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ORTHOLITHIATION AS A TOOL FOR THE SYNTHESIS OF EBSELEN ANALOGUES

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Abstract : Ortholithiation reactions are shown to be effective tools for the synthesis of Ebselen (N-phenyl-benzisoselenazolin-3-one) derivatives.

The recent work of ENGMAN L.[1] on "Ebselen expedient synthesis" prompts us to disclose the results of our work in this field since they have now been patented. It is well established, especially in our laboratory, that N-substituted benzamides undergo ortholithiation reactions [2] allowing chalcogen introduction [1,3]. We have examined extensions of this reaction to several substituted arylamides, which are possible precursors of Ebselen analogues.

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Ortholithiations

When treated with n-BuLi substituted benzamides afford dilithiospecies 1A which can be quenched with dimethyldiselenide or elemental selenium, leading to selenides 2A or diselenides 3A respectively. The yields are usually about sixty percent except for R_1 = - CH_3 (see table 1). The reaction also works with isonicotinanilide [4] giving 2Cc in good yield.

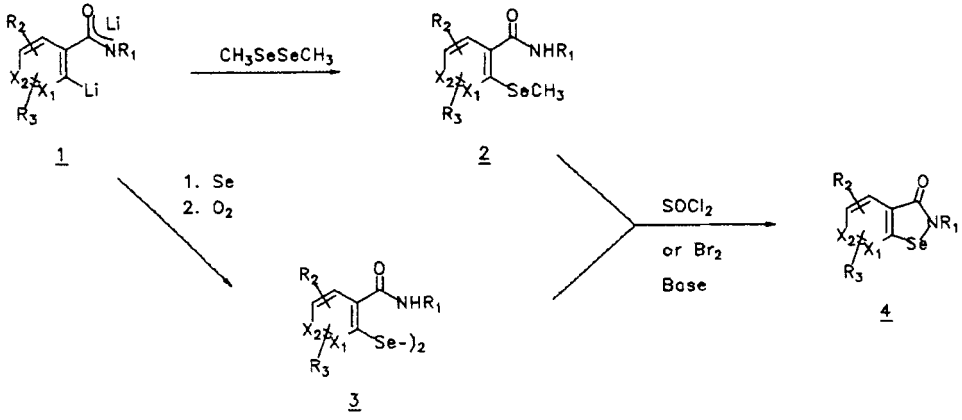
The isomeric amide 2Bc has been obtained by amidation of the 2-(methylseleno)nicotinic acid [5] or by an alternative pathway : the nucleophilic substitution of the chlorine atom in 2-chloro-nicotinanilide with methaneselenolate anion. After protection of the 5-position in furan-2-carboxylic acid [6], it has been possible to metallate 5d in the 3-position with L.D.A. and thus to introduce the methylseleno moiety to obtain 6d.

Thiophene-2-carboxamides can be lithiated at the 3-position [7] affording the chalcogenated product 7e on quenching with dimethyldiselenide. The isomeric compound 8 has been obtained by reacting thiophene-3 carboxylic acid successively with L.D.A. [8] and dimethyl diselenide, followed, as for 6d, by aminolysis of the corresponding acid chloride. We have also obtained more sophisticated species (9 and 10) through metallation of 2-phenyl-2-imidazoline [9] and 2-phenylbenzimidazole [10]. However, we never succeeded in either introducing the -$SeCH_3$ moiety into 2-phenylimidazole via lithiation or in aromatizing 9. Finally, all our attempts at transforming the dilithiated species directly into heterocycles with a chalcogen bis-electrophile failed. With selenium dibromide we obtained the corresponding monoselenide, even after reverse addition, and with selenium tetrabromide or disulfur dibromide, we were unable to isolate any identifiable reaction product.

Ring closures

Cyclisation of selenides 2 or diselenides 3 is usually realised through an intermediate selenenyl halide [11] obtained from 2 or 3 by reaction with thionylchloride, sulfurylchloride or bromine. The ring closure is then accomplished by treatment with a base (sodium hydrogenocarbonate, sodium carbonate, triethylamine or

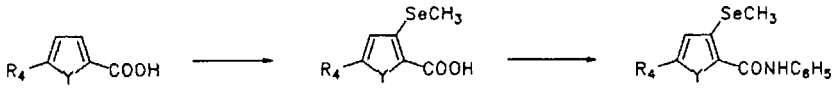
pyridine). Unfortunately, the results strongly depend on both the group R and the aromatic ring. In the benzene series, all the anilides (R_1 = $-C_6H_5$) readily cyclise to Ebselen derivatives with yields around 50 percents while the N-methylbenzamides yielded very small quantities of the corresponding 4a.



