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Dehydroxymethylation: an unusual reverse reaction of nucleophilic addition to formaldehyde

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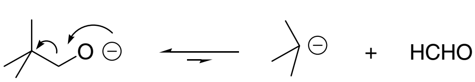
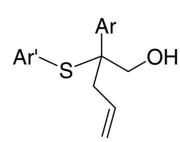
Abstract—An unusual dehydroxymethylation has been observed in an acyclic primary alcoholic system. The relief of steric congestion is considered as the primary driving force in this reaction.

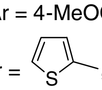
The nucleophilic additions of carbon nucleophiles to aldehydes or ketones are highly favourable processes. Nucleophilic addition of carbon anion to a carbonyl group is normally exothermic. This is attributed to the high reactivity of carbon anion. Moreover, thermodynamically stable products are generated in this reaction. As a result, the reverse process, β-cleavage of alkoxy anion, is rare. The β-cleavage of alkoxy anion becomes a facile process mainly in a ring-fused system, in which the hydroxyl group is positioned at a bridgehead. The driving force for this process is obviously the relief of the fused-ring strain. This type of β-cleavage has been successfully utilized in the synthesis of medium- to large-sized rings.[1] In this letter, we report an unusual alkoxy anion β-cleavage in a non-cyclic system.



In connection with our study on stereoselective [2,3] σ rearrangement of sulfur ylides generated from metal carbene and allyl sulfides, a series of tertiary sulfides **1a**–**j** was prepared.[2]

Oxidation of the sulfides **1a** with *m*CPBA gave sulfone **2a**. When sulfone **2a** was treated with sodium hydride, a new product was isolated. Inspection of the spectral data suggested that the structure of this product was



1a, Ar = 4-BrC_6H_4, Ar' = 2-ClC_6H_4
1b, Ar = 3,4-$Cl_2C_6H_3$, Ar' = 2-ClC_6H_4
1c, Ar = 4-$NO_2C_6H_4$, Ar' = 2-ClC_6H_4
1d, Ar = 3-MeC_6H_4, Ar' = 2-ClC_6H_4
1e, Ar = C_6H_5, Ar' = 2-ClC_6H_4
1f, Ar = 4-ClC_6H_4, Ar' = C_6H_5
1g, Ar = 3-ClC_6H_4, Ar' = C_6H_5
1h, Ar = 4-$MeOC_6H_4$, Ar' = C_6H_5
1i, Ar = , Ar' = C_6H_5
1j, Ar = C_6H_5, Ar' = C_6H_5

3a, in which the hydroxymethyl group was lost (Scheme 1). The structure of **3a** was further confirmed by X-ray crystallography analysis, as shown in Figure 1.

This dehydroxymethylation was found to be general for sulfones **2b**–**j**. As shown in Table 1, the oxidation of **1b**–**j** with *m*CPBA gave sulfones **2b**–**j** in high yields, subsequent treatment of **2b**–**j** with sodium hydride in THF afforded dehydroxymethylation products in moderate to good yields. The substituent on the Ar group was found to have no influence on the reaction. As shown by entries 2 and 7, both the electron-withdrawing NO_2 group and electron-donating OMe group gave dehydroxymethylation products in similar yields.

The extrusion of hydroxymethyl group from **2a** is surprising.[4] A mechanism is proposed for this process. Upon treatment with sodium hydride, the alkoxy anion **A** is first generated and then followed by the β-cleavage of C–C bond to afford **3a** after protonation. The carbon

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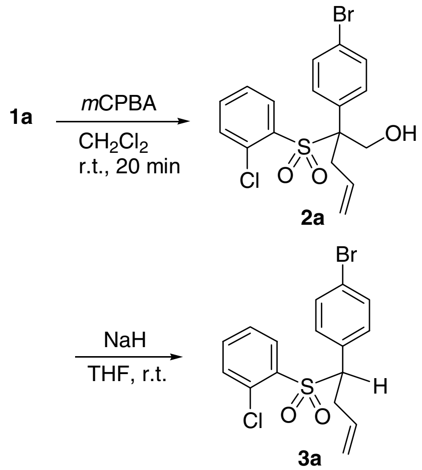
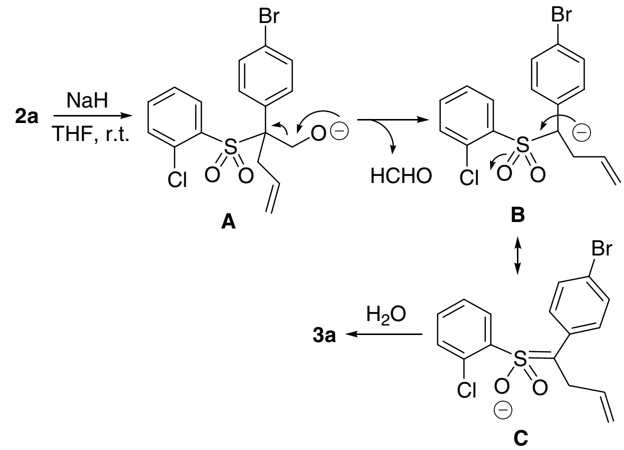


Scheme 1. Oxidation and reaction of **1a** with NaH.



