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NOVEL SYNTHESIS AND APPLICATION OF MIXED ACETALS (ACETYL METHYL ACETALS)

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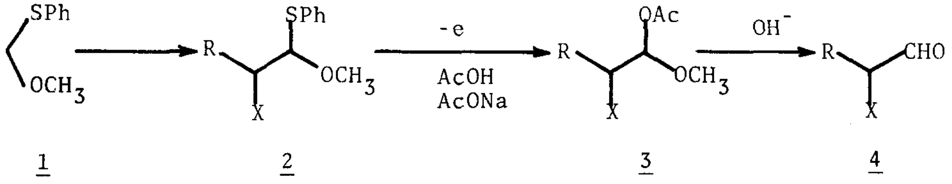
Summary: A novel synthetic method for mixed acetals (acetyl methyl acetals) by electrolysis of hemithioacetals derived from methoxy(phenylthio)methane is newly developed. Synthetic application of these mixed acetals as an aldehyde equivalent is also demonstrated.

Protected α-hydroxy aldehydes[1)] have been widely used in syntheses of a variety of natural products. There have appeared several useful method for protected α-hydroxy aldehydes employing sulfur containing reagents such as β-hydroxy sulfoxides,[2)] 1,3-dithiane,[3)] FAMSO,[4)] and formaldehyde di-*p*-tolyldithioacetal S-oxide.[5)] In addition, the method using α,α-diethoxy acetoamide has been reported.[6)]

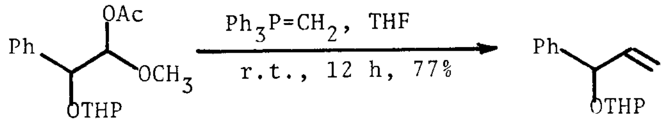
During a study on utilization of methoxy(phenylthio)methane (1)[7)] as a homologation reagent, we have previously disclosed that alkylation products of 1 can be effectively transformed to aldehydes by oxidation with m-CPBA.[7a)] To our regret, however, we have failed to obtain satisfactory results in the cases of protected α-hydroxy products 2, probably because an α-substituents (OAc or OTHP) retards smooth oxidation of a thiophenyl group and subsequent decomposition of the resulting sulfoxides. Hence, we have chosen an electrochemical procedure to overcome this drawback and have disclosed that hemithioacetals 2 can be successfully transformed to new mixed acetals 3 in an AcOH-AcONa medium. Further, we have found that 3 thus obtained can be readily converted into aldehydes 4 by the weak alkaline hydrolysis or by the simple subjection to column chromatography on silica gel. Even more interesting is the fact that 3 themselves act as an aldehyde equivalent in the reaction with ylides and alkyllithiums.



X=H, OAc, OTHP, and $OSi^{t}BuMe_2$

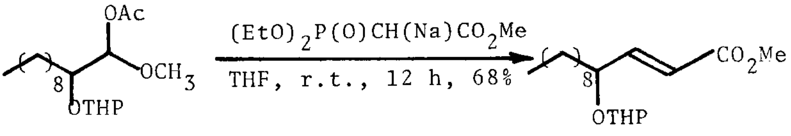
The electrolysis of 2 was carried out in an undivided cell equipped with two platinum elctrodes (4 cm x 2 cm). A mixture of 2 (1.0 mmol) and AcONa (20 mmol) in AcOH (30 ml) was elctrolyzed under a constant current (0.06 A) at applied voltage of 10 V at 18-20 °C. The reaction mixture was diluted with benzene (100 ml) and washed with water repeatedly followed by neutralization with $NaHCO_3$. The benzene layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The results are summarized in Table 1. In entries 1-3, ^1H NMR spectra indicate that the crude oil of 3 is contaminated with a considerable amount of corresponding aldehyde (10-20%) probably due to a partial hydrolysis of labile 3 during the reaction course. However, subjection of a crude oil of 3 to column chromatography on silica gel gives pure aldehyde 4 in high yields. In sharp contrast, α-substituted mixed acetals 3 (X = OAc, OTHP, and OSi^tBuMe_2) are rather stable and allow easy isolation in a pure form by column chromatography without hydrolysis (entries 4-10). Mildness of the reaction conditions employed seems apparent from the fact that acid-labile functional groups such as ketals (entries 3 and 9), tetrahydropyranyl ethers (entries 6 and 7), and siloxy ethers (entries 9 and 10) remain intact during the reaction course. As represented in the last column of Table 1, the mixed acetals thus obtained can be converted into aldehydes 4 by treatment with K_2CO_3 in $MeOH-H_2O$.

