds with inversion of configuration as expected, and that no racemization within the sequence takes place. We assume that the same should be true for the other substrates used in this study. The optical purity of (*R*)-**7** was further investigated by $^1$H-NMR. Upon addition of chiral Eu(TFC)$_3$ to independently prepared racemic **7** the NMR. spectrum showed two neatly separated doublets for the protons of the methyl groups. Under the same conditions the spectrum of (*R*)-**7** showed only one doublet, and the enantiomer (*S*)-**7** could not be detected in the reaction product.

*Scheme 3*


**Preparation of disulfonamides.** – In order to make displacement of amino groups *via* ditosylamides synthetically attractive, a convenient procedure for preparation of ditosylamides is required. The two-step method of *Baumgarten* [12] gives excellent yields but necessitates isolation of the intermediate monotosylamide because of a solvent change. We have simplified the procedure by conducting the reactions in DMF. Conversion to the monotosylamide is carried out in the presence of triethylamine *(Scheme 3).* The second sulfonyl group is introduced by sequential addition of 2 mol-equiv. of NaH to generate the sodium salt of the monotosylamide, followed by reaction with TsCl. Yields of isolated products from this not optimized one-pot procedure are comparable to those obtained with the two-step sequence *(Table 2);* however, the former is much less time-consuming. In addition it appears possible to even carry out the subsequent displacement reaction without isolation of the ditosylamide.

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Table 2. *Isolated yields for one-pot preparation of ditosylamides*

| Amine | Ditosylamide | Yield %[a]) |
|---|---|---|
| Benzyl | **1** | 69 |
| Hexyl | **2** | 79 |
| 1-Phenylethyl | **3** | 56 |
| 2-Heptyl | **4** | 58 |

[a]) This work.

## Experimental Part

*General remarks.* IR. spectra were recorded in $CHCl_3$ on a *Perkin-Elmer* 257 spectrophotometer and $^1$H-NMR. spectra on a *Varian* T-60 instrument in $CDCl_3$. Chemical shifts are expressed in ppm with respect to TMS. Mass spectra were measured on a *Varian* CH-4 spectrometer at 70 eV.

*Reaction of ditosylamides* **3** *and* **4** *with thiophenolate anion.* A solution of thiophenolate anion (10.1 mmol) in 50 ml of DMF, prepared from diphenyldisulfide (1.10 g, 5.05 mmol) and sodium borohydride (0.44 g, 11.6 mmol) [9] was added under Ar to ditosylamide **3** (1.0 g, 2.33 mmol) in 20 ml of DMF at RT. The mixture was heated to 80° for 30 min. After cooling 400 ml of water were added, followed by extraction with ether. Analysis of the concentrated organic phase by GC. (Apiezon column, 175°) using bibenzyl as internal standard revealed the presence of 347 mg of 1-phenylethyl phenyl sulfide (70% yield). *1-Phenylethyl phenyl sulfide* (b.p. 163°/15 Torr) was also prepared from 1-phenylethyl chloride and thiophenolate ion [17]. – IR.: 3080, 3020, 2940, 2880, 1620, 1600, 1500, 1460, 1400, 1090, 1040, 710, 690. – $^1$H-NMR.: 1.6 (*d*, 3 H); 4.3 (*qa*, 1 H); 7.0–7.4 (*m*, 10 H).

The same procedure applied to **4** (1 g, 2.36 mmol) but with heating for 2 h at 80°, then 2 h at 120°, afforded 295 mg (60%) *2-heptylphenylsulfide* (b.p. 144.5°/13 Torr [16]). – IR.: 3080, 2940, 2880, 1600, 1480, 1460, 1400, 1110, 1040, 710, 690. – $^1$H-NMR.: 0.8–1.6 (*m*, 1 H); 1.2 (*d*, 3 H); 3.1 (*m*, 1 H); 7.0–7.4 (*m*, 5 H).