Scheme 2. Proposed reaction mechanism for the dehydroxymethylation.

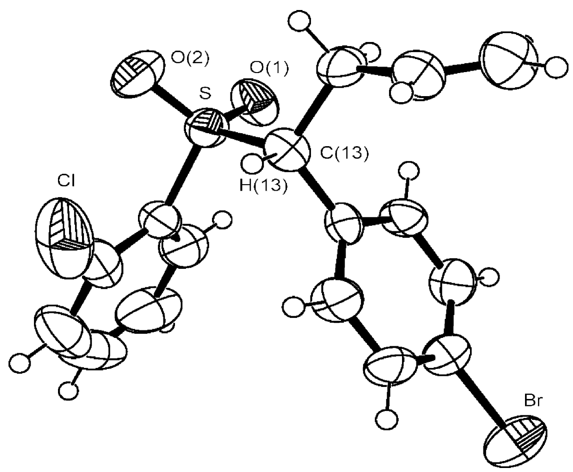
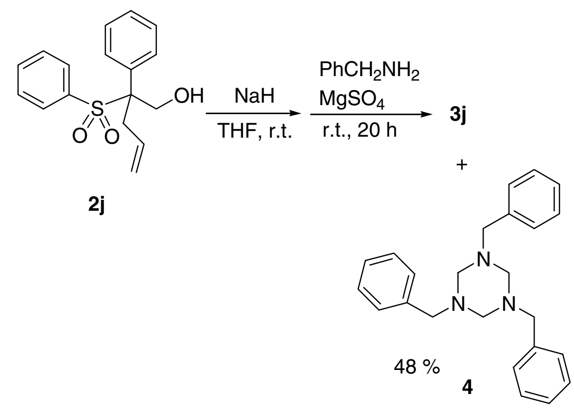
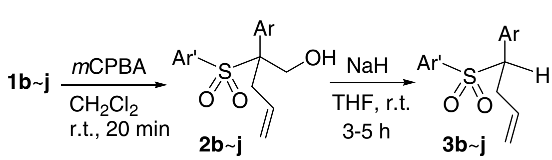


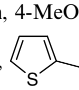
Figure 1. X-ray structure of **3a**.



Scheme 3. Formaldehyde-trapping experiments with **2e**.

Table 1. Oxidation of **1b–j** and subsequent reaction with NaH[3]



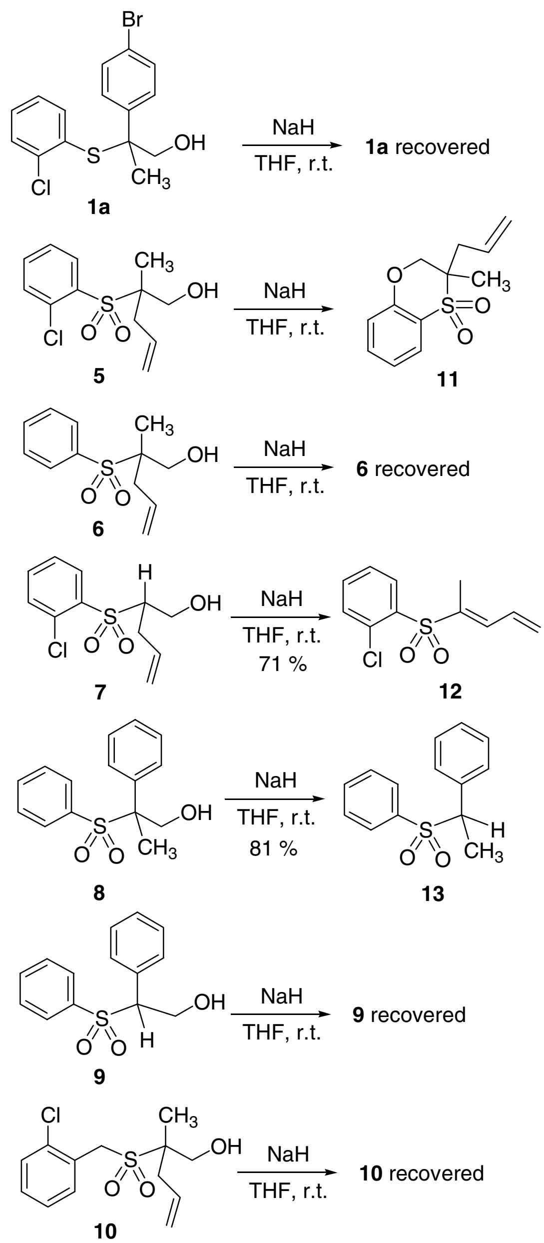
Entry	Sulfide **1** (Ar=, Ar′=)	Product **3**	Yield[a] (%)
1	**1b**, 3,4-$Cl_2C_6H_3$, 2-ClC_6H_4	**3b**	81
2	**1c**, 4-$NO_2C_6H_4$, 2-ClC_6H_4	**3c**	83
3	**1d**, 3-MeC_6H_4, 2-ClC_6H_4	**3d**	75
4	**1e**, C_6H_5, 2-ClC_6H_4	**3e**	82
5	**1f**, 4-ClC_6H_4, C_6H_5	**3f**	65
6	**1g**, 3-ClC_6H_4, C_6H_5	**3g**	53
7	**1h**, 4-$MeOC_6H_4$, C_6H_5	**3h**	62
8	**1i**,  S, C_6H_5	**3i**	79
9	**1j**, C_6H_5, C_6H_5	**3j**	70

