154. Displacement of Activated Amino Groups. C,N- *vs.* N,S-Bond Cleavage in the Reaction of *N*-Alkyl-disulfonamides with Nucleophiles

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Dedicated to Professor *Edgardo Giovannini* on occasion of his 70th birthday

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Summary

Sodiumthiophenoxide and sodiumphenylselenide react with *N*-benzyl- and *N*-hexyl-di-*p*-toluenesulfonamides (**1** and **2**) *via* displacement at the C-atom to afford the corresponding organosulfides and selenides in yields of 68-96%. In contrast, sodium cyanide converts disulfonamides to monosulfonamides by attack on the S-atom. The different selectivities of phenylsulfide and selenide as compared to cyanide anions with respect to attack on the C- and S-atoms are rationalized on the grounds of the HSAB (hard and soft acids and bases) principle of *Pearson.*

Introduction. – Transformation of amines into other functional groups is difficult to accomplish owing to the poor leaving-group ability of the amino substituent. Several methods of activation have been developed in order to achieve such conversions. For example, diazotization of a primary amine with isoamyl nitrite in presence of carboxylic acids under anhydrous conditions gives the corresponding carboxylates with minimal rearrangement [1]. Other methods are based on nitrosoamides [2], nitroamides [3], triazines [4] and triazoles [5]. A procedure investigated by *Katritzky* [6] consists in transformation of amines into 2,4,6-triphenylpyridinium salts. The latter react with nucleophiles by displacement at the carbon atom bearing the pyridinium group thereby liberating triphenylpyridine.

Some time ago *Baumgarten et al.* [7] reported that nucleophiles, in particular halide ions, react with *N*-alkyl-disulfonamides *via* displacement at the carbon atom. Subsequently, several reports dealing with this approach have appeared from the groups of *Glass* [8], *Hutchins* [9], *Andersen* [10] and *Hendrickson* [11]. It was hoped that activation of amino groups with sulfonyl substituents would enhance their nucleofugacity to such an extent that they would undergo nucleophilic substitutions as readily as tosylates. This concept could in part be realized; however, displacement at the carbon atom represents only one of several pathways available to disulfonamides (*Scheme 1*, path a). Under the conditions of nucleophilic substitution they

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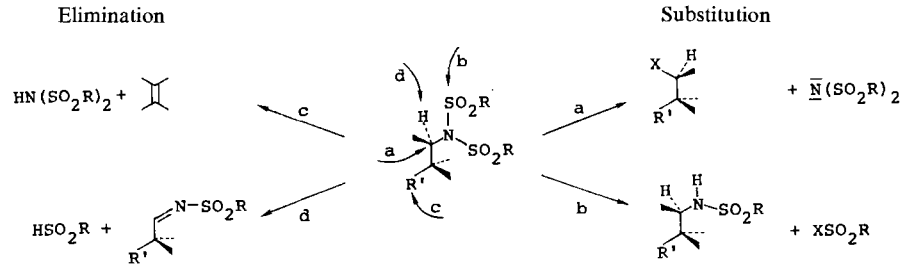
Scheme 1



may as well undergo N,S-bond cleavage or two different types of elimination. The N,S-bond cleavage (path b) reportedly occurs with reagents such as sodium cyanide and sodium hydrogen sulfide [12]. It has also been observed to various degrees during reaction of ditosylamides with organocuprate reagents [13]. The cleavage reaction presumably takes place *via* attack of the nucleophile at the S-atom and leads to the monosulfonamide. Eliminations to alkenes (path c) occur with disulfonamides carrying primary alkyl groups to various degrees with bases as weak as lithium iodide [10] [12] and becomes predominant with secondary alkyl groups [14]. If H-atoms in β-position are lacking, β-elimination becomes impossible and the reaction takes still another course, namely elimination at the C,N-bond, giving rise to formation of sulfonimines (path d). This reaction has been observed upon exposure of *N*-benzyl-di(*p*-toluenesulfon)amide (**1**) to *t*-BuOK or NaCN in HMPA [8b]. The relative importance of the competing pathways is dependent on the structure of the alkane substituent, and also varies significantly with the substituents of the activating sulfonyl groups. As a consequence of these complications direct displacement of disulfonamides is not as general as that of alkyl tosylates. Best results are obtained with halide ions, especially iodide, on primary substrates. Since iodide is at the same time an excellent nucleophile and leaving group, it is often advantageous to use a double displacement reaction with iodide catalysis [10] [12] [15].

