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Single and Double Reductive Cleavage of C-O Bonds of Aromatic Dimethyl Acetals and Ketals: Generation of Benzylic Mono- and Dicarbanions

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Abstract: The reductive cleavage of aromatic dimethyl acetals and ketals, **1**, with Li metal in THF at low temperature allows the generation of stable α -alkoxy- α -arylsubstituted carbanions, avoiding the Wittig rearrangement. Reaction of these carbanions with various electrophiles afforded the expected products **2**. Further *in situ* reaction of compounds **2** afforded the products of reductive electrophilic disubstitution, **3**.

The generation of carbanions by reductive cleavage of carbon-oxygen bonds is a topic of increasing current interest.^{1,2} As a recent example, two different research groups have reinvestigated the generation of dianions of diaryl ketones by reductive lithiation in the presence of catalytic amounts of 4,4'-di-*t*-butylbiphenyl³ or naphthalene.⁴ Depending upon the procedure of electrophilic quenching, products of mono- or di-alkylation were obtained.³

On the contrary, the reductive cleavage of aromatic acetals and ketals by electron transfer from alkali metals in ethereal solvents has found little practical application. This reaction has been investigated so far at room temperature; under these conditions α -alkoxy- α -arylsubstituted carbanions form but readily undergo Wittig rearrangement to the corresponding alkoxides.⁵⁻⁷ Very recently, however, it was reported that 2-phenyl-1,3-dioxolanes undergo reductive opening by a naphthalene-catalysed lithiation in THF at -40 °C with formation of stable α -(2-ethoxide)oxy- α -phenylsubstituted carbanions.⁸ This prompted us to report our results with open chain aromatic acetals and ketals.

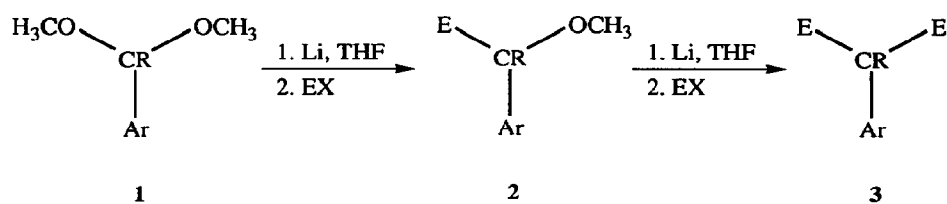
We have reinvestigated the behaviour of aromatic dimethyl acetals and ketals, **1**, under electron-transfer conditions⁷ and wish to report that the use of Li powder in THF at low temperature allowed the successful generation and trapping with electrophiles of α -methoxy- α -arylsubstituted carbanions, avoiding the Wittig rearrangement. Aqueous quenching and work up afforded the products of reductive electrophilic mono-substitution, **2** (Method A).⁹ As an alternative, in the presence of a large excess of Li powder, further reductive cleavage of compounds **2** can be achieved *in situ*; a second electrophilic quenching led to the formation of the products of disubstitution, **3** (Method B)¹⁰ (Scheme). Selected results are reported in the Table.

The reductive cleavage of benzaldehyde dimethyl acetal, **1a**, with Li powder in THF was investigated at different reaction temperatures. After several attempts, it was found that quantitative mono-demethoxylation of **1a** could be accomplished by reaction with Li metal (2.8 equivalents) at -40 °C. Formation of the intermediate **1**

methoxy-1-phenylmethyl carbanion was evidenced by D₂O quenching (Table, entry 1). Trapping of this carbanion with electrophiles was successful; under the conditions reported above, 1-phenylpentyl methyl ether, **2b**, and 3-methoxy-3-phenyl-1-propanol, **2c**, were obtained in satisfactory yields from **1a** upon quenching with 1-bromobutane and ethylene oxide, respectively (Table, entries 2 and 3). In no case the product of Wittig rearrangement, *i.e.*, 1-phenylethanol, was detected.¹¹

Comparable results were obtained in the reductive cleavage of 2-methoxybenzaldehyde dimethyl acetal, **1b**, and of 4-methoxybenzaldehyde dimethyl acetal, **1c**; compounds **2d** and **2e**, respectively, were obtained in satisfactory yields by treatment of these compounds with Li metal followed by quenching with 1-bromobutane (Table, entries 4 and 5).

