On the Alkylation Behavior of 2-(Phenylseleno) Nitriles

U. Jahn[1], D. P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Fax: 001-(412)-624-9861, e-mail: curran+@pitt.edu

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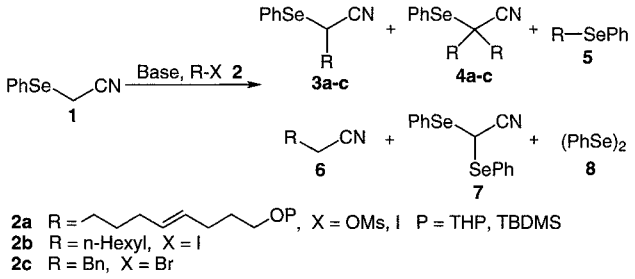
Abstract: Alkylation of (phenylseleno)acetonitrile **1** with alkyl iodides provides preferentially monoalkylated derivatives **3** with LiHMDS as base. 2-(Phenylseleno) nitriles **3** yield dialkylated derivatives in excellent yields.

Organoselenium compounds are useful intermediates in organic synthesis. Their ability to stabilize carbenium ions as well as carbanions and to generate radicals efficiently renders them as versatile intermediates.[2] In the course of our investigations towards radical polycyclization approaches to the steroid skeleton[3] we became interested in the application of α-(phenylseleno) nitriles as precursors for the generation of the initial radicals. Known methods for the preparation of these compounds were not suitable.[4] Therefore we turned our attention to the development of a general strategy that is based on the alkylation of α-(phenylseleno) nitriles **1** and **3**. So far, little was known about the alkylation of **1** and **3**. Application of the only alkylation method of (phenylseleno)acetonitrile[5] **1** met only with limited success (*vide infra*). However, a single example of the alkylation of a α-(phenylseleno) nitrile indicated that alkylation should be a feasible strategy.[6] In this letter we disclose the results of our studies on the alkylation behavior of (phenylseleno)acetonitrile **1** and selected α-(phenylseleno) nitriles **3**.

The alkylation of easily accessible **1**[7] with alkyl halides **2a-c**[8] led to mono- and dialkylation products **3** and **4**.[9] Furthermore, the phenylseleno ether **5**, the deselenylated alkylated nitrile **6**, bis(phenylseleno)acetonitrile **7**, and diphenyl diselenide **8** were isolated in varying amounts, depending on the conditions applied (Scheme 1). The outcome of the alkylation was strongly dependent on the applied base, additives, the electrophile, reaction time and temperature. Selected results of the alkylation are summarized in the Table.

Bases: Lithium and sodium bis(trimethylsilyl)amide (entries 1-8), sodium hydride (entry 9), and sodium hydroxide under PTC conditions



2a R = ⟋⟋⟋⟋⟋⟋OP, X = OMs, I P = THP, TBDMS
2b R = n-Hexyl, X = I
2c R = Bn, X = Br

Scheme 1. Alkylation of Phenylselenoacetonitrile

(entry 10)[5] were applied for the deprotonation of **1**. Lithium hexamethyldisilazide provided the best overall alkylation yields (see Table). The major side products were varying amounts of bis(phenylseleno)acetonitrile **7** (entries 1-7) and the deselenylated nitrile **6** (entries 3 and 5). **7** must arise from partly decomposition of **1** (*vide infra*), and thus diminishes the alkylation yield with stoechiometric amounts of **1**, LiHMDS, and **2**. Therefore, a 2.5fold excess of **1** and LiHMDS was applied. The phenylseleno ether **5** was formed in trace amounts if at all (entries 1-7). Separate deprotonation/aqueous quench experiments of **1** with LiHMDS showed that the formation of **7** occurred only slowly at -78°C - -40°C, giving an **1/7** ratio of 20 : 1 (^{1}H nmr), but on raising the temperature further the **1/7** ratio dropped considerably. With addition of HMPA the formation of **7** was surpressed even on rising temperature to 0°C providing **1** and **7** in a ratio of 40 : 1.

