Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 11998–12006
Tetrahedron

Ion pairing effects on the regioselectivity of arylic versus benzylic C–O bond reductive cleavage: synthetic applications

Ugo Azzena,* Giovanna Dettori, Ilaria Mascia, Luisa Pisano and Mario Pittalis

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

Received 15 June 2007; revised 16 August 2007; accepted 6 September 2007
Available online 11 September 2007

Dedicated to Professor Domenico Spinelli on the occasion of his 75th birthday

Abstract—The regioselectivity of the reductive cleavage of 3,4,5-trimethoxybenzyl methyl ether strongly depends on the alkali metal employed as a reducing agent and solvent effects. Reactions run using Na as a reducing agent led to aromatic C(4)–O bond cleavage, whilst reductions run in the presence of Na/15-crown-5, or using Li as a reducing agent, led to highly regioselective benzylic C–O bond cleavage. This regioselectivity turnaround is discussed in terms of major solvent effects affecting the fragmentation paths of a common reaction intermediate. Synthetic applications of these findings led to the synthesis of biologically active compounds, like 2,5-dialkyl-substituted resorcinols, or 1-(3,4,5-trimethoxyphenyl)-2-arylethanes structurally related to combretastatin.

1. Introduction

The regioselective generation of functionalized organometallic reagents is a topic of current interest in synthetic organic chemistry.[1]

Following our interest in the generation of polar organometallic reagents by the reductive cleavage of aromatic[2] and benzylic ethers,[3] as well as the employment of the resulting carbanions in the synthesis of biologically active compounds,[4,5] we investigated the effect of different alkali metals, namely Na and Li, on the reductive metallation of 3,4,5-trimethoxybenzyl methyl ether (**1**).

Indeed, ether **1** can be considered as a cheap starting material allowing either the synthesis of 2,5-dialkylresorcinols, a class of naturally occurring compounds endowed with cytotoxic[6] and antibiotic[7–10] activities, or of 1,2,3-trimethoxyarenes, a class of compounds endowed, inter alia, with interesting anticancer properties.[11]

The key steps of these transformations rely on the set up of highly regioselective procedures, allowing the reductive metallation of ether **1**, either at the aromatic C(4)–O bond, or at the benzylic C–O bond, as depicted in Scheme 1. Known results on this topic draw attention to the possibility of achieving this goal by an appropriate choice of reaction conditions. Indeed, literature reports show that reductive cleavage reactions of aromatic[12] and benzylic[13] ethers proceed via fragmentation of intermediate radical anions, and point out the importance of counterion and solvent effects on the regioselectivity of the cleavage step.[12–17] Accordingly, besides developing new synthetic applications of the reductive metallation procedure, this work is devoted to highlight the factors governing the regioselectivity of the reductive cleavage reaction under investigation.

2. Results and discussion

2.1. Synthesis of 3,4,5-trimethoxybenzyl methyl ether, 1, and reductive cleavage reactions

3,4,5-Trimethoxybenzyl methyl ether (**1**) was prepared in 88% isolated yield by the reaction of 3,4,5-trimethoxybenzyl alcohol with NaH in dry tetrahydrofuran (THF), followed by reaction of the resulting alkoxide with CH_3I.

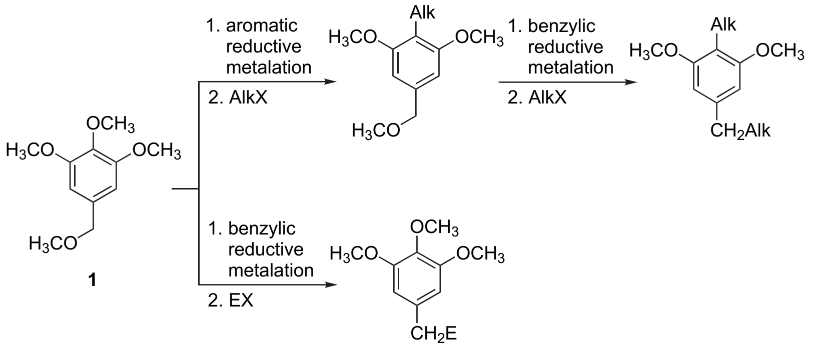
Reductive metallations of ether **1** were carried out under Ar, with an excess of Na or Li metal in dry THF, at temperatures ranging from rt to −50 °C. Na chunks and Li wire (0.32 mm) were freshly cut under dry 2,4,4-trimethylpentane (isooctane) immediately before use. Reductive lithiations were run in the presence of 10 (mol %) of naphthalene ($C_{10}H_8$). Selected reactions were quenched with D_2O to provide

Keywords: Alkali metals; Metallation; Cleavage reactions; Regioselectivity; Ionic pairs; Natural products.