Scheme



1a: Ar = C₆H₅, R = H; **1b:** Ar = 2-(CH₃O)C₆H₄, R = H; **1c:** Ar = 4-(CH₃O)C₆H₄, R = H; **1d:** Ar = C₆H₅, R = C₆H₅; **2a:** Ar = C₆H₅, R = H, E = D; **2b:** Ar = C₆H₅, R = H, E = C₄H₉; **2c:** Ar = C₆H₅, R = H, E = (CH₂)₂OH; **2d:** Ar = 2-(CH₃O)C₆H₄, R = H, E = C₄H₉; **2e:** Ar = 4-(CH₃O)C₆H₄, R = H, E = C₄H₉; **2f:** Ar = C₆H₅, R = C₆H₅, E = D; **2g:** Ar = C₆H₅, R = C₆H₅, E = CH₃; **2h:** Ar = C₆H₅, R = C₆H₅, E = CH₃; **2i:** Ar = C₆H₅, R = C₆H₅, E = COOCH₃; **2j:** Ar = C₆H₅, R = C₆H₅, E = CH(OH)C₆H₅; **3a:** Ar = C₆H₅, R = H, E = C₄H₉; **3b:** C₆H₅, R = H, E = CH(CH₃)₂; **3c:** Ar = 2-(CH₃O)C₆H₅, R = H, E = C₄H₉; **3d:** Ar = 4-(CH₃O)C₆H₅, R = H, E = C₄H₉

Generation of the α -methoxy-diphenylmethyl carbanion by reduction of benzophenone dimethyl ketal, **1d**, was successfully performed at -20 °C, with no evidence of the rearrangement product, *i.e.*, 1,1-diphenylethanol.¹² As above, the carbanion was trapped with different electrophiles (D₂O, CH₃I, ClCOOCH₃, PhCHO), affording compounds **2f-j** in satisfactory yields (Table, entries 6-9).

Compounds **2** were contaminated by minor amounts of products of further demethoxylation as well as of products of reductive electrophilic disubstitution, **3**. This finding prompted us to develop a second methodology to achieve the disubstitution reaction in satisfactory yield. Reductive cleavage of **1a** was performed in THF at -40 °C with an excess of Li metal; a double quenching with 1-bromobutane allowed the recovery of 5-phenylnonane, **3a**, in good yield (Table, entry 10).¹⁰ Following this procedure, 2,4-dimethyl-3-phenylpentane, **3b** (Table, entry 11), 5-(2'-methoxyphenyl)nonane, **3c** (Table, entry 12), and 5-(4'-methoxyphenyl)nonane, **3d** (Table, entry 13) were obtained in good yields.

It should be pointed out that formation of compounds **3** was not observed in the recently reported⁸ reductive opening of 2-phenyl-1,3-dioxolanes, with the only exception of the benzophenone derivative. Furthermore,

Table. Reductive Electrophilic Substitution of Compounds 1

entry	compound	EX	T (°C)	t, h	quenching method ^a	product, E =	yield (%) ^b
1	1a	D ₂ O	- 40	6	A	2a, D	>90
2	1a	C ₄ H ₉ Br	- 40	6	A	2b, C ₄ H ₉	69
3	1a	(CH ₂ CH ₂)O ^c	- 40	6	A	2c, (CH ₂) ₂ OH	52 ^d
4	1b	C ₄ H ₉ Br	- 40	7	A	2e, C ₄ H ₉	70
5	1c	C ₄ H ₉ Br	- 40	7	A	2f, C ₄ H ₉	80
6	1d	D ₂ O	- 20	4	A	2g, D	>90
7	1d	CH ₃ I	- 20	4	A	2h, CH ₃	78
8	1d	ClCOOCH ₃ ^e	- 20	4	A	2i, COOCH ₃	58 ^d
9	1d	PhCHO	- 20	4	A	2j, PhCHOH	64 ^d
10	1a	C ₄ H ₉ Br	- 40	6	B	3a, C ₄ H ₉	86
11	1a	(CH ₃) ₂ CHBr	- 40	6	B	3b, (CH ₃) ₂ CH	84
12	1b	C ₄ H ₉ Br	- 40	6	B	3c, C ₄ H ₉	92
13	1c	C ₄ H ₉ Br	- 40	6	B	3d, C ₄ H ₉	90