On the other hand, sodium bases showed a different behavior. Sodium bis(trimethylsilyl)amide (**1** : NaHMDS : **2a**: 1 : 1 : 1) provided the monoalkylation product **3a** in slightly lower yield than the lithium base with only minor formation of dialkylated product **4a** and small amounts of the phenylseleno transfer product **7** (entry 8). However, the sodium anion of **1** decomposed partly to sodium phenylselenide, which acted as a nucleophile towards **2** resulting in considerable formation of the

Table: Alkylation of (Phenylseleno)acetonitrile

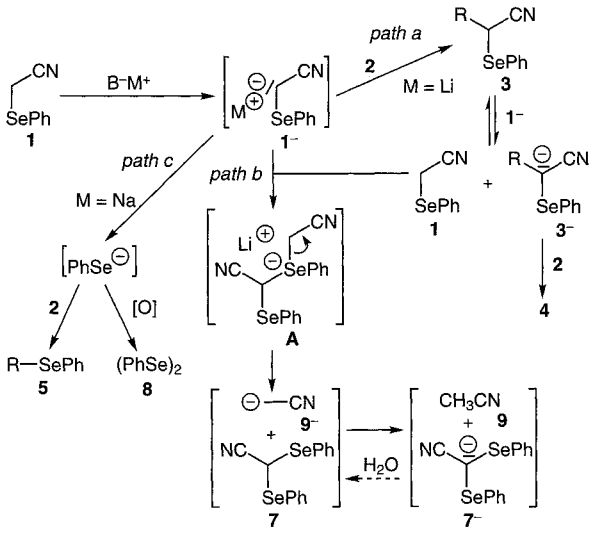
Entry	R-X	Base (ratio **1** : Base : **2**)	Temp.[a] [°C]	Time [h]	Solvent	Overall (**3** : **4**)	Yield [%][b] **3**[c]	**4**[c]	**5**	**6**	**7**[d]	**8**[d]
1	**2a**[e]	LiHMDS (2.5 : 2.5 : 1)	−78 - 0	5	THF	74 (3.6 : 1)	58	16	10	-	32	1
2	**2a**[e]	LiHMDS (2.5 : 2.5 : 1)	−78	9	THF	94 (2.0 : 1)	63	31	3	-	3	1
3	**2a**[e]	LiHMDS (2.5 : 2.5 : 1)	−78 - −20	1.5	THF	84 (5.6 : 1)	73	13	-	11	22	-
4	**2a**[e]	LiHMDS (2.5 : 2.5 : 1)	−78	5	THF/HMPA 10 : 1	90 (1 : 1.5)	36	54	1	-	7	0.2
5	**2a**[f]	LiHMDS (2.5 : 2.5 : 1)	−78 - +20	10	THF	33 (100 : 0)	33	-	2	11	20	6
6	**2b**	LiHMDS (2.5 : 2.5 : 1)	−78 - −30	1.25	THF	83 (1.4 : 1)	48	35	-	-	1	-
7	**2c**	LiHMDS (2.5 : 2.5 : 1)	−78 - −20	3	THF	95 (1 : 1.1)	46	49	-	-	22	-
8	**2a**[e]	NaHMDS (1 : 1 : 1)	−78 - 0	4	THF	55 (100 : 0)	55	-	28	-	10	6
9	**2a**[f]	NaH (1 : 1 : 1)[g]	+65	15	THF	15 (100 : 0)	15	-	29	-	-	21
10	**2a**[e]	NaOH (1 : 1 : 1)[h,i]	+20	72	CH_2Cl_2/H_2O	41 (100 : 0)	41	-	7	-	-	-

a) After addition of electrophile. b) All yields are isolated yields. c) Yield based on electrophile **2**. d) Yield based on **1**. e) Iodide. f) Mesylate. g) 17 % **2a** recovered. h) 50 % NaOH, cat. $Bu_4N^+I^-$, CH_2Cl_2, cf. [5]. i) 42 % **2a** recovered. In an analogous experiment at reflux the reaction remained incomplete but with an increase in the yield of **5** (48 %).

selenoether **5**. Deprotonation of **1** with sodium hydride occurred very sluggishly. A separate deprotonation/aqueous quench experiment between 0 and 20 °C during 6 hours gave **1**, sodium phenylselenide (isolated as diphenyl diselenide **8** on aerobic workup) together with **7** and a not fully identified product in a ratio of 1.5 : 1 : 1.6 : 1.4.[10] Consequently, **3** was isolated in only 15 % after 15 hours (entry 9). Application of the method of Masuyama et al.[5] provided selectively the monoalkylation product **3** in 40 % yield; however, we were not able to drive the reaction to completion (entry 10).