[a] Isolated yields for the two steps combined.

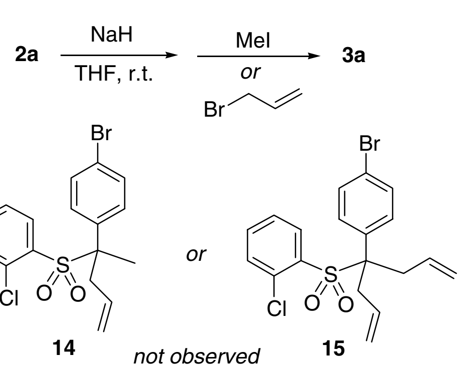
anion **B** is stabilized by the strong electron-withdrawing sulfonyl group and the aromatic substituent, as shown by its resonance structure of **C** (Scheme 2).

To confirm the extrusion of formaldehyde, the reaction of **2j** with NaH was carried out, and then the reaction mixture was treated with benzylamine (Scheme 3). The reaction gave **3j**, together with **4**, which was derived from the reaction of formaldehyde with benzylamine.[5] The isolation of **4** is a conclusive evidence to support the extrusion of formaldehyde.

In order to gain insights into the effects of the structure on this reaction, alcohols **1a** and **5–11** were subjected to identical conditions with NaH in THF (Scheme 4). First, no reaction occurred for **1a** under the same conditions. Compound **5**, in which the aryl group on the carbon is replaced with methyl, was found to give an aromatic substitution product **11**. No dehydroxymethylation product was identified. If the chloro substituent on the sulfonyl aromatic ring is removed, no dehydroxymethylation occurred under the same conditions, as shown by **6**. Interestingly, compound **7**, in which the methyl group has been replaced by hydrogen, gave a diene derivative **12** in 71% yield. On the other hand, when phenylsulfonyl substrate **8** was subjected to NaH/THF, the dehydroxymethylation product **13** was isolated in 81% yield. However, when the substituent on sulfur is changed to *o*-chlorobenzyl group, no dehydroxylation product could be observed, as shown by the example of **10**.



Scheme 4. Reaction of alcohols **5**–**10** with NaH in THF.



Scheme 5. Attempted trapping of intermediate anion.

Finally, with alcohol **2a** as the substrate we tried to trap the intermediate anion by the addition of methyl iodide or allyl bromide. However, only dehydroxymethylation product **3a** could be isolated. The expected product **14** or **15** was not observed (Scheme 5).

These experiments demonstrate the remarkable influence of the structure on this unusual dehydroxymethylation reaction. The results suggest that the reaction is very sensitive to steric congestion around the reaction site, as demonstrated by the reactions of **8** and **9**. The relief of steric congestion seems to be a major driving force for the dehydroxylmethylation. On the other hand, electronic effect is also critical for the reaction. A strong electron withdrawing group is required to stabilize the carbon anion. The aromatic substituent is also important in stablizing the anion, as shown by the reactions of **5** and **6**.

In conclusion, we have observed an unusual dehydroxymethylation reaction. This unusual reaction suggests that the steric congestion and electronic effect may work together to reverse the equilibrium of carbon anion addition to carbonyl group, although the latter is usually a highly favourable process.

Acknowledgements

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3. General procedure for oxidation and subsequent reaction with NaH. Sulfides **1** (0.5 mmol) and *m*CPBA (1.5 mmol) were mixed in CH_2Cl_2 at room temperature. After about 0.5 h, **1** disappeared as judged by TLC. Then saturated $NaHSO_3$ was added and the mixture was extracted with CH_2Cl_2, the organic layers were washed by saturated $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent in vacuo gave **2**. Under a nitrogen atmosphere, **2** and NaH (0.6 mmol) were mixed in THF at room temperature. When **2** disappeared as judged by TLC, saturated NH_4Cl was added. After removal of THF in vacuo the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by silica gel column, eluted with petroleum ether/acetone (30:1) to afford **3**.
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