Next, it has been found that the mixed acetals 3 can serve efficiently as an aldehyde equivalent. Namely, treatment of 3a with methylenetriphenylphosphorane (2 equiv.) in THF provided the vinyl compound 5a in 77% yield. Accordingly, usefulness of this reaction is apparent for methylenation of difficult-to-obtain aldehydes such as mandelaldehyde. The Horner-Wittig reaction also proved to be effective. Thus, treatment of 3b with a carbanion of methyl diethylphosphonoacetate (2.5 equiv.) in THF gave the α,β-unsaturated ester 5b in 68% yield.



3a

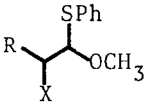
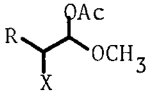
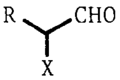
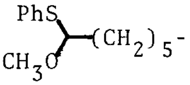
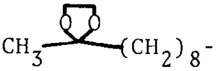
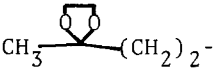
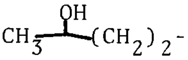
5a



3b

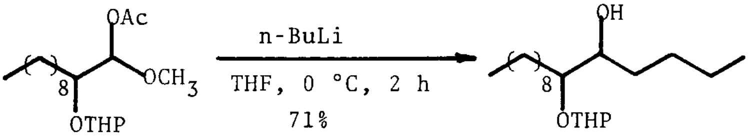
5b

Table 1. Electrochemical Transformation of 2 into 3 and 4

entry	 2	current (F/mol)	 3 (%)	 4 (%)[a]
1	$R=CH_3(CH_2)_{12}$- X=H	30		85
2	R=  X=H	14		83 $(R=CHO(CH_2)_5$-)
3	R=  X=H	29		93
4	$R=CH_3(CH_2)_8$- X=OAc	6	91	b
5	R=Ph X=OAc	9	93	b
6	R=Ph X=OTHP	13	90	70
7	$R=CH_3(CH_2)_8$- x=OTHP	23	88	62
8	R=H $X=CH_3(CH_2)_7O$-	5	78	76
9	R=  $X=OSi^tBuMe_2$	17	85	b
10	R=  $X=OSi^tBuMe_2$	39	81	b

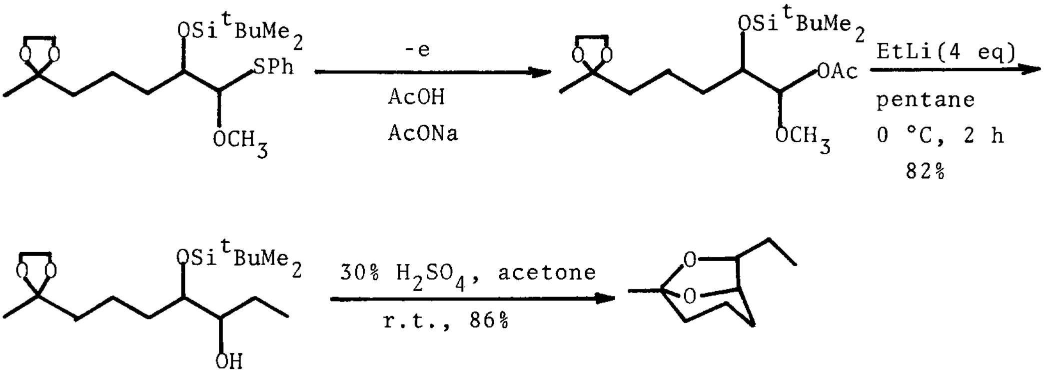
[a] Isolated yields based on 2. [b] Under the present conditions ($K_2CO_3/MeOH-H_2O$), 4 was not obtained.

Finally, the reaction with alkyllithiums will be described. Addition of 3c in THF to n-BuLi (4 equiv.) in hexane yielded an alkylated product 6. This reaction was conveniently applied to a synthesis of brevicomin (7)[8] as shown below.



3c

6



brevicomin (7)
endo/exo 6:1

In conclusion, the mixed acetals obtained in this study proved to be versatile masked aldehydes and undergo the Wittig reaction and alkylation by alkyllithiums as an aldehyde equivalent.

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