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One-pot Dialkylation of Allylphenylsulfide Induced by Aminoalkoxides-activated $NaNH_2$. Application to the Synthesis of Unsymmetrical Ketones

Sabine Choppin, Philippe Gros and Yves Fort*

Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Faculté des Sciences, Université Henri Poincaré - Nancy 1, B.P. 239, 54506 Vandoeuvre-Les-Nancy, France.

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Abstract: *It is shown that the activation of $NaNH_2$ by sodium aminoalkoxides, leading to new superbases, induced an efficient one-pot dialkylation of allylphenylsulfide. The regioselectivity of the reaction (α,α' vs α,γ) was found as strongly dependent on the nature of the alkyl halide. As an application, α,γ dialkylated products were efficiently converted into the corresponding unsymmetrical ketones.*

In the course of our studies on the activation of lithiating reagents, we have evidenced that their association with aminoalkoxides led to new reagents displaying unusual behaviour and/or increased reactivity.[1] For example, the nucleophilicity of BuLi towards π-deficient aromatic compounds was dramatically decreased thanks to an association with lithium dimethylaminoethoxide ($Me_2N(CH_2)_2OLi$).[1] As a consequence, the new basic system allowed the metallation of electrophilic heterocycles such as pyridines and quinolines.[1a] In addition, pyridines bearing alkoxy groups at C-2 were regioselectively lithiated at C-6 due to a specific complexation of lithium by the heterocycle and the aminoalkoxide.[1b] Furthermore, aminoalkoxides were also found useful in the activation of NaH during Ni(0)-catalysed desulfurisation of aryl and alkylthio compounds.[2] These unprecedented changes of reactivity prompted us to envision aminoalkoxides as activating agents for sodium amide.[3] Then, we chose to study the metallation-alkylation of allylphenylsulfide **1.** This reaction has been essentially performed with lithium reagents using several methods of activation[4] or by the bimetallic Schlosser's superbases BuLi-*t*-BuOK (LICKOR).[5] Sodium-containing bases have scarcely been employed.[6] Nevertheless, we have shown that the $NaNH_2$-*t*-BuONa base allowed an efficient monoalkylation of the substrate.[7] As a general trend, all the basic systems presented above led to varying amounts of isomers **2** and **3** (Scheme 1). In this paper we report the preparation of aminoalkoxide-activated $NaNH_2$ superbases and their particular behaviour in the alkylation of allylphenylsulfide **1**.

* Email: Yves.Fort@sor.u-nancy.fr; Fax: 33(0)383404558

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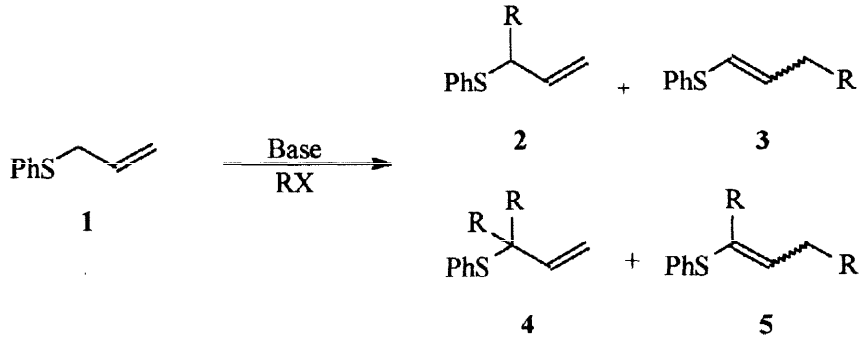
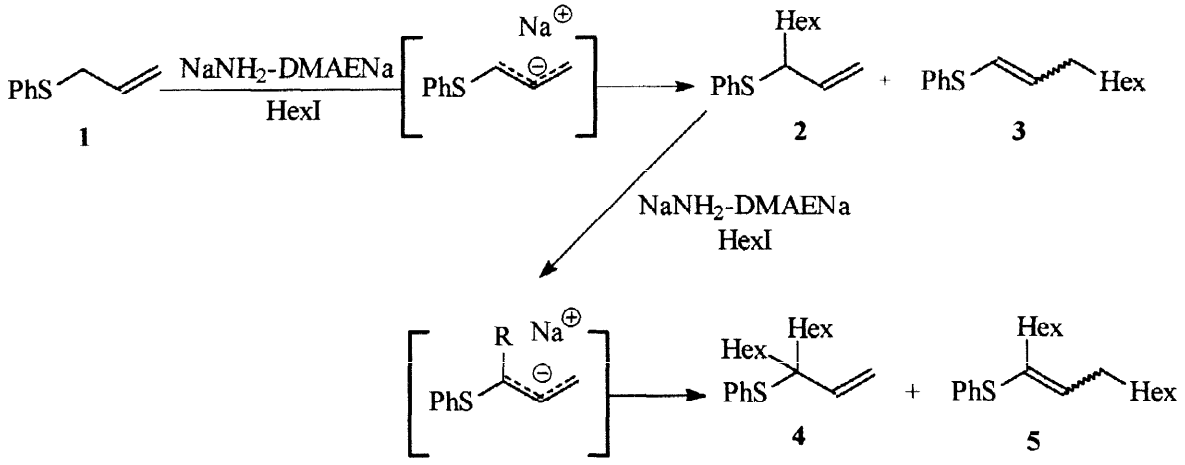