Alkylating Agents: Iodides proved to be the most efficient alkylating agents with regard to reaction time and yield (entries 1-4,6,8). Activated bromides such as **2c** reacted smoothly to a inseparable mixture of the alkylation products **3c** and **4c**. Mesylates required longer reaction times at higher temperatures, thus leading to diminished yields of the desired alkylation product (entries 5,9). However, the selectivity of the monoalkylation with iodides required careful optimization. Best results were obtained, when the reaction times were not longer than two hours with the reaction temperature not exceeding -20 °C (entries 1-3,8). Addition of HMPA facilitated the alkylation considerably, but led to the formation of substantial amounts of dialkylation product **4** (entry 4).

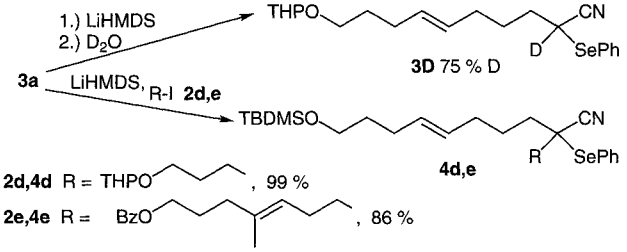
The results can be rationalized as follows on the basis of deprotonated $\mathbf{1}^-$. Lithium and sodium bis(trimethylsilyl)amide deprotonate **1** efficiently (Scheme 2). A part of the lithium compound $\mathbf{1}^-$ is alkylated by the alkyl halide **2** to **3** (path a). With increasing reaction time deprotonation of **3** by unreacted carbanion $\mathbf{1}^-$ provides $\mathbf{3}^-$, leading to dialkylated product **4** and free **1**. This is in agreement with the necessity of two equivalents of base observed by Heathcock et al. for the phenylselenylation of nitriles.[4f] In a second pathway, free (phenylseleno)acetonitrile **1** can undergo phenylseleno transfer with its anion *via* ate-complex **A** (path b) to give bis(phenylseleno)acetonitrile **7** and the anion of acetonitrile $\mathbf{9}^-$,[11] which in turn may deprotonate **1**, **3** or **7**. The large amounts of **7** formed in entries 1, 3, 5, and 7 are due to facile phenylseleno transfer of **1** at higher temperatures and/or extended reaction times for completion of the alkylation (*vide supra*). The formation of deselenylated nitrile **6** can be explained on the same basis *via* $\mathbf{3}^-$ or alkylation of $\mathbf{9}^-$.



Scheme 2. Reaction Pathways of Phenylselenoacetonitrile

The sodium derivative of **1** does not seem to undergo proton exchange ($\mathbf{1}^- \leftrightarrow \mathbf{3}^-$) so easily thus providing almost exclusive monoalkylation (*via* path a) but decomposes instead partly under formation of sodium phenylselenide, which competes efficiently for the alkylating agent **2** thus forming selenoether **5** and diphenyl diselenide[12] (path c). We were, however, not able to trace the fate of the acetonitrile fragment.

To obtain information about the stability of carbanions of **3** we conducted a deprotonation experiment of **3a** (LiHMDS, THF, -78 °C - 20 °C, 5 hours) and quenched the reaction mixture with D_2O. This led to quantitative recovery of **3a** with 75 % deuterium incorporation (^{1}H nmr) thus indicating a stable anion. Alkylation of **3a** (ratio **3a** : LiHMDS : **2d** or **2e**: 1 : 1 : 1) with the iodides **2d** and **2e** following the general procedure[8] provided **4d** and **4e** in 99 and 86 % yield (Scheme 3).



Scheme 3. Deuteration and Alkylation of 2-(Phenylseleno)nitrile **3a**

In summary, we have shown that (phenylseleno)acetonitrile **1** can be alkylated under optimized conditions. Although dialkylation could never be completely suppressed, the application of LiHMDS and alkyl iodides in short reaction times with temperatures not exceeding -20 °C provided best yields of monoalkylation products (*cf.* entry 3) and minimized facile proton and phenylseleno transfer, as shown in control experiments. The alkylation of 2-(phenylseleno) nitriles **3** gives access to dialkylated derivatives in excellent yields. The application of this methodology in macrocyclizations will be reported in due course.