The objective of the present study was to find nucleophilic systems capable of effecting displacements on disulfonamides without side reactions. Furthermore, the nucleophiles introduced should lend themselves to synthetically useful transformations. It was expected that the high nucleophilic reactivity *vs.* saturated carbon atoms of anions such as thiophenoxide and phenyl selenide [16], accompanied by their weak basicity would greatly favor the substitution pathway.

Results and discussion. – The main results of our study are summarized in *Table 1*. It was found that both thiophenoxide and phenylselenide anions convert *N*-benzyl-ditosylamide (**1**) as well as the hexylditosylamide (**2**) in DMF at 150° in excellent yield to the corresponding organosulfur and organoselenium compounds. The reactions are remarkably clean, the only side products observed being diphenyldisulfide and diphenyldiselenide respectively, but no products derived from N,S-bond cleavage. Considering the large spectrum of organic functional group transformations based on organosulfur [17] and organoselenium [18] [19]

Table 1. *Displacement with C–N-bond cleavage*

Substrate	No.	Reagent	Conditions	Products	Yield
$PhCH_2NTs_2$	**1**	PhS^-	DMF/150°/15 min	$PhCH_2SPh$	94%
$n\text{-}C_6H_{13}NTs_2$	**2**	PhS^-	DMF/150°/1.5 h	$n\text{-}C_6H_{13}SPh$	68%
$PhCH_2NTs_2$	**1**	$PhSe^-$	DMF/150°/15 min	$PhCH_2SePh$	74%
$n\text{-}C_6H_{13}NTs_2$	**2**	$PhSe^-$	DMF/150°/1 h	$n\text{-}C_6H_{13}SePh$	96%
$PhCH_2NTs_2$	**1**	–	HMPT/180°/2.5 h	$PhCH_2N(CH_3)_2$	quantitative
$PhCH_2NTs_2$	**1**	Me_2CuLi	THF/Et_2O[a])	$PhCH_2CH_3$	< 30% [13]
$PhCH_2NTf_2$	**3**	Me_2CuLi	$THF/Et_2O/-25°/2$ h	$PhCH_2CH_3$	60–70% [13]

compounds, these replacements of amino groups *via* ditosylamides to phenylsulfides and selenides should be of considerable preparative interest. To our knowledge the only analogous example consists in nucleophilic displacement of the methyl group of chiral *N*-methyl-ditosylamide by the homocysteine anion in HMPA [20]. The reaction presumably proceeded with inversion of configuration, but was accompanied by partial racemization.

The latter is hard to reconcile with an S_N2 displacement; however, a possible explanation may be provided on the grounds of the observation that HMPA attacks alkyl-di-trifluoromethanesulfonamides **4** at the carbon atom, giving rise to formation of a salt **5** *(Scheme 2)* [21] under very mild conditions.

Scheme 2

$$\underset{\mathbf{4}}{n\text{-}C_5H_{11}CH_2\text{–}N(SO_2CF_3)_2} \xrightarrow{\text{HMPA}} \underset{\mathbf{5}}{n\text{-}C_5H_{11}\text{–}CH_2\text{–}O\text{–}\overset{+}{P}[N(CH_3)_2]_3}$$

The salts are efficient alkylating agents and undergo a second substitution in the presence of other nucleophiles. It has been suggested [21] that nucleophilic displacement reactions in HMPA might generally, at least in part, proceed *via* double substitution involving cationic intermediates such as **5**. HMPA is also reactive towards **1**. When **1** was heated with CuCN in HMPA at elevated temperatures *N*-benzyl-*N*,*N*-dimethylamine was formed in variable amounts. Neat HMPA converted **1** to the amine at 150–200° in quantitative yield. Transfer of dimethylamino groups from HMPA to electrophiles is well established [22], and an analogous case of transfer from a phosphonium salt *via* S_NAr displacement has been described [23].