1 2 3 4

A : X_1=X_2=CH
B : X_1=N, X_2=CH
C : X_1=CH, X_2=N

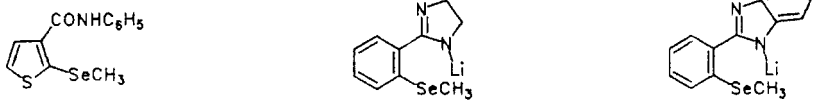
a : R_1=$-CH_3$
b : R_1=$-tert-C_4H_9$
c : R_1=$-C_6H_5$



5 6 7

d : R_4=$-Si(CH_3)_3$ Y=O

e : R_4=-H Y=S



8 9 10

With N-tert-butyl derivatives we sometimes observed formation of a nitrile product of the VON BRAUN reaction. Only two derivatives of the pyridine series 2Bb and 2Bc have been cyclised. The isomeric compounds undergo a bromodeselenisation reaction on the pyridine ring with bromine. No cyclic compound was obtained in the furan and thiophene series. Finally none of our experiments on 9 or 10 have afforded the required tricyclic compound.

Experimental

Melting points are uncorrected. I R spectra were recorded on a Beckman IR 20 (1 % in weight in KBr pellets). NMR spectra were taken on a Varian EM 360 L or a Bruker WP 200 SY in $CDCl_3$ or d_6 - DMSO solution (δ ^{77}Se are given with respect to dimethylselenide as internal standard). Mass spectra were obtained with a Varian MAT 112 or a Finnigan MAT 311 A at 70 eV [12]. Analytical data, determined on a Hewlett-Packard 185B are correct within the accepted limits of experimental error.

I- Ortholithiation procedure

To a solution of the substrate (10^{-2} mole) to be metallated in anhydrous THF (100 ml); was added a solution of the corresponding base (2 10^{-2} mole) at - 78°C. After stirring for 2 h. at room temperature (RT) the mixture is quenched with 10^{-2} mole (1.9 g, 1.2 ml) of dimethyldiselenide and stirred for a further hour at RT. The usual work-up generally afforded a solid which was recrystallized from toluene. When elemental selenium was used as electrophile, the mixture was saturated with oxygen for 2 h. before the work-up and the resulting diselenides were recrystallized from toluene-ethanol.

II. Synthesis of amides from methylseleno-acids

The acid (10^{-2} mole) was left overnight with an excess of dichloromethyl methylether (10 ml) in the presence of anhydrous $ZnCl_2$ (100 mg). The reagent is then removed in vacuo and to the residue, dissolved in 100 ml of CH_2Cl_2, is added 3 10^{-2} mole of amine. After stirring for 2 h. at RT and standard work-up, the residue was recrystallized from toluene (table 1).

table 1 : acyclic precursors

Compounds	R_2	R_3	Yields %	Mp (°C)	$\nu_{C=O}$ (cm^{-1})	^1H RMN (ppm)
2Aa	-5-CH_3	H	2	162-165	1640	6,72-7,34 (m, 3H, ArH + NH) 2,83 (d, J=5Hz, 3H, NH-CH_3 2,16 (s, J_{SeCH_3}=13Hz, 3H, $SeCH_3$) 2,1 (s, 3H, CH_3)
2Ab	-5-CH_3	H	65	102-105	1630	6,82-7,28 (m, 3H, ArH) 5,83 (s, broad , 1H, NH) 2,22 (s, J_{SeCH_3}=14Hz, 3H, $SeCH_3$) 2,16 (s, 3H, CH_3) 1,4 (s, 9H, t-C_4H_9)
2Ac	-5-CH_3	H	73	128-130	1640	7,88 (s, broad , 1H, NH) 6,64-7,8 (m, 8H, ArH) 2,26 (s, J_{SeCH_3}=13Hz, 3H, $SeCH_3$) 2,06 (s, 3H, CH_3)
3Aa	-3-OCH_3	H	1,5	201-205	1640	8 (s, broad, 1H, NH) 6,7-7,5 (m, 3H, ArH) 3,8 (s, 3H, OCH_3) 2,47 (d, J=10Hz, 3H, CH_3)

(continued)

Table 1 (continued)