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(8) **General Procedure:** A solution of n-BuLi (27 ml, 43.3 mmol, 1.6*M* in hexanes) was added at -25°C under a nitrogen atmosphere to a stirred mixture of 9.4 ml (44.3 mmol) hexamethyldisilazane and 50 ml dry THF. After stirring for 30 min between -25°C and 0°C, the mixture was cooled to -78°C and a solution of 8.50 g (43.3 mmol) of **1** in dry THF (5 ml + 5 ml rinse) was added. The clear, pale yellow solution was stirred between -78°C and -50°C for 30 min. A THF solution (5 ml + 1 ml rinse) of the iodides **2a-c** (17.7 mmol) was added *via* syringe at -78°C during 5 min. The temperature was raised to -20°C in one hour and kept at -20°C until completion (TLC monitoring, silica gel, hexanes/EtOAc 7.5 : 1, ≈30 min). The yellow-orange reaction mixture was quenched at -20°C by 5 ml of saturated $NaHCO_3$. The mixture was concentrated *in vacuo* and 50 ml of ether was added. After separation, the aqueous layer was extracted with three 5 ml portions of ether and the combined organic layers were washed with brine. After drying over Na_2SO_4, evaporation provided an orange oil which was purified with column chromatography (silica gel, hexanes/EtOAc).

