Pergamon

Tetrahedron Letters, Vol. 36, No. 32, pp. 5711-5714, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01112-9

Chemoselective Synthesis of Functionalized Diselenides

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Abstract: The action of $LiEt_3BH$ or DIBAL-H on various functionalized selenocyanates was proven to be an efficient means to establish chemoselectively the diselenide bond, under very mild conditions. The mechanism was shown to involve a selenophilic hydride attack rather than a carbophilic one, supporting a selenol as the intermediate to the diselenide.

Among the vast array of methods aimed at the preparation of diselenides, the most versatile avenues exploited may be exemplified either by the action of metal diselenides M_2Se_2 (usually obtained from various reduction modes of elemental selenium) on halides,[1] or by the preparation of selenols whose further oxidation would lead to the corresponding diselenated compounds.[2] Although selenocyanates have been used to form selenides when exposed to sodium borohydride,[3] it was only with potassium hydroxide that the synthesis of diselenides was reported from them.[4]

Principally, only very simple diselenides have been prepared via all these methods, probably because of functional incompatibility between the substrates and the reagents and/or conditions used. Hence, it seemed to us that a method opening access to more complex diselenides along with very good yields, would anticipate a foreseeable growth of such a synthetic need, when put in context with new natural occurrences[5] and developing biological activity[6] of diselenides.

Trying to exploit the selenocyanate function to its full potential, it was then used in conjunction with easily handled non basic hydrides, like $LiEt_3BH$ (Super-Hydride® from Aldrich Chem. Co. Inc.) or DIBAL-H, under very mild standard conditions such as dry THF at -78°C.[7] (Equation 1)

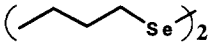
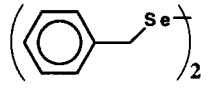
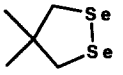
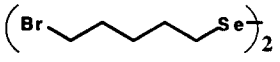
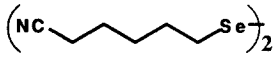
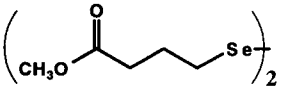
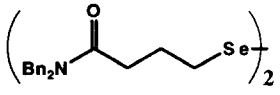
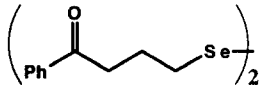
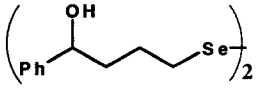
Eq. 1

Thus, we were able to prepare very high yields of various functionalized diselenides, in an almost instantaneous time scale. (see Table 1) Entries 1 to 4 compare favorably with yields already reported.[8] Primary alkyl bromides did not undergo SN_2 displacement,[9] and as anticipated, only afforded the diselenide (entry 5). In the same way, the untouched nitrile function lead to the isolation of the desired diselenide (entry 6). Ester and amide groups (entries 7 and 8), though reducible by Super-Hydride®,[10] did not react at all at that temperature, allowing excellent yields of diselenated compound.

Attempt to reproduce these positive results on a ketone (entry 9) was not completely successful, and lead instead to a mixture of 3 diselenides: the expected diketone (53%); and the corresponding hydroxy-ketone (9%) and diol (24%). In order to circumvent what appeared to be the limit of $LiEt_3BH$

selectivity, K-Selectride™ - softer and more hindered - was used, but instead produced a very complex mixture. In fact, the best selectivity was recorded with DIBAL-H, which lead to 86 % of the desired diketo-diselenide; while use of 3 equivalents of hydride gave an easy and direct access to the dihydroxylated derivative (entry 10).

Table 1. Yields and Functional Compatibility.