Scheme 1

During exploratory studies performed with *in situ* generated $Me_2N(CH_2)_2ONa$ (noted DMAENa), we observed that the activation of $NaNH_2$ led to the formation of dialkylated products **4** and **5** besides usual monoalkylation products **2** and **3** (Scheme 1). We subsequently determined that a maximum dialkylation yield (47%; Run 1; Table 1) was reached when $NaNH_2$, DMAENa and **1** were used in a 3/1.5/1 ratio respectively. Moreover, we found that the electrophile *i.e.* HexI had to be present in the reaction medium in order to trap the carbanionic species thus preventing further isomerisation and protonation. This was in agreement with our previous observations.[7] Accordingly, the formation of **4** and **5** could be interpreted as resulting from the deprotonation-alkylation of *in situ* generated **2** (Scheme 2).

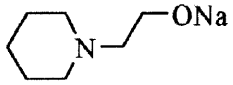
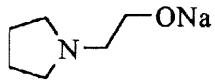
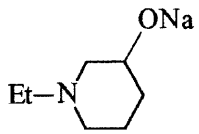
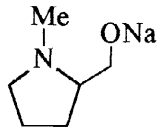


Scheme 2

Thus, the reaction course was probably dependent on complexation of sodium cation and consequently on the structure of the activating agent. So, we decided to prepare a series of basic systems including various aminoalkoxides. The results obtained in dialkylation of **1** by hexyl iodide are reported in Table 1.

At this stage, it must be noted that **3**, **4** and **5** were cleanly and quantitatively obtained as mixtures. Whereas **3** could be isolated after repeated flash chromatography (using hexane as eluent), **4** and **5** remained inseparable. The isolation of **4** and a derivative of **5** will be described below.

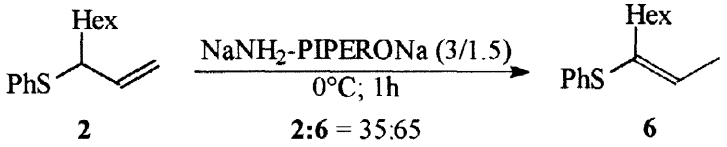
Table 1. Effect of activating agents on dialkylation of **1**[a]

Run	RONa	t (h)	**2+3** Yield (%)[b]	**2:3**	**4+5** Yield (%)[b,c]
1	$Me_2N(CH_2)_2ONa$	5	52	55:45	47
2	$Me_2N(CH_2)_3ONa$	5	70	74:26	29
3	$Me_2NCH_2CH(CH_3)ONa$	4	18	0:100	82
4		2	17	0:100	83
5		2	18	0:100	82
6	$i\text{-}Pr_2N(CH_2)_2ONa$	3	26	23:77	73
7		3	19	5:95	80
8		1	19	0:100	81
9	$MeO(CH_2)_2ONa$	5[d]	67	79:21	tr.
10	$MeS(CH_2)_2ONa$	5[e]	70	70:30	6

(a) Conditions : **1** (10 mmol) ; $NaNH_2$/RONa (3/1.5) (30 mmol) ; $C_6H_{13}I$ (22.5 mmol) ; 0°C ; 12 mL of THF; (b) GC yields; (c) **4/5** = 40/60; (d) conversion: 70%; (e) conversion: 85%