In contrast, when **1** and **2** were heated in DMF to 150° over a period exceeding that used for reaction with the sulfide and selenide anions, no reaction occurred. The displacements taking place in DMF are therefore due to direct attack of the nucleophilic reagents. This should be of importance for work with chiral molecules.

While methylmagnesium iodide was unreactive towards *N*-benzyl-ditosylamide (**1**), partial conversion of **1** to ethylbenzene was obtained with dimethylcopper lithium. At the same time partial cleavage to the monotosylamide occurred. Although reaction conditions were varied over an extensive range, substitution never exceeded 30%. Yields could be improved by the use of the more activating trifluoromethanesulfonyl in place of the tosyl substituents. Displacement by cuprate

Table 2. *Iodide catalyzed displacement*

Substrate	No.	Reagents	Conditions	Product	Yield
$PhCH_2NTs_2$	1	Ph_3P/LiI (10%)	DMF/150°/3 h	$PhCH_2-\overset{+}{P}Ph_3\dot{N}Ts_2$	71%
n-$C_6H_{13}NTs_2$	2	Ph_3P/LiI (20%)	DMF/150°/20 h	n-$C_6H_{13}-\overset{+}{P}Ph_3X^-$	*ca.* 65%
$PhCH_2NTs_2$	1	AcOH/LiI (3 equiv.)	AcOH, reflux, 24 h	$PhCH_2OAc$	57%
$PhCH_2NTs_2$	1	$NaCu(CN)_2$/LiI	DMF/150°/2 h	$PhCH_2CN$	20%

is however restricted to benzylic and allylic CH_2NTf_2 groups. In all other cases studied, the starting compounds were either recovered unchanged or converted to the monotrifluoromethanesulfonamides [13] (*Scheme 1*, path b).

Weak nucleophiles are incapable of attacking ditosylamides, but reaction becomes possible *via* double displacement with the help of iodide catalysis *(Table 2)* [10] [15]. For example, no reaction was observed between *N*-benzyl-ditosylamide (**1**) with triphenylphosphine in refluxing ether, THF or toluene, but in the presence of 0.1 equiv. of lithium iodide reaction proceeded at 160° in DMF in 12 h to the crystallizable phosphonium salt (71% yield). Similarly, *N*-hexyl-ditosylamide (**2**) reacted in presence of 0.2 equiv. of lithium iodide; however, in this case the salt could not be crystallized. Furthermore, *N*-benzyl-ditosylamide (**1**) was stable in hot acetic acid, but was converted to benzyl acetate in the presence of excess lithium iodide. No conversion was obtained with LiI/ethanol at 80°. The reaction of **1** with sodium dicyanocuprate [24] in presence of lithium iodide was investigated in the hope of suppressing the side-reactions occurring with NaCN (see below). Although some conversion to benzylcyanide took place, it was not possible to obtain synthetically acceptable yields.

Table 3 summarizes the results of reactions proceeding *via* S,N-bond cleavage or eliminations. The comportment of sodium cyanide is particularly intriguing in this respect. *Glass et al.* [8b] reported a yield of 38% of benzonitrile (double elimination) and 44% *N*-benzyltosylamide (**6**) (S,N-bond cleavage, path b) upon exposure of **1** to NaCN/HMPA at RT. They also reported that NaCN/HMPA reacts with *N*-benzyl-ditrifluoromethanesulfonamide (**3**) to benzyl cyanide [8a] although it was later found that this transformation does not take place *via* cyanide attack on **3**, but rather on the salt **5** which had been formed by reaction of the substrate with the solvent [20]. With *N*-benzyl-dinosylamide (**7**) and NaCN in HMPA or DMF at RT. neither benzonitrile nor benzyl cyanide were formed, the only isolable products being the *N*-benzyl-nosylamide (**8**) which was obtained in 51% yield. Similarly, the hexyl derivative **9** afforded a 59% yield of *N*-hexyl-nosylamide (**10**). At elevated temperatures, both **7** and **9** rearranged to *p*-nitroanilines upon exposure to NaCN/HMPA, presumably *via* the sulfonamide-*N*-anions which are formed by cyanide attack at the sulfur atom [25]. Thus, attack at the sulfur atom is the preferred pathway for cyanide ion with disulfonamides, while elimination at the C,N-bond can be considered a side-reaction. In no case, however, substitution at the carbon atom has been observed.