Entries	Diselenides	Hydrides	Isolated yields (%)
1		LiEt3BH	97 (40)[8a]
2		LiEt3BH	93 (46)[8a]
3		LiEt3BH	94 (92)[8b]
4		LiEt3BH	79 (76)[8c]
5		LiEt3BH	90
6		LiEt3BH	94
7		LiEt3BH	96
8		LiEt3BH	92
9		DIBAL-H	86
10		LiEt3BH	72

A typical experiment is as follows: To a solution of methyl ester seleno-cyanate[11] (206 mg, 1 mmole) (entry 7) in dry THF (15 mL) maintained at -78°C under nitrogen, was added dropwise the Super-Hydride® (1 mL of 1M solution in THF, 1 mmole). The flask was then opened to allow contact with air, and the cooling bath removed until room temperature was reached. The yellow solution was

concentrated in vacuo, and the resulting residue filtered on a pad of silica (ethyl acetate/hexane - 2/8). The filtrate was then concentrated under high vacuum to afford the corresponding pure diselenide as a yellow oil (173 mg, 96%).[12]

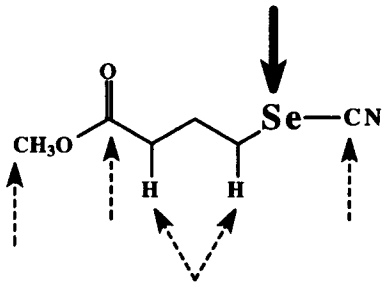


Fig. 1. Chemoselectivity of the hydride attack.

As a dominant feature, chemoselectivity clearly emerges from Table 1, as the high yields obtained underline it. For example, on the methyl ester selenocyanate represented in Figure 1, it is possible to identify no less than six electrophilic/acidic sites, including the alpha selenocyanate proton whose lability has already been exploited to form selenoaldehydes.[11] However, the reagents/conditions used allowed a marked differentiation in favor of the selenated group.

In the same vein and a priori, it was not obvious to determine whether the reaction intermediate was the selenol or the selenolate (respectively resulting from hydride selenophilic vs carbophilic attacks), inasmuch as the final product would be the same in both cases. To resolve this chemoselective aspect of the reaction mechanism,[13] we used what had to be a substantial difference of nucleophilicity between the selenol and the selenolate, as a probe. Therefore, when the reaction (entry 7) was quenched with 10 equivalents of acetic anhydride at -78°C before exposure to air, a mixture of the usual diselenide and of the selenoacetate (11) [$MeO_2C(CH_2)_3SeAc$],[12] was produced with 57 and 17% of respective isolated yields (77/23). However, when 2 equivalents of hydride were used prior to the acetic and then oxidative quench, a 91% isolated yield of the sole (11) was obtained. Consequently, these results strongly suggest that the species responsible for these two reactions were the selenol in the first case, and the more powerful selenolate in the second one. This allows us to propose the selenol as the definitive intermediate in the reaction illustrated in equation 1, which may be considered as the mildest and most efficient methodology to now reach functionalized diselenides.

The knowledge of these active species allows us presently to study the systematic extension of this method to functionalized unsymetrical diselenides (R_1SeSeR_2) and selenenyl sulfides (R_1SeSR_2).

ACKNOWLEDGEMENT

We are grateful to the Medical Research Funds of New Brunswick for financial support. We are also thankful to Professor Stuart Grossert (Department of Chemistry, Dalhousie University) for the mass spectrometry analysis.

