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A NOVEL METHOD FOR THE GEMINAL DIALKYLATION OF THE CARBONYL GROUP OF AROMATIC ALDEHYDES AND KETONES

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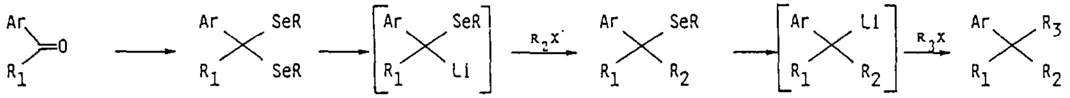
The title transformation is efficiently achieved by using the selenium methodology which involves the sequential reductive alkylation of arylselenoacetals and of benzylselenides.

Although selenoacetals derived from aliphatic aldehydes and ketones have been widely used in organic syntheses, [1,2] those derived from aromatic compounds have been scarcely described [3,4]. We now demonstrate that these can serve as intermediates in the synthesis of aryl alkanes through a process which allows the gem-dialkylation of the carbonyl group of aromatic aldehydes and ketones as shown in Scheme I.

Scheme I

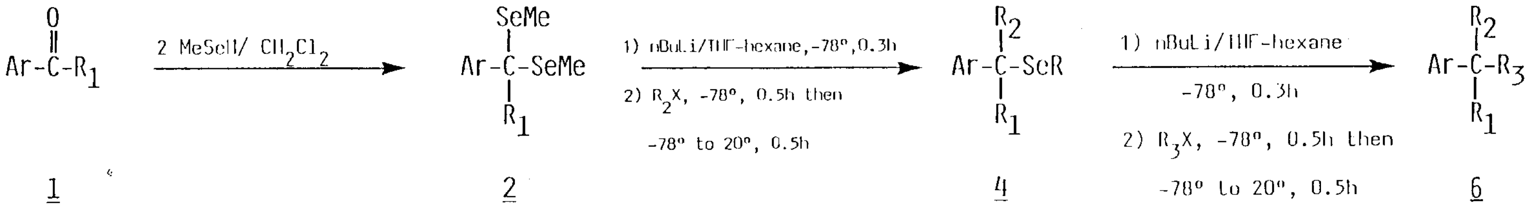


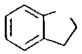
1 2 3 4 5 6

This valuable transformation requires a five-steps three pots reaction, which involves the selenoacetalisation of the aromatic carbonyl compound [3] and the sequential selenium-metal exchange and alkylation reaction on the selenoacetal 2 and on the benzylselenide 4 intermediates, respectively.

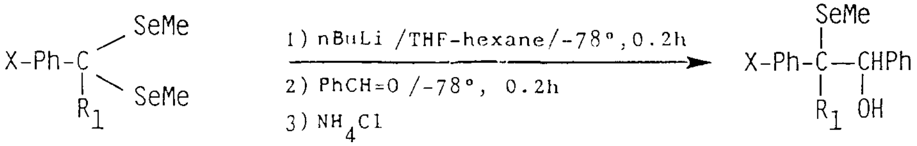
The selenoacetalisation of aromatic aldehydes is efficiently achieved [3] with methylselenol and zinc chloride (method A, Scheme II, a-e) whereas the reaction is more difficult [3] with aromatic ketones which have a high propensity to be reduced to selenides 4' [$ArCH(R_1)SeR$] under similar conditions. In the last case, the replacement of zinc chloride by titanium tetrachloride provides, except in the case of the quite hindered phenyl isopropyl ketone (Scheme II, j), better yields of the corresponding selenoacetals (method B, Scheme II g-i, k). We have found (Schemes II, III) that these selenoacetals react more rapidly [2,5] at -78° with n-BuLi in THF, than their aliphatic analogues, and that contrarily to these latter [2], the reaction even works in ether [5] and produces, in all cases the corresponding α-selenobenzyllithiums almost quantitatively. Interestingly, no competing metallation is observed when selenoacetals derived from aromatic aldehydes are reacted. All these α-selenobenzyllithiums were reacted with benzaldehyde in order to standardise the results and they give rise to excellent yields of a diasteroisomeric mixture of the corresponding β-hydroxyselenides 7 (Scheme III).