As expected, these results underlined the strong complexation of $NaNH_2$ by aminoalkoxides leading to an increase in the basicity of the newly formed superbase allowing deprotonation of **2**. This increase of basicity was not accompanied by a notable change of nucleophilicity since the base did not consume the electrophile. This also clearly indicated that **4** and **5** actually derived from **2**. Highest dialkylation yields were reached after complete consumption of **2** while **3** persisted in the reaction medium thus remaining in quite constant yields (17-20%). The reaction course was strongly affected by the nature of the aminoalkoxide: i) A notable effect of carbon chain length between nitrogen and alkoxide site was observed. A two-carbon atoms spacer chain was required to ensure efficient activation process (Runs 1-2); ii) The branching of the spacer chain induced a spectacular increase of the dialkylation yield (Run 3). iii) The steric hindrance at the amino site had to be moderated (Runs 4-6). These observations were confirmed by the results obtained with cyclic aminoalkoxides (Runs 7-8). We finally showed that the bi-site activation was nitrogen-specific. Indeed, sulfur- and oxygen-containing ethoxides led to quite inefficient dialkylating reagents (Runs 9,10). From these results we decided to perform further studies with the sodium salt of 1-(2-hydroxyethyl)piperidine (noted PIPERONa) as activating agent.[8]

Concerning the regioselectivity of the dialkylation, a 40:60 **4**:**5** ratio was typically found. This contrasted with previous works on monoalkylation,[4a,7] in which 80:20 **2**:**3** ratios were usually obtained. These results could be interpreted as a consequence of increased steric hindrance at the α position in **2**. In addition, when **2** was placed in the presence of the $NaNH_2$/PIPERONa base, isomerisation into **6** was observed (Scheme 3).



2 **2:6** = 35:65 **6**

Scheme 3

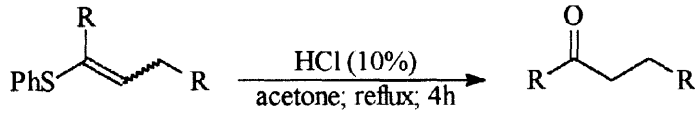
After 1h of reaction the obtained 35:65 **2**:**6** ratio remained constant and was comparable to the previous **4**:**5** ratio found in the presence of electrophile. This result contrasted with the complete isomerisation of **1** in the same conditions (absence of electrophile).[7] Then, the regioselectivity had to depend on the substitution at Cα and consequently on the nature of the alkyl halide. So, we decided to study the influence of the chain length of alkyl halide on the **4**:**5** ratio using $NaNH_2$-PIPERONa (Table 2). As expected, it appeared that an increase of chain length from 1 to 8 carbon atoms led to a reversal of the **4**:**5** ratio (ranging from 63:37 to 32:68). Note that experiments performed with CH_3I remained unsuccessful leading to quaternisation of the amino group of the aminoalkoxide and isomerisation of **1**.

Table 2. Effect of alkyl chain length on the dialkylation regioselectivity.[a]

Run	R	**4** (yield%)[b]	**5** (yield%)[b]	**4:5**
1	C_2H_5	**4a** (53)	**5a** (31)	63:37
2	C_3H_7	**4b** (40)	**5b** (42)	48:52
3	C_4H_9	**4c** (38)	**5c** (45)	42:58
4	C_5H_{11}	**4d** (35)	**5d** (49)	39:61
5	C_6H_{13}	**4e** (33)	**5e** (50)	38:62
6	C_8H_{17}	**4f** (25)	**5f** (57)	32:68

(a) Conditions : **1** (10 mmol) ; $NaNH_2$/PIPERONa (3/1.5) (30mmol) ; RI (22.5 mmol) ; 0°C ; 12 mL of THF; (b) GC yields; the complement to 100% was unreacted **3a-f**.

As mentioned above, the separation of **4** and **5** by classical chromatographic techniques appeared as particularly tedious. But, as compounds **5** could be considered, *via* classical acidic treatment,[9] as useful starting materials for ketones, we performed the acidic hydrolysis of the reaction mixtures (**3**+**4**+**5**) previously obtained. After treatment with HCl (10%) in refluxing acetone (4h), **5a-f** were quantitatively converted into the corresponding unsymmetrical ketones **7a-f** (84-88% isolated yields, Scheme 4).



5a-f

7a: R= C_2H_5; 85% **7d**: R= C_5H_{11}; 84%

7b: R= C_3H_7; 87% **7e**: R= C_6H_{13}; 84%

7c: R= C_4H_9; 88% **7f**: R= C_8H_{17}; 84%

Scheme 4

The overall yields calculated from **1** varied from 26 to 48% and were comparable to those obtained by other synthetic methods described in the literature.[10,11,18-21] During isolation of ketones, unreacted **4** and the main part of unreacted **3**[12] were also easily separated.

As a conclusion, we have shown once more that the activation of anionic reagents by aminoalkoxides led to unusual results. As observed with BuLi,[1] the association of $NaNH_2$ with an aminoalkoxide led to an increase of the basicity/nucleophilicity ratio of this reagent. The new $NaNH_2$-aminoalkoxides bases allowed to perform an efficient one-pot dialkylation of allylphenylsulfide **1** and consequently provided a useful source for unsymmetrical ketones.