3Ab	-3-OCH_3	H	65	221-227	1630	6,7-7,3 (m, 3H, ArH) 6,23 (s, broad, 1H, NH) 3,16 (s, 3H, OCH_3) 1,3 (s, 9H, t-But)
3Ac	-3-OCH_3	-4-OCH_3	41	235	1640	9,9 (s, 1H, NH) 6,7-7,53 (m, 7H, ArH) 3,64 (s, 3H, OCH_3) 3,47 (s, 3H, OCH_3)
2Ac	-3-OCH_3	H	50	115-120	1640	8,36 (s, 1H, NH) 6,9-7,9 (m, 8H, ArH) 4,13 (s, 3H, OCH_3) 2,13 (s, J_{SeCH_3}=12Hz, 3H, $SeCH_3$)
2Aa	-3Cl	H	48	122-124	1630	7,4 (m, 1H, ArH) 7,2 (m, 2H, ArH) 6,65 (s, broad, 1H, NH) 2,97 (d, J=5Hz, 3H, CH_3) 2,32 (s, J_{SeCH_3}=20Hz, 3H, $SeCH_3$)

2Ab	-3Cl	H	69	109-111	1640	7,4 (dd, J_A=7Hz, J_B not meas., 1H, ArH) 7,2-7,32 (m, 2H, ArH) 5,66 (s, 1H, NH) 2,16 (s, J_{SeCH_3}=14Hz, 3H, $SeCH_3$) 1,36 (s, 9H, t-C_4H_9)
2Ac	-3Cl	H	81	167-170	1680	7,81 (s, 1H, NH) 6,9-7,47 (m, 8H, ArH) 2,17 (s, J_{SeCH_3}=12Hz, 3H, $SeCH_3$)
2Cb	H	H	75	98-100	1660	8,62 (s, 1H, H_2) 8,47 (d, $J_{H_5-H_6}$=5Hz, 1H, H_6) 7,32 (d, $J_{H_5-H_6}$=5Hz, 1H, H_5) 6,27 (s, broad, 1H, NH) 2,35 (s, J_{SeCH_3}=13Hz, 3H, $SeCH_3$) 1,45 (s, 9H, t-C_4H_9)
2Cc	H	H	80	110-112	1650	9,07 (s, broad, 1H, NH) 8,4 (d, J=5Hz, 1H, H_6) 8,37 (s, 1H, H_2) 8,17 (d, J=5Hz, 1H, H_5) 7,04-7,61 (m, 5H, C_6H_5) 2,25 (s, J_{SeCH_3}=13Hz, 3H, $SeCH_3$)

(continued)

Table 1 (continued)

2Bb [13]	H	H	87	149-150	1640	8,5 (dd, $J_{H_5-H_6}$=5Hz; $J_{H_4-H_6}$ not meas., 1H, H_6) 7,65 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_4-H_6}$ not meas., 1H, H_4) 7,05 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_5-H_6}$=5Hz, 1H, H_5) 6 (s, broad , 1H, NH) 2,37 (s, J_{SeCH_3}=13Hz, 3H, $SeCH_3$) 1,45 (s, 9H, t-C_4H_9)
2Bc [13]	H	H	75	180-182	1650	8,65 (dd, $J_{H_5-H_6}$=5Hz; $J_{H_4-H_6}$ not meas.,1H, H_6) 8 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_4-H_6}$ not meas., 1H, H_4) 7,6 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_5-H_6}$=5Hz, 1H, H_5) 6,8-7,4 (m, 5H, H lateral arom. ring) 6,5 (s,broad , 1H, NH) 2,15 (s, J_{SeCH_3}=15Hz, 3H, $SeCH_3$)
6d [13]	-	-	50	165-167	1670	(solvent : CD_3OD) 6,56 (s, 1H, H_4) 2,23 (s, J_{SeCH_3}=15Hz, 3H, $SeCH_3$) 0,26 (s, 9H, $Si(CH_3)_3$) COOH : not observed

7d [13]	-	-	40	120-122	1670	6,76-7,33 (m, 7H, H_4 + NH, C_6H_5) 2,2 (s, J_{SeCH_3}=15Hz), 3H, $SeCH_3$) 0,25 (s, 9H, $Si(CH_3)_3$)
7e but $-C_6H_5$ = tert $-C_4H_9$	-	-	47	64	1620	7,77 (d, J=5Hz, 1H, H_5) 7,5 (s, broad, 1H, NH) 7,12 (d, J=5Hz, 1H, H_4) 2,3 (s, J_{SeCH_3}=14Hz, 3H, $SeCH_3$) 1,36 (s, 9H, ^{t}-C_4H_9)
7e	-	-	40	108-110	1630	9,98 (s, broad, 1H, NH) 7,75 (d, J=5Hz, 1H, H_5) 7,65 (d, J=8Hz, 2H, ArH) 7,32 (dd, J_A=J_B=8Hz, 2H, ArH) 7,15 (d, J=5Hz, 1H, H_4) 7,1 (t, J=8Hz, 1H, ArH)

(continued)

Table 1 (continued)

