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α-Methoxy-Benzylmetals : Original Synthesis and Reactivity

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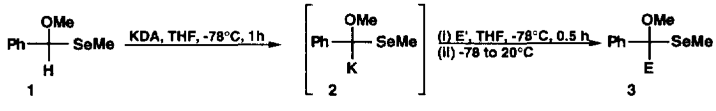
***Abstract*:** Although 1-methoxy-1-methylseleno-toluene is efficiently metallated by KDA, the same compound as well as its higher homologues react with *t*-butyllithium producing 1-methoxy benzyllithiums via the C-Se bond cleavage. These species are efficiently alkylated by alkyl halides, even the secondary ones and react with THF in the presence of BF_3-OEt_2 to produce the homologated tetrahydropyran derivative in good yield.

α- Methoxyalkyl selenides proved to be useful compounds in synthesis allowing, by cleavage of their C-Se bond, the production of α-methoxyalkyl radicals, -cations and -anions and of vinyl ethers via selenoxide elimination reaction.[1]

The presence of a methoxy substituent on the carbon directly attached to the selenium atom in selenides usually inhibits both the H/Li and the C/Se exchange by lithium amides[2a] or alkyllithiums[2b-d] respectively which would have led to α-methoxy-α-seleno-alkyllithiums and to α-methoxy-alkyllithiums. The synthesis of the later derivatives was nevertheless achieved[1b,d] using arenyllithiums, especially LiDBB.

We now report that 1-methoxy-1-methylseleno-toluene **1**, which possesses an extra phenyl stabilizing group, is metallated by KDA in THF (1eq., -78°C, 1h) providing 1-methoxy-1-methylseleno-benzylpotassium **2**, almost quantitatively. This one is stable at -78°C and reacts efficiently with a large variety of electrophiles including epoxides and organic halides even the sec-alkyl-, benzylic- and allylic ones (Scheme 1).

Scheme 1

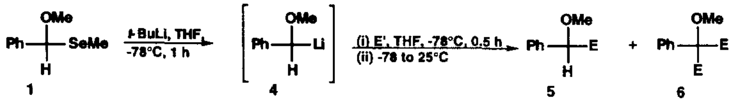


Entry	E'	E	Product	Yield in 3
a	Me_3Si-Cl	Me_3Si	**3 a**	88
b	Oxidopropene	$CH_2CH(OH)Me$	**3 b**	72
c	*n*-Pentyl-Br	*n*-Pentyl	**3 c**	77
d	*i*-Propyl-I	*i*-Propyl	**3 d**	98
e	$PhCH_2$-Cl	$PhCH_2$	**3 e**	98
f	Allyl-I	Allyl	**3 f**	73

1-Methoxy-1-methylseleno toluene **1** also reacts with butyllithiums. Best conditions involve the addition of **1** to a precooled solution of *t*-butyllithium in THF (-78°C, 1h) to provide the α-methoxy-benzyllithium **4** by selective cleavage of the C-Se bond (Scheme 2).[3] Further alkylation, benzylation and silylation of **4** delivers **5** in high yield besides trace amount (< 5%) of **6** (Scheme 2).

Dedicated Professor D. Seebach at the occasion of his 60 th Birthday with great appreciation for his fundamental contribution to Organic Chemistry .

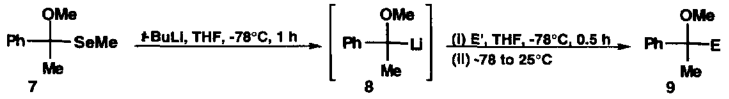
Scheme 2



Entry	E'	Product	E	Yield in **5**
a	PhCH$_2$-Cl	**5 e**	PhCH$_2$	86
b	*n*-Pentyl-Br	**5 c**	*n*-Pentyl	95
c	Me$_3$Si-Cl	**5 a**	Me$_3$Si	85

It must be recalled that the presence of an aryl substituent on the α-alkoxyalkyl selenide is crucial for the success of this reaction.[3b] The reaction of *t*-butyllithium has been successfully extended to homologous 1-methoxy-1-phenyl-1-methylseleno-ethane **7** and the resulting organolithium **8** has been reacted with a large variety of electrophiles to produce functionalized methoxy-arylalkane **9** in high yields (Scheme 3). It is worthwhile to mention that the reaction conditions are so smooth that products resulting from the well known Wittig rearrangement of the intermediate α-methoxy-benzyllithium **8** were never observed.[4]

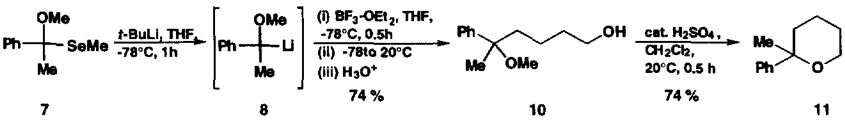
Scheme 3



Entry	E'	E	Product	Yield in **9**
a	Me$_3$Si-Cl	Me$_3$Si	**9 a**	100
b	Oxidopropene	CH$_2$CH(OH)Me	**9 b**	97
c	*n*-Pentyl-Br	*n*-Pentyl	**9 c**	85
d	*s*-Butyl-Br	*s*-Butyl	**9 d**	86
e	PhCH$_2$-Cl	PhCH$_2$	**9 e**	90
f	Allyl-Br	Allyl	**9 f**	77

α-Methoxy-benzyllithium **8** does not react, under the experimental conditions used above, with THF. Nevertheless ring opening of this heterocycle has been efficiently achieved in the presence of boron trifluoride etherate used as Lewis acid catalyst (Scheme 4). The resulting ε-methoxy-alcohol **10** has been successfully cyclised, in acidic media, to the corresponding tetrahydropyran **11** (Scheme 4). In the above five to six membered heterocycle homologation reaction, 1-methoxy-1-phenyl-1-methylseleno-ethane **7** has played the role of a methyl phenyl carbene.[1d]

Scheme 4



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3. (a) These conditions are by far more efficient than those involving instead *n*- or *s*-butyllithiums which are less chemoselective and often lead to irreproducible results[1d] (b) For unsuccessful reactions involving the parent compound or α-alkylated derivatives.[2b-d]
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