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7. All reported reactions gave the same results even when carried out at -105°C.
8. a) Gladysz, J.A.; Hornby, J.L.; Garbe, J.E. *J. Org. Chem.* **1978**, *43*, 1204-1207; b) Klayman, D.; Griffin, T.S. *J. Am.Chem. Soc.* **1973**, *95*, 197-199. c) Syper, L.; Mlochowski, J. *Tetrahedron* **1988**, *44*, 6119-6130.
9. For bromides: Brown, H.C. *J. Am.Chem. Soc.* **1973**, *95*, 1669; for tosylates: Krishnamurthy,S.; Brown, H.C. *J. Org.Chem.* **1976**, *41*, 3064.
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11. Meinke, P.T.; Krafft, G.A. *J. Am. Chem. Soc.* **1988**, *110*, 8679-8685, includes a general preparation of selenocyanates from halides and potassium selenocyanate.
12. All spectra were taken on an AC 200 Bruker NMR machine (200 MHz), in $CDCl_3$, and the chemical shifts are expressed as δ ppm. **1:** ^{1}H: 2.95 (4H, t, J=7Hz), 1,71 (4H, quintet, J=7Hz), 1.39 (4H, sextet, J=7Hz), 0.92 (6H, t, J=7Hz); ^{13}C: 33.07, 29.95, 22.63, 13.56. **2:** ^{1}H: 3.10-2.96 (2H, m), 2.11-2.05 (4H, m), 1.79-1.25 (16H,m); ^{13}C: 43.45, 34.61, 26.96, 25.66. **3:** ^{1}H: 7.33-7.18 (10H, m), 3.82 (4H, s); ^{13}C: 139.04, 129.03, 128.45, 127.10, 32.65. **4:** ^{1}H: 3.11 (4H, s), 1.29 (6H, s); ^{13}C: 49.28, 44.49, 26.60. **5:** ^{1}H: 3.42 (4H, t, J=7Hz), 2.92 (4H, t, J=7Hz), 1.97-1.51 (12H, m); ^{13}C: 33.55, 32.25, 30.11, 29.59, 28.03. **6:** ^{1}H: 2.91 (4H, t, J=7Hz), 2.38 (4H, t, J=7Hz), 1.86-1.52 (12H, m); ^{13}C: 119.62, 30.09, 29.18, 28.44, 24.89, 11.54. **7:** ^{1}H: 3.68 (6H, s), 2.93 (4H, t, J=7Hz), 2.45 (4H, t, J=7Hz), 2.07 (4H, quintet, J=7Hz); ^{13}C: 173.30, 51.62, 33.43, 28.70, 26.97. **8:** ^{1}H: 7.36-7.12 (20H, m), 4.59 (4H, s), 4.44 (4H, s), 2.95 (4H, t, J=7Hz), 2.53 (4H, t, J=7Hz), 2.14 (4H, quintet, J=7Hz); ^{13}C: 172.62, 137.41, 136.51, 129.00, 128.63, 128.28, 127.65, 127.43, 126.41, 49.96, 48.29, 32.38, 29.30, 26.24. **9:** ^{1}H: 7.98-7.41 (10H, m), 3.12 (4H, t, J=7Hz), 3.01 (4H, t, J=7Hz), 2.20 (4H, quintet, J=7Hz); ^{13}C: 199.31, 136.89, 133.09, 128.62, 128.05, 37.73, 29.23, 25.09. **10:** ^{1}H: 7.39-7.22 (10H, m), 4.69 (2H, t, J=7Hz), 2.88 (4H, t, J=7Hz), 2.09 (2H, s), 1.97-1.70 (8H, m); ^{13}C: 144.53, 128.53, 127.66, 125.84, 74.08, 38.66, 29.83, 27.22; IR (neat, ν cm^{-1}): 3115-3620 (OH). **11:** ^{1}H: 3.62 (3H, s), 2.86 (2H, t, J=7Hz), 2.34 (3H,s), 2.28 (2H, t, J=7Hz), 1.91 (2H, quintet, J=7Hz); ^{13}C: 197.39, 172.28, 50.42, 34.74, 34.43, 25.82, 24.94. All compounds displayed good MS-EI data for diselenated structures.
13. An analogous question was raised in the following reference, although: 1) the reported case dealt with a thiocyanate; 2) the HSAB rationalization was there more obvious to assess, with RS^- doing a thiophilic attack, and OH^- a carbophilic one. Huber, U.A.; Bergamin,.D. *Helv. Chim. Acta* **1993**, *76*, 2528-2536.

(*Received in USA* 13 *April* 1995; *revised* 8 *June* 1995; *accepted* 15 *June* 1995)