Experimental

^1H and ^{13}C-{^1H}NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, with TMS as internal standard and $CDCl_3$ as solvent. GC analysis were performed with an internal standard on a Shimadzu GC-14A apparatus using a HP1 25m column and temperature programming. GC-MS measurements (EI and CI) were performed on a HP5971A spectrometer. Elemental analyses were performed by the Service Central d'Analyses du CNRS (Vernaison, France). Powdered sodium amide was purchased from MERCK. All alcohols, aminoalcohols and alkyl halides were commercially available and distilled before use. THF was distilled and stored over sodium wires.

Typical procedure for one-pot dialkylation of allylphenyl sulfide **1**

A solution of 1-(2-hydroxyethyl)piperidine (1.93 g; 15 mmol) in THF (3 mL) was added dropwise to a suspension of $NaNH_2$ (1.76 g; 45 mmol) in THF (6 mL). The reaction mixture was heated at 45°C for 2h. After this time the reaction mixture was cooled to 0°C and a solution of allylphenylsulfide (1.5 g; 10 mmol) and hexyl iodide (4.77 g; 22.5 mmol) in THF (10 mL) was added dropwise. GC showed completion after 2 h at 0°C. The reaction was then hydrolysed with an ice-water mixture and extracted twice with diethyl ether (50mL). After drying over $MgSO_4$ and evaporation of solvent, the residue was eluted with hexane on a short

column of silica. Evaporation of hexane gave 2.7 g of a mixture containing **3e**:17%; **4e**:33%; **5e**; 50% (GC) which was submitted to the following acidic treatment.

Typical procedure for acidic separation of mixtures of **4** *and* **5**.

The above obtained mixture was dissolved in acetone (50 mL) and HCl 10% (16 mL) was added dropwise for 15 min. The reaction medium was stirred under reflux for 5 h. After cooling at room temperature the mixture was filtered over a pad of celite, washed with ether (80 mL). The filtrate was then treated with aqueous 10% KOH (100 mL). The organic phase was extracted with ether (50 mL), washed with brine and dried over $MgSO_4$ and the solvents were evaporated. The products were then separated by flash-chromatography (hexane) giving 0.4 g of **3e** (15%), 0.95 g of **4e** (30%) and 0.84 g of **7e** (42%; 84% from **5e**).

1,1-diethylallyl phenyl sulfide (4a). Yield: 45%; ^{1}H NMR δ ppm: 0.90 (t, *J*=7 Hz, 6H); 1.55 (q, *J*=7 Hz, 4H); 4.60 (d, ^1J=17 Hz, 1H); 5.00 (d, ^2J=11 Hz, 1H); 5.80 (dd, ^1J =17 Hz and ^2J =11 Hz, 1H); 7.20-7.40 (m, 5H); ^{13}C NMR δ ppm: 8.3; 26.9; 58.4; 113.2; 128.2; 128.4, 132.0; 137.1; 143.2; m/z (EI) 206 (M^+; 19%); 149 (1%); 135 (4%); 110 (43%); 96 (80%); 81 (12%); 67 (14%); 55 (100%); Anal.Calcd for $C_{13}H_{18}S$: C, 75.73; H, 8.73; S, 15.53. Found: C, 75.70; H, 8.71; S, 15.39

1,1-dipropylallyl phenyl sulfide (4b): Yield: 32%; ^{1}H NMR δ ppm: 0.90 (t, *J*=7 Hz, 6H); 1.30-1.60 (m, 8H); 4.60 (d, ^1J=17 Hz, 1H); 4.95 (d, ^2J=11 Hz, 1H); 6.00 (dd, ^1J =17 Hz and ^2J =11 Hz, 1H); 7.20-7.40 (m, 5H); ^{13}C NMR δ ppm: 14.4; 17.3; 37.2; 57.7; 112.6; 128.1; 128.5, 131.9; 137.2; 143.7; m/z (CI) 235 (M^++1; 18%); 234 (100%); 191 (68%); 149 (56%); 135 (99%); 124 (31%); 110 (54%); 95 (24%); 81 (47%); 69 (79%); 55 (35%); Anal.Calcd for $C_{15}H_{22}S$: C, 76.92; H, 9.40; S, 13.67. Found: C, 76.81; H, 9.70; S, 13.35