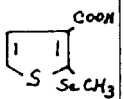
8 [13]	-	-	20	153-155	1630	9,9 (s, broad, 1H, NH) 7,82 (d, J=5Hz, 1H, H_5 7,75 (d, J=5Hz, 1H, H_4) 7,68 (d, J=7Hz, 2H, H arom.) 7,35 (dd, $J_A=J_B=7Hz$, 2H, ArH) 7,12 (t J=7Hz, 1H, ArH) 2,35 (s, $J_{SeCH_3}=15Hz$, 3H, $SeCH_3$)
acide [14] 	-	-	42	153-159	1670	12,85 (s, broad, 1H, CO_2H) 7,55 (d, J=5Hz, 1H, H_5) 7,35 (d, J=5Hz, 1H, H_4) 2,37 (s, $J_{SeCH_3}=13Hz$, 3H, $SeCH_3$)
9	-	-	47	84-89	-	7,16-7,56 (m, 4H, ArH) 4,75 (s, broad, 1H, NH) 3,8 (s, broad, 4H, $2CH_2$) 2,25 (s, $J_{SeCH_3}=13Hz$, 3H, $SeCH_3$)
10 [15]	-	-	43	240-245	-	12,9 (s, broad, 1H, NH) 7,2-7,92 (m, 8H, ArH) 2,17 (s, $J_{SeCH_3}=15Hz$, 3H, $SeCH_3$)

table 2

Compounds	R_2	R_3	Cyclis. method	Yield	Mp (°C)	$\nu_{C=O}$ cm^{-1}	^{77}Se RMN	^1H RMN (ppm)
4Ac	$-5-CH_3$	H	B	12	175-180	1630		7,97 (d, J=7Hz, 1H, H_7) 7,75 (s, 1H, H_4) 7,65 (d, J=7Hz, 2H,H lat.arom.cycle) 7,5 (d, J=7Hz, 1H, H_6) 7,37-7,55 (m, 2H,H lat. arom. cycle) 7,27 (t,J = 7Hz, 1H,H lat. arom. cycle) 2,42 (s, 3H, CH_3)
4Ac	$-6-OCH_3$	$-7-OCH_3$	B	73	139-141	1660		7,8-6,76 (m, 7H, ArH) 3,81 (s, 6H, OCH_3)
4Ac	H	$-7-OCH_3$	B	66	139-140	1640	963	7,76-6,83 (m, 8H, ArH) 3,86 (s, 3H, OCH_3)
4Ac	H	-7Cl	B	95	101-103	1670	967	7,78 (dd, J_A=3Hz; J_B=2Hz, 1H, ArH) 7-7,45 (m, 7H, ArH)

(continued)

Table 2 (continued)

4Bb	H	H	A	45	173-175	1630		8,75 (dd, $J_{H_5-H_6}$=5Hz; $J_{H_4-H_6}$ not meas., 1H, H_6) 8,2 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_4-H_6}$ not meas., 1H, H_4) 7,37 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_5-H_6}$=5Hz, 1H, H_5) 1,67 (s, 9H, t-C_4H_9)
4Bc	H	H	A	74	209-211	1640		8,8 (dd, $J_{H_5-H_6}$=5Hz; $J_{H_4-H_6}$ not meas. 1H, H_6) 8,33 (dd, $J_{H_4-H_5}$=8Hz; $J_{H_4-H_6}$ not meas. 1H, H_4) 7,1-7,76 (m, 6H, H_5 + C_6H_5)

III. Cyclisation procedure

A) Br_2-pyridine

To a solution of the amide (10^{-2} mole) in CH_2Cl_2 (200 ml) was added dropwise a solution of bromine (1.6 g, 0.51 ml, 10^{-2} mole) in CH_2Cl_2 (20 ml).The resulting solution was stirred for 1 h. at RT and 10 ml of dry pyridine was added. The reaction mixture was hydrolysed after 1 h. with 200 ml of 2 M HCl. After usual work-up, the residue is recrystallized from toluene. (table 2)

B) $SOCl_2$ - $NaHCO_3$

A mixture of 10^{-2} mole of amide and 50 ml of $SOCl_2$ was refluxed for 4 h. The excess of reagent was removed under reduced pressure and the residue was taken up in 200 ml of CH_2Cl_2. 2 10^{-2} mole of $NaHCO_3$ was added and the mixture stirred overnight. Hydrolysis by 100 ml of HCl 1M afforded after the usual work-up a residue which was recrystallized from toluene.
(table 2)

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12. All new compounds give correct mass spectra in agreement with natural abundance of isotopes present in the molecule.
13. See experimental II
14. LDA was used as the base to obtain 2-methylseleno-3-thiophene carboxylic acid.
15. 3 equiv. of tert-BuLi were used.

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