Scheme II



	Ar	R$_1$	yield in 2 (yield in 4')	method, temperature time	R$_2$X	yield in 3	R$_3$X	yield in 4
a	Ph	H	92	A, 20°, 2h	nBuI	92	nHexBr	74
b					iPrI	92	iPrI	81
c					tBuI	00	-	--
d	pClPh	H	81	A, 20°, 2h	MeI	93	nHexBr	81
e	pCNPh	H	58	A, 20°, 2h	iPrI	83	iPrI	72
f					tBuI	00		
g	Ph	Me	70(15)	B, -50°, 0.2h; 20°, 2h	nPrBr	88	nHexBr	95
h					iPrI	86	iPrI	87
i	Ph	nPr	71	B, -50°, 0.2h; 20°, 2h	MeI	91	sBuBr	93
j	Ph	iPr	00(52)	B, -50°, 72h	-	--	-	--
k			56	B, 1eq.NEt$_3$, 20°, 2h	EtI	86	EtI	75

Scheme III



2

7

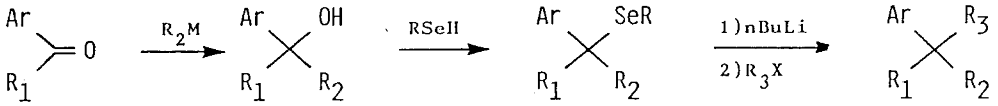
	a	b	c	d	e	f	g	h
X	PMeO,	oMeO,	pCl,	pCN,	pMeO,	pMe,	H.	H
R_1	H,	H,	H,	H,	Me,	Me,	Me,	nPr
Yield %	79,	82,	77,	81,	81,	90.	87,	80

The alkylation of the α-selenobenzyllithiums is particularly facile and takes place in THF with both primary and secondary alkylhalides (Scheme II) but unfortunately not with tertiary homologues (Scheme II, entries c,f). This reaction differs from the one we reported [1,2,6] in the aliphatic series, which requires the use of HMPA as a cosolvent when primary alkylhalides where used and which does not work with secondary alkylhalides. The benzylselenides thus prepared can be transformed directly to the corresponding benzyllithiums [7] on reaction with n-BuLi in THF which can be in turn, efficiently alkylated [8] with primary or even secodary alkylhalides (Scheme II).

On the whole, the process reported therefore allows the efficient gem-dialkylation of the carbonyl group of aromatic aldehydes and ketones (Scheme II). Our method differs from the few already reported [9-13], which are usually restricted to the mono- or the dimethylation of the carbonyl group.

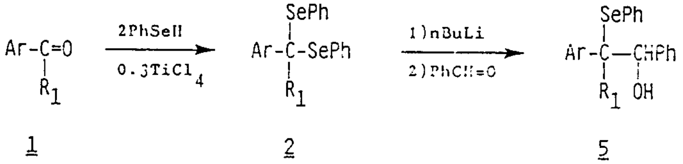
It is also a good alternative, although the carbonyl group of the starting material must not to be too hindered (Scheme II, j), to another approach we have recently achieved [1,8] (Scheme IV). An interesting feature of this novel transformation is that the two alkyl groups are introduced as electrophilic species.

Scheme IV



During the course of this study we have also generalized the synthesis of α-selenobenzyllithiums to the case of phenylseleno derivatives. In fact, these phenylselenoacetals behave similarly to their methyl seleno analogues towards n-BuLi (Scheme V) and, again, no competitive metallation [1,2] is observed in the case of acetals derived from aldehydes. However, the access to phenylselenoacetals from aromatic ketones is very limited and is an important limitation [15] for the use of phenylseleno derivatives for the gem dialkylation of this carbonyl group (Scheme I, II).

Scheme V



	Ar	R_1	Yield in 2(%)	Yield in 7(%)
a	Ph	H	64	83
b	pMeOPh	H	52	79
c	pClPh	H	67	
d	Ph	Me	39	82
e	pMePh	Me	25	
f	pMeOPh	Me	05	

This novel approach to α-selenobenzyllithiums from α-aryl selenoacetals compares well with the one which involves the metallation of benzylselenides [14-16].

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