^aSee text and notes 8 and 9. ^bYields estimated by ¹H-NMR analysis, unless otherwise indicated. ^cGaseous (CH₂CH₂)O was bubbled into the reaction mixture for 5 minutes. ^dIsolated yield after flash chromatography. ^eClCOOCH₃ was added at -70 °C.

although dialkylation products can be obtained by the reductive lithiation of diaryl ketones,³ the same reaction does not apply to aromatic aldehydes.¹³ The results reported in this work with aromatic dimethyl acetals and ketals show the potential synthetic usefulness of our procedure, which allows the use of compounds 1 either in the generation of α -methoxy-substituted arylmethyl carbanions or as a source of arylmethyne dianions.

From a mechanistic point of view, it is interesting to observe that generation of a stable α -methoxy phenylmethyl carbanion in THF has been unsuccessfully attempted by the action of butyllithium on benzyl methyl ether^{14,15} or on α -tributylstannylbenzyl methyl ether:¹⁶ the resulting carbanion immediately rearranged, even at low temperature. Several synthetic procedures have been developed to prevent this undesired reaction: conversion of benzyl methyl ether into the chromium tricarbonyl complex,¹⁴ or conversion of benzyl alcohol into the lithium carboxylate salt¹⁵ or the *N,N*-diisopropylcarbamate,¹⁶ allowed the generation of stable α -oxyphenylmethyl carbanions. Also the intermediate carbanions obtained by reductive lithiation of 2-phenyl-1,3-dioxolane⁸ may be considered stabilised by the α -(2-ethoxide)oxy side-arm.¹⁷ In this context, the generation of stable α -methoxy-substituted arylmethyl carbanions according to our procedure is unprecedented. Under our reaction conditions, however, these carbanions might be intermolecularly stabilised by the lithium methoxide¹⁸ present in the reaction mixture. This point is under active investigation in our laboratories.^{19,20}

References and Notes

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- 9 Method A: The substrate (2.5 - 3 mmol) was added under Ar to a vigorously stirred suspension of 2.8 equivalents of Li powder in THF (30 ml) at the reported temperature, and the mixture stirred for the reported time. 1.2 equivalents of the electrophile, dissolved in a minimum amount of THF, were added, and the resulting mixture was stirred for 10 minutes. The reaction was quenched by dropwise addition of water (*caution!*), the cold bath removed, and the resulting mixture extracted with Et₂O. Crude products were purified by flash-chromatography or distillation.
- 10 Method B: The substrate (2.5 - 3 mmol) was added under Ar to a suspension of 6 equivalents of Li powder in THF. 1.2 equivalents of the electrophile, dissolved in a minimum amount of THF, were added, and the resulting mixture was stirred for 1 h. A second portion of the electrophile (1.2 equivalents) was added, and the resulting mixture stirred for 10 minutes. The reaction was quenched (*caution!*) and worked up as described above. We observed that a single quenching with 3 equivalents of the electrophile afforded a lower yield of compound **3**.
- 11 1-Phenylethanol is the main reaction product of the reductive cleavage of **1a** with Li metal in THF both at room temperature (70% yield, see ref. 7) and at -20 °C (62% yield).
- 12 1,1-Diphenylethanol is the main reaction product of the reductive cleavage of **1d** with Li metal in THF at room temperature (75% yield).
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- 19 All compounds gave analytical and spectral (¹H and ¹³C NMR, IR) data in accord with the assigned structures.
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