The different comportment of the organosulfur and selenide anions as compared to cyanide may be understood on the grounds of *Perason*'s theory of 'hard and soft acids and bases' (HSAB principle [26]). The former are very soft nucleophiles and

Table 3. *Reactions proceeding via elimination or S,N-bond cleavage*

Substrate	No.	Reagents	Conditions	Products	Yield
$PhCH_2NTs_2$	**1**	NaCN	HMPA/25°/4 d	PhCN	38% [8b]
				+ $PhCH_2NHTs$ (**6**)	44% [8b]
$PhCH_2NNs_2$	**7**	NaCN	HMPA/25°/1 h	$PhCH_2NHNs$ (**8**)	51%
n-$C_6H_{13}NNs_2$	**9**	NaCN	HMPA/25°/1 h	n-$C_6H_{13}NHNs$ (**10**)	59%
n-$C_6H_{13}NTs_2$	**1**	NaSH	DMF/60°/17 h	n-$C_6H_{13}SH$ +	25% [12]
				n-$C_6H_{13}NHTs$	55% [12]
$PhCH_2NTs_2$	**1**	$CH_2{=}PPh_3$	THF/80°/24 h	$PhCH_2SO_2PhCH_3$ (**12**)	10%

show a pronounced preference for substitution at sp^3 hybridized carbon atom, which is a soft electrophilic center. Thus sodiumthiophenoxide and phenylselenide react *ca.* 10^3 and 10^4 times faster than cyanide with methyl iodide in methanol solution [16]. The sulfonyl group has the characteristics of a hard electrophile [27] and the rates for attack at the sulfur atom parallel those for carbonyl attack [28]. The latter increase with increasing basicity of the reacting nucleophile [29]. Although cyanide ion is generally considered a soft nucleophile [30] it is still harder than thiophenoxide, judging from its pK_A, and therefore has a stronger preference for sulfonyl attack than the latter. For example, from data extrapolated from the literature [31], cyanide will react with *p*-nitrophenylacetate about 5 times faster than thiophenoxide in aqueous solutions. These tendencies should be enhanced in DMF, where inefficient solvation will increase the hardness of cyanide. In this context, sodium hydrogen sulfide reacts with **2** preferentially with N,S-bond cleavage (55%) while substitution at the carbon atom occurs only to 25% [12]. In terms of softness HS^- is intermediate between thiophenoxide and cyanide and this may explain the borderline behavior. The success of substitutions with disulfonamides using iodide as nucleophile [7] can also be ascribed to the soft character of the reagent. In addition, iodide attack at the sulfur atom, if it does occur, results in formation of tosyl iodide and the RCH_2-$\bar{N}Ts$-anion **11** *(Scheme 3)* in a non-productive equilibrium lying completely on the left side.

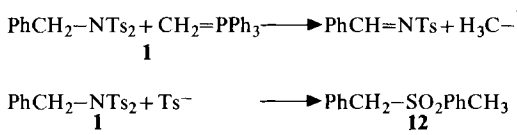
Scheme 3

$$RCH_2\bar{N}Ts_2 + J^{\ominus} \rightleftharpoons RCH_2{-}\bar{N}Ts^{\ominus} + TsJ$$