1,1-dibutylallyl phenyl sulfide (4c): Yield: 27%; ^{1}H NMR δ ppm: 0.90 (t, *J*=7 Hz, 6H); 1.20-1.40 (m, 8H); 1.40-1.60 (m, 4H); 4.60 (d, ^1J=17 Hz, 1H); 4.95 (d, ^2J=11 Hz, 1H); 6.00 (dd, ^1J =17 Hz and ^2J =11 Hz, 1H); 7.20-7.40 (m, 5H); ^{13}C NMR δ ppm: 13.9; 14.1; 23.1; 26.1; 34.5; 57.7; 112.6; 126.1; 128.1; 132; 137.2; 143.7; m/z (EI) 262 (M^+; 10%); 152 (37%); 123 (9%); 109 (31%); 97 (75%); 95 (18%); 83 (54%); 69 (63%); 55 (100%); Anal.Calcd for $C_{17}H_{26}S$: C, 77.86; H, 9.92; S, 12.21. Found: C, 77.57; H, 9.72; S, 12.55

1,1-dipentylallyl phenyl sulfide (4d): Yield: 24%; ^{1}H NMR δ ppm: 0.85 (t, *J*=7 Hz, 6H); 1.20-1.40 (m, 12H); 1.40-1.60 (m; 4H); 4.60 (d, ^1J=17 Hz, 1H); 4.95 (d, ^2J=11 Hz, 1H); 6.15 (dd, ^1J =17 Hz and ^2J =11 Hz, 1H); 7.20-7.40 (m, 5H); ^{13}C NMR δ ppm: 14.1; 22.6; 23.6; 32.2; 34.8; 57.7; 112.7; 128.5; 128.9; 132.0; 137.2; 143.8; m/z (CI) 291 (M^++1; 0.6%); 290 (4%); 180 (38%); 151 (9%); 111 (47%); 109 (40%); 97 (61%); 83 (60%); 69 (100%); 55 (56%); Anal.Calcd for $C_{19}H_{30}S$: C, 78.62; H, 10.34; S, 11.03. Found: C, 78.39; H, 10.40; S, 11.32.

1,1-dihexylallyl phenyl sulfide (4e): Yield: 30%; ^{1}H NMR δ ppm: 0.90 (t, *J*=7 Hz, 6H); 1.20-1.35 (m, 16H); 1.35-1.50 (m; 4H); 4.60 (d, ^1J=17 Hz, 1H); 4.95 (d, ^2J=11 Hz, 1H); 6.20 (dd, ^1J =17 Hz and ^2J =11 Hz, 1H); 7.20-7.50 (m, 5H); ^{13}C NMR δ ppm: 14.1; 22.6; 23.8; 29.1; 31.6; 34.8; 57.7; 112.6; 126.0; 128.7; 132.0; 137.2; 143.8; m/z (EI) 318 (M^+; 2%); 208 (13%); 165 (3%); 139 (4%); 125 (13%); 111 (31%); 97 (54%); 69

(100%); 55 (60%); Anal.Calcd for $C_{21}H_{34}S$: C, 79.25; H, 10.69; S, 10.06. Found: C, 79.43; H, 10.89; S, 10.28.

1,1-dioctylallyl phenyl sulfide (4f): Yield: 20%; ^{1}H NMR δ ppm: 0.80-0.90 (t, J=7 Hz, 6H); 1.20-1.35 (m, 24H); 1.35-1.50 (m; 4H); 4.60 (d, ^1J=17 Hz, 1H); 4.95 (d, ^2J=11 Hz, 1H); 5.90 (dd, ^1J=17 Hz and ^2J=11 Hz, 1H); 7.20-7.50 (m, 5H); ^{13}C NMR δ ppm: 14.1; 22.7; 23.9; 29.3; 29.5; 30.0; 31.9; 34.9; 57.7; 112.6; 128.1; 128.4; 137.3; 143.8; m/z (EI) 374 (M^+; 19%); 261 (13%); 193 (1%); 166 (23%); 150 (100%); 135 (20%); 125 (15%); 123 (27%); 111 (36%); 97 (50%); 69 (30%); 55 (28%); Anal.Calcd for $C_{25}H_{42}S$: C, 80.21; H, 11.23; S, 8.56. Found: C, 80.27; H, 11.29; S, 8.71.

1-Pentenyl phenyl sulfide **3a**,[13] 1-hexenyl phenyl sulfide **3b**,[14] 1-heptenyl phenyl sulfide **3c**,[15] 1-octenyl phenyl sulfide **3d**,[16] 1-nonenyl phenyl sulfide **3e**,[10] 1-undecenyl phenyl sulfide **3f**,[17] 3-heptanone **7a**,[10] 4-nonanone **7b**,[18] 5-undecanone **7c**,[19] 6-tridecanone **7d**,[20] 7-pentadecanone **7e**,[21] 9-nonadecanone **7f**[11] were found identical (spectroscopic data) to authentic or commercial samples.

Acknowledgements

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