(9) Selected Data: **3a**: ^{1}H nmr (300 MHz, $CDCl_3$): δ = 7.70 (m, 2 H); 7.38 (m, 3 H); 5.39 (t of AB-system, *J* = 5.8, 6.0, 15.4 Hz, 2 H); 4.57 (m, 1 H); 3.86 (m, 1 H); 3.73 (ddd, *J* = 6.7, 6.8, 9.5 Hz, 1 H); 3.60 (t, *J* = 7.4 Hz, 1 H); 3.50 (m, 1 H); 3.37 (ddd, *J* = 6.6, 6.8, 9.5 Hz, 1 H); 2.04 (m, 4 H); 1.87 - 1.51 (m, 12 H). - ^{13}C nmr (75 MHz, $CDCl_3$): δ = 136.2 (PhSe), 130.9 (HC=), 129.5 (PhSe), 129.4 (PhSe), 129.0 (HC=), 125.9 (PhSe), 120.0 (CN), 98.7 (THP), 66.8 (THP), 62.2 (CH_2OTHP), 32.0, 31.4, 30.6 (THP), 29.4, 29.1, 27.5, 25.8, 25.4, 19.5 (THP). - **4a**: IR (film): 2932, 2863, 2220, 1437, 1350, 1320, 1258, 1198, 1181, 1134, 1119, 1074, 1030, 968, 903, 868, 812, 741, 691. - ^{1}H nmr: δ = 7.71 (m, 2 H); 7.40 (m, 3 H); 5.39 (t of AB system, *J* = 5.8, 15.3 Hz, 4 H); 4.52 (m, 2 H); 3.80 (m,2 H); 3.73 (ddd, *J* = 6.7, 6.8, 9.5 Hz, 2 H); 3.50 (m, 2 H); 3.38 (ddd, *J* = 6.5, 6.6, 9.5 Hz, 2 H); 2.03 (m, 8 H); 1.78 - 1.46 (m, 24 H). - ^{13}C nmr: δ = 137.7 (PhSe), 131.0, 129.8 (PhSe), 129.1 (2 C) (PhSe), 125.7 (PhSe), 121.9 (CN), 98.7 (THP), 66.9 (THP), 62.2 (CH_2OTHP), 41.6 (PhSe*C*CN), 36.4, 32.0, 30.6 (THP), 29.4, 29.1, 25.4 (THP), 19.6 (THP). - MS *m/z*, (^{80}Se), (%): 533 (M^+ - THP^+, 0.5), 449 (2.5), 431 (0.5), 376 (1), 358 (1), 292 (20), 274 (11), 256 (2), 158 (6), 129 (57), 85 (100), 55 (22). - HRMS *m/z*, (M^+ - 2 DHP): calcd.: 449.1833 found: 449.1833. - **5**: IR (film): 2936, 2868, 1478, 1437, 1200, 1136, 1119, 1074, 1034, 970, 735, 691. - ^{1}H nmr: δ = 7.48 (d, *J* = 7.7 Hz, 2 H); 7.25 (m, 3 H); 5.40 (t of AB system, *J* = 5.7, 5.8, 15.4 Hz, 2 H); 4.56 (m, 1 H); 3.85 (m, 1 H); 3.72 (dt, *J* = 6.8, 9.6 Hz, 1 H); 3.47 (m, 1 H); 3.37 (dt, *J* = 6.6, 9.6 Hz, 1 H); 2.89 (t, *J* = 7.4 Hz, 2 H); 2.08 (m, 4 H); 1.85 - 1.50 (m, 10 H). - ^{13}C nmr: δ = 132.2, 131.4, 130.7, 129.2, 128.8, 126.4, 98.6, 66.8, 62.1, 32.4, 30.6, 29.7, 29.4, 29.1, 27.1, 25.4, 19.5. - MS *m/z*, (^{80}Se), (%): 368 (M^+, 5.5), 284 (3), 266 (1), 237 (1), 211 (2), 195 (55), 157 (9), 129 (24), 109 (10), 93 (7), 85 (100), 67 (27), 55 (17). - HRMS *m/z*, (M^+): calcd.: 368.1255 found: 368.1276. - **6**: ^{1}H nmr: δ = 5.41 (t of AB system, *J* = 5.1, 6.0, 15.4 Hz, 2 H); 4.55 (m, 1 H); 3.84 (m, 1 H); 3.71 (ddd, *J* = 6.7, 6.8, 9.6 Hz, 1 H); 3.49 (m, 1 H); 3.38 (m, 1 H); 2.31 (t, *J* = 7.0 Hz, 2 H); 2.04 (m, 4 H); 1.85 - 1.46 (m, 12 H). - ^{13}C nmr: δ = 130.8, 129.5, 119.8 (CN), 98.8 (THP), 66.9 (THP), 62.3 (CH_2OTHP), 31.6, 30.7, 29.5, 29.1, 28.3, 25.4, 24.7, 19.6, 17.0. - **7**: IR (film): 3056, 2944, 2226,1574, 1476, 1437, 1067, 1020, 999, 741, 691. - ^{1}H nmr: δ = 7.71 (d, *J* = 7.5 Hz, 4 H); 7.41 (m, 6 H); 4.64 (s, 1 H). - ^{13}C nmr: δ = 136.0, 129.9, 129.5, 127.4, 117.7, 14.2. - MS *m/z*, (^{80}Se), (%): 353 (M^+, 21), 196 (65), 169 (47), 157 (26), 116 (100), 77 (60), 51 (30). - HRMS *m/z*, (M^+): calcd.: 352.9222 found: 352.9242. - **4d**: IR (film): 3074, 3057, 3018, 2950, 2904, 2858, 2224, 1471, 1439, 1386, 1360, 1255, 1201, 1159, 1103, 1078, 1035, 968, 837, 776, 743, 692. - ^{1}H nmr: δ = 7.71 (d, *J* = 7.5 Hz, 2 H); 7.38 (m, 3 H); 5.36 (t of AB system, *J* = 5.7, 15.3 Hz, 2 H); 3.74 (m, 2 H); 3.58 (t, *J* = 6.4 Hz, 2 H); 3.47 (m, 1 H); 3.36 (m, 1 H); 1.99 (m, 4 H); 1.90 - 1.49 (m, 16 H); 0.87 (s, 9 H); 0.03 (s, 6 H). - ^{13}C nmr: δ = 137.8 (PhSe), 131.1 (PhSe), 129.9, 129.2 (PhSe), 129.0, 125.7 (PhSe), 121.8 (CN), 98.73/98.68 (THP), 66.4/66.3 (THP), 62.5, 62.2, 41.5 (PhSe*C*CN), 36.4, 33.9, 32.0, 30.6 (THP), 28.7, 25.9 (*t*-Bu), 25.8, 25.4, 25.2, 19.4, 18.3 (*t*-Bu), -5.3 ($SiCH_3$). - MS *m/z*, (^{80}Se), (%): 579 (M^+, 0.05), 564 (0.5), 522 (39), 438 (13), 411 (7), 364 (11), 280 (72), 264 (19), 253 (40), 236 (8), 188 (7), 155 (67), 133 (12), 119 (15), 97 (23), 85 (100), 75 (84). - HRMS *m/z*, (M^+ - *t*-Bu): calcd.: 522.1943 found: 522.1947.

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