11

Some exploratory experiments were undertaken in order to investigate the possibility of obtaining displacement reactions of **1** with soft nucleophiles such as lithium diphenylphosphide [32], triphenyltinlithium [35] and trimethyltinlithium [36]. However, these reactions proceeded sluggishly and gave complex product mixtures containing the monotosylamides to various degrees, but none of the desired products. Similarly, **1** upon exposure to methylidenetriphenylphosphorane [37] afforded a mixture which contained, in addition to *N*-benzyl-tosylamide (**6**), a low yield of benzyl-tolylsulfone (**12**) [38]. The latter could originate by attack of the *p*-toluenesulfinate ion, formed in the reaction of the *Wittig* reagent with **1** *(Scheme 4):*

Scheme 4



This suggests that the sulfinate ion should be an effective nucleophile towards **1**. Experiments in this direction are now under way and will be reported in due course.

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Experimental Part

General remarks. IR. spectra were recorded in $CHCl_3$ on a *Perkin-Elmer* 257 spectrophotometer and ^{1}H-NMR. 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.

Preparation of disulfonamides. *N*-Benzyl and *N*-hexyl-di(*p*-toluenesulfon)amides **1** and **2** as well as the corresponding di(*p*-nitrobenzenesulfon)amides **7** and **9** were obtained from the amines and arylsulfonyl chlorides by the 2-step procedure described by *Baumgarten et al.* [12] [37]. *N*-Benzyl-di(trifluoromethanesulfon)amide (**3**) was prepared from benzylamine and trifluoromethanesulfonic anhydride in the presence of 2 equiv. of triethylamine [8a] [12] [38].

Reaction of N-*benzyl-di(trifluoromethanesulfon)amide* (**3**) *with dimethylcopper lithium.* To a solution of dimethylcopper lithium [47] prepared from 11.9 g of CuI and 0.14 mol methyllithium in 100 ml of ether at $-25°$ was added dropwise **3** (5.2 g, 0.014 mol) [38] in 125 ml of ether. After 72 h the mixture was treated with 300 ml of saturated NH_4Cl solution, then filtered, and the layers were separated. After several washings (sat. NaCl) and drying, the organic phase was concentrated. The product, ethylbenzene, was separated by preparative GC. and identified by MS. and ^{1}H-NMR. spectra. The yield (70%) was determined by GC.

Reaction of N-*benzyl-ditosylamide* (**1**) *with cuprate reagents.* A solution of 4.07 g of **1** in 100 ml of ether/THF 1:1 at $-40°$ was treated with 5 equiv. of dimethylcopperlithium. The temperature was kept at $-30°$ during 4 days and then allowed to rise to 25°. Work-up as described above gave ethylbenzene in 28% yield. Other reaction conditions (higher temperature, longer reaction time, more excess of reagent and solvent changes) were tried without success. With Me_3CuLi_2 [48] the yield of ethylbenzene was 6%, while 88% of **1** was recovered.

Reaction of ditosylamides **1** *and* **2** *with sodium thiophenoxide. – General procedure.* A solution of sodium thiophenoxide (10.1 mmol) in 50 ml of DMF, prepared from diphenylsulfide (1.1 g, 5.05 mmol) and sodium borohydride (0.44 g, 11.6 mmol) [39] was added under argon to **1** (1.05 g, 2.5 mmol) in 10 ml of DMF at 150°. After 15 min the solution was hydrolyzed with 400 ml of water and the aqueous phase extracted with ether. After evaporation of the solvent the crude reaction mixture contained 0.48 g (94%) of benzylphenylsulfide, m.p. 41–42° ([40]: 41–42°, [41]: 44.5°). Analytical samples were prepared by preparative GC. (column 1 m Apiezon L 5% on Chromosorb, 155°). – IR.: 3080, 3020, 1600, 1510, 1490, 1450, 1230, 1100 cm^{-1}. – ^{1}H-NMR.: 4.1 (*s*, 2 H); 7.3 (*s*, 10 H) [42].