---

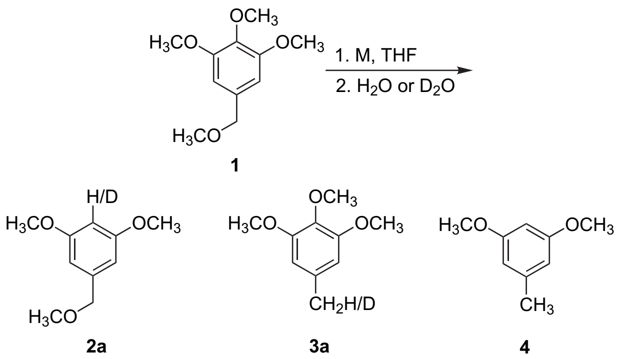
* Corresponding author. Tel.: +39 079229549; fax: +39 079229559; e-mail: ugo@uniss.it

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.010



Scheme 1. Reductive metallation routes to 2,5-dialkylresorcinols and 1,2,3-trimethoxyarenes.

evidence for the formation of intermediate organometals (Scheme 2 and Table 1).



Scheme 2. Reductive cleavage of 3,4,5-trimethoxybenzyl methyl ether (**1**). M=Na or Li.

Depending upon the reaction conditions, we recovered reaction mixtures containing different amounts of 3,5-dimethoxybenzyl methyl ether (**2a**), 3,4,5-trimethoxytoluene (**3a**) and 3,5-dimethoxytoluene (**4**). Although reductive metallations of 1,2,3-trimethoxyarenes are usually accompanied by the formation of minor amounts (5–15%) of phenolic compounds,[2] we did not take into consideration the formation of these by-products. It is however worth noting that recovered reaction products always account for more than 90% of the starting material.

Table 1. Reductive cleavage of ether **1**

Entry	Metal (equiv)	*T* (°C)	*t* (h)	Product distribution (%)[a]		
				2a (%D)[b]	**3a** (%D)[b]	**4**
1	Na (1.5)	20	16	80[c]	—	—
2	Na (1.5)	0	16	>95 (66)	—	—
3	Na (5.0)	−20	14	>95 (78)	—	—
4	Li (2.5)	0	5	—	78	22
5	Li (2.5)	−20	5	—	85	15
6	Li (2.5)	−50	16	—	>95 (77)	—
7	Na (5)[d]	−20	16	—	>95	<5
8	Li (2.5)[e]	0	12	—	>95	<5

[a] As determined by ^1H NMR of crude reaction mixture.

[b] As determined by ^1H NMR spectroscopy by monitoring the percentage of deuteration after D_2O quenching.

[c] Alcohol **5** (20%) was also detected.

[d] In the presence of 1 equiv of 15-crown-5.

[e] In the presence of 1 equiv of 12-crown-4.

Reduction of ether **1** with 1.5 equiv of Na metal at rt for 16 h, afforded a reaction mixture containing, besides 3,5-dimethoxybenzyl methyl ether (**2a**), minor amounts of 1-(3,5-dimethoxyphenyl)ethanol (**5**) (Table 1, Entry 1).

Formation of this by-product can be rationalized in several ways, all of which, however, require the intermediate formation of (at least) one α-methoxy-substituted benzylic carbanion, as depicted in Scheme 3. Na-mediated reductive metallation of starting material leads to the formation of 2,6-dimethoxy-4-methoxymethylphenyl sodium (**I**), probably undergoing acid–base equilibration with the parent compound, to afford the α-methoxy-substituted benzylic carbanion **II**.

Once benzylic organometal **II** is formed, it undergoes a 1,2-Wittig rearrangement to the corresponding alkoxide **III**.[18] Scheme 3 further describes a likely transformation of intermediate **III** into 1-(3,5-dimethoxyphenyl)ethanol (**5**), via reductive dealkoxylation and protonation. Other possibilities (not reported in Scheme 3) could involve, e.g., acid–base equilibration between ether **2a** and organometallic intermediate **I** (or **IV**) leading to a new α-methoxy-substituted benzylic carbanion.

Lowering the temperature to 0 °C led to exclusive formation of ether **2a**, although a relatively low amount of deuterium was incorporated onto the aromatic ring upon D_2O quenching (Table 1, Entry 2). After several attempts, we obtained a better result by running the reaction at −20 °C in the presence of 5 equiv of Na metal (Table 1, Entry 3). It is worth noting that a reductive metallation run in the presence of a catalytic amount (10 mol %) of naphthalene ($C_{10}H_8$), did not improve this result, nor affect the regioselectivity of the reductive cleavage (not reported in Table 1).

At variance with these results, metallations run in the presence of Li metal (and a catalytic amount of $C_{10}H_8$), led to preferential or exclusive cleavage of the benzylic carbon–oxygen bond. Indeed, reactions run at temperatures ranging from 0 to −20 °C afforded reaction mixtures containing, besides 3,4,5-trimethoxytoluene (**2a**), minor amounts of 3,5-dimethoxytoluene (**4**), i.e., the product of a double dealkoxylation reaction (Table 1, Entries 4 and 5), whilst lowering the reaction temperature to −50 °C allowed the highly regioselective generation of 3,4,5-trimethoxybenzyllithium (Table 1, Entry 6).