*Reaction of ditosylamides* **3** *and* **4** *with phenylselenolate anion.* To a solution of phenylselenolate anion (9 mmol) in 50 ml of DMF, prepared from diphenyldiselenide (1.4 g, 4.5 mmol) and sodium borohydride (0.45 g, 11.8 mmol), was added the ditosylamide **3** (0.93 g, 2.16 mmol) in 20 ml of DMF at RT. Reaction was complete after 15 min at 80°. Work-up and analysis (*Apiezon* column, 160°) as above afforded 456 mg (80%) of 1-phenylethyl phenyl selenide, which was independently prepared from 1-phenylethyl chloride [18]. – IR.: 3080, 3020, 2980, 1590, 1490, 1460, 1040, 1020, 710, 690. – $^1$H-NMR.: 1.8 (*d*, 3 H); 4.4 (*qa*, 1 H); 7.0–7.5 (*m*, 10 H).

The same procedure, applied to ditosylamide **4** (1.0 g, 2.36 mmol) with heating for 45 min at 150°, afforded 464 mg (77%) of 2-heptyl phenyl selenide. – IR.: 3080, 2980, 2940, 2880, 1600, 1480, 1460, 1400, 1040, 1020, 710, 690. – $^1$H-NMR.: 0.6–1.8 (*m*, 14 H); 3.2 (*m*, 1 H); 7.0–7.7 (*m*, 5 H).

*Conversion of* (−)-(*S*)-*1-phenylethylamine to 1-*(*R*)-*phenylethyl phenyl sulfone.* The ditosylamide (*S*)-**3** was prepared as described for the racemic compound [5] [6]: $[\alpha]_D^{23} = +16.5$ ($c = 1.33$, $CHCl_3$). Displacement with thiophenolate anion was carried out as described above. After cooling, 20 ml of acetic acid was added to the reaction mixture, which was then heated to 70° and oxidized by dropwise addition of 12 ml of 30% $H_2O_2$ in 12 ml of acetic acid [13]. After stirring for 3 h at RT. it was added to 300 ml of ice-water. The sulfone **7** precipitated and was recrystallized from methanol. Yield: 60%. M.p. 115–116° (Lit. 115° [14]); $[\alpha]_D^{23} = +103 \pm 1°$ ($c = 1.5$, MeOH) (Lit. 94° [15]).

The optical purity of **7** was checked by stepwise addition of up to 30.5 mg of $Eu(TFC)_3$ (europium-tris[3(trifluoromethylhydroxymethylene)-d-camphorate]) to 30 mg of **7** in 0.5 ml of $CDCl_3$. No splitting of the doublet for the methyl group was observed in the NMR. The same experiment, carried out with racemic **7**, gave splitting which became visible after addition of 15.5 mg of $Eu(TFC)_3$.

*One-pot procedure for preparation f ditosylamides.* A mixture of 4.9 mmol of TsCl, 5.4 mmol of triethylamine and 4.5 mmol of the amine in 10 ml of DMF was allowed to react for 20–30 min at 25°, after which 10 ml of DMF and 14 mmol of NaH (55% dispersion in mineral oil) were added. After 10 min the reaction was achieved by addition of 9.5 mmol of TsCl and stirring for 30 min. The mixture was quenched with 100 ml of ice/water under vigorous stirring. The crude ditosylamide precipitated and was recrystallized from ethanol. The yields of the products are presented in *Table 2*.

The ditosylamides **1**–**3** are characterized in the literature [5] [6] [12]. Properties of **4**: m.p. 88–90°. – IR. ($CHCl_3$): 3040, 2960, 2940, 2880, 1610, 1380, 1180, 900, 670. – NMR. ($CDCl_3$): 0.8–1.4 (*m*, 12 H); 1.8 (*m*, 2 H); 2.5 (*s*, 6 H); 4.2 (*qa*, 1 H); 7.5 and 8.2 (2 *d*, 8 H). – MS.: 423 ($M^+$), 408, 352, 325, 307, 267, 198, 155, 91, 65. – *Properties of* **5**: m.p. 124–126°. – IR. ($CHCl_3$): 3040, 2980, 2940, 1740, 1610, 1380, 1150, 1130, 1100, 900. – NMR. ($CDCl_3$): 1.3 (*s*, 9 H); 1.75 (*d*, 3 H); 2.5 (*s*, 6 H); 4.75 (*qa*, 1 H); 7.4 and 8.1 (2 *d*, 8 H). – MS.: 453 ($M^+$), 352, 198, 155, 97, 91, 83, 71, 69, 55.

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