The same procedure, applied to **2** (1.0 g, 2.44 mmol) (reaction time 1.5 h) afforded 320 mg (68%) of *n*-hexylphenylsulfide [43]. – IR. (liq.): 3080, 2940, 1600, 1490, 1450, 1100, 1080. – ^{1}H-NMR.: 0.7–1.9 (*m*, 11 H); 2.85 (*t*, $J = 7$ Hz, 2 H); 7.0–7.5 (*m*, 5 H).

Reaction of ditosylamides **1** *and* **2** *with sodium phenylselenide. – General procedure.* A solution of sodium phenylselenide (9 mmol) in 50 ml of DMF, prepared from diphenyldiselenide (1.4 g, 4.5 mmol) and sodium borohydride (0.44 g, 11.6 mol) [44] was added to **1** (1.0 g) in 20 ml of DMF at 150° under argon. After 15 min the mixture was decomposed with 400 ml of water and the aqueous phase was extracted with ether. The solvent was evaporated and the residue purified by column chromatography

in hexane on silica gel. Benzylphenylselenide [45] was isolated in 84% yield. – IR.: 3060, 3040, 1610, 1590, 1450, 1500, 1190, 1080. – ^{1}H-NMR.: 4.0 (*s*, 2 H); 7.0–7.4 (*m*, 10 H). – MS.: 248/246 (33, M^+), 202/200, 157/159 (7), 91 (100), 77 (6), 65 (10).

The same procedure applied to **2** (1.0 g, 2.44 mmol) (reaction time 1 h) afforded 0.536 g (96%) of hexylphenylselenide [46]. – IR.: 3080, 2980, 2940, 2880, 1590, 1490, 1450. – ^{1}H-NMR.: 0.7–1.8 (*m*, 11 H); 2.8 (*t*, J = 7 Hz, 2 H); 7.0–7.5 (*m*, 5 H). – MS.: 242/240 (35, M^+), 158/156 (62), 79 (21), 78 (16), 42 (100).

Iodide-catalysed reaction of ditosylamides **1** *and* **2** *with* Ph_3P. The ditosylamide **1** (2.0 g, 5 mmol) was heated with triphenylphosphine (2.62 g, 10 mmol) and dry LiJ (0.07 g, 0.5 mmol) in 80 ml of DMF to 150° for 3 h. After distillation of the solvent, unreacted triphenylphosphine was separated from the residue by extraction with ether. Recrystallization from ethanol afforded 2.4 g (71%) of benzyltriphenylphosphonium ditosylamide, m.p. 138–139°. – IR.: 3000, 1600, 1500, 1450, 1290, 1160, 1130, 1010, 1000. – ^{1}H-NMR.: 2.2 (*s*, 6 H); 4.9 (*d*, $J_{P,H}$ = 14 Hz, 2 H); 6.8–7.8 (*m*, 28 H).

$C_{39}H_{36}NO_4PS_2$	Calc.	C 69.10	H 5.35	N 2.00	P 4.57	S 9.46%
(677.88)	Found	„ 69.21	„ 5.37	„ 2.00	„ 4.72	„ 9.55%

Ditosylamide **2** (2.05 g, 5.0 mmol) and LiJ (0.13 g, 0.97 mmol) were heated in 80 ml of DMF for 15 min. After addition of triphenylphosphine (2.62 g, 10 mmol) heating was continued for 20 h. Work-up as described above afforded 3.0 g (65%) of crude hexyltriphenylphosphonium salt. – ^{1}H-NMR.: 0.8–1.8 ppm (*m*, 11 H); 2.3 (*s*, 6 H); 3.4 (*m*, 2 H); 6.7–7.8 (*m*, 23 H).

*Reaction of di-(*p*-nitrobenzenesulfon)amides* **7** *and* **9** *with NaCN.* The dinosylamides **7** and **9** (1 mmol) were stirred with 4.5 equiv. of NaCN in 10 ml of HMPA at RT. After 15 min the black solution was diluted with H_2O and extracted with ether. Purification of the extract by column chromatography in CH_2Cl_2 on silica gel afforded *N*-benzyl- and *N*-hexyl-(*p*-nitrobenzenesulfon)amides (**8** and **10**) [37] in 51 and 59% yield.

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