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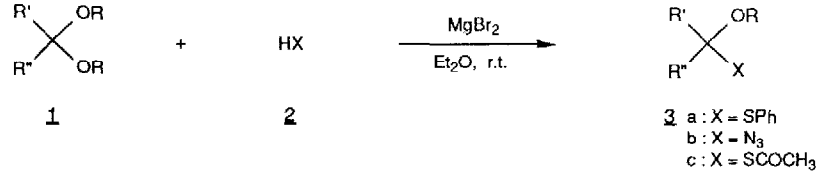
CONVERSION OF ACETALS INTO MONOTHIOACETALS, α-ALKOXYAZIDES AND α-ALKOXYALKYL THIOACETATES WITH MAGNESIUM BROMIDE

Sunggak Kim*, Jung Ho Park and Sangphil Lee
Department of Chemistry
Korea Advanced Institute of Science & Technology, Seoul 130-012, Korea

Summary: Magnesium bromide in ether has been found to be a very mild and highly efficient reagent for the conversion of acetals into the corresponding monothioacetals, α-alkoxyazides and α-alkoxyalkyl thioacetates.

Recently, we have reported that magnesium bromide is a mild and efficient reagent for the selective removal of tetrahydropyranyl (THP) ethers in the presence of tert-butyldimethylsilyl (TBDMS) ethers[1] and selective thioacetalization of acetals without affecting ketones.[2] On the basis of the mildness and hardness of magnesium bromide,[2,3] we have investigated the possibility of the selective displacement of one alkoxy group in acetals with several soft nucleophiles such as thiols, hydrazoic acid and thiolacetic acid which are not complexed with magnesium bromide. We wish to report a very mild and highly efficient method for the conversion of dialkyl acetals (1) into monothioacetals (3a), α-alkoxyazides (3b) and α-alkoxyalkyl thioacetates (3c) using magnesium bromide as an efficient catalyst.



1 2 3 a: X = SPh; b: X = N_3; c: X = $SCOCH_3$

The importance of monothioacetals as useful carbonyl protective groups[4] and intermediates[5] in organic synthesis has been well recognized. Acyclic monothioacetals are usually prepared by the transacetalization of acetals using a limited amount of thiols in the presence of Lewis acids such as boron trifluoride etherate[6] in aprotic solvents, in which cases the choice of reaction temperature and solvents has been proved to be important in the yields of the desired compounds. Although some organometal thiophenoxides[5b,7] and dimethylboron bromide[8] have been recently reported to be efficient thioacetalization methods, the development of a more practical, efficient and mild method is still required.

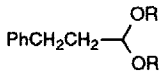
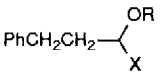
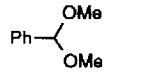
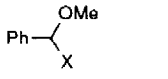
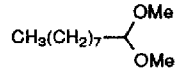
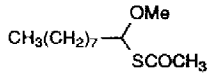
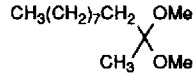
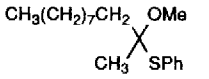
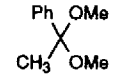
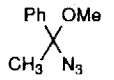
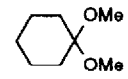
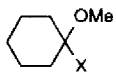
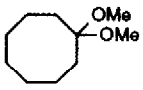
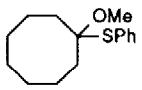
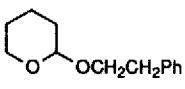
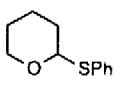
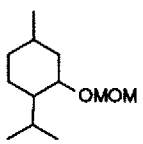
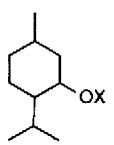
In the course of studying thioacetalization of acetals,[2] we have found that monothioacetalization of dialkyl acetals can be successfully performed with magnesium bromide under mild conditions. Table 1 summarizes some results of our experiments. When dimethyl acetals of aldehydes and ketones were allowed to react with equimolar amounts of thiophenol and magnesium bromide in ether at room temperature for 10 min, the corresponding O-methyl, S-phenyl acetals were obtained in equally good yields after basic workup and flash chromatography. The only detectable side product was a trace amount of the parent carbonyl compounds. Under the identical conditions, diethyl acetal worked equally well (entry 4). It is noteworthy that dimethyl acetals of cyclic ketones can be successfully converted into the desired monothioacetals in good yields without formation of vinyl sulfides (entry 10, 12), which are the only products by the previously described methods.[5b,8]

In order to find out further applicability of this method, we have briefly investigated the reactivity of several acetal-type ethers such as THP, methoxymethyl (MOM), and β-methoxyethoxymethyl (MEM) ethers under the present conditions. As shown in Table 1, THP ether of β-phenethyl alcohol gave 2-phenylthiotetrahydropyran and the parent alcohol in 93% and 92% yields, respectively (entry 13), which is consistent with the facts that cleavage of exocyclic carbon-oxygen bond is the favored process when this type of acetals are treated with Lewis acids.[9] MOM ether of n-nonyl alcohol (ROMOM, R=n-C_9H_{19}) gave a mixture of $ROCH_2SPh$ and ROH in a ratio of 75:18. In the case of menthyl MOM ether, the ratio (86:9) was improved (entry 16).[10] Similar result was obtained with n-butyl mercaptan (entry 17). Although phenylthiomethyl ethers were inert to further thioacetalization with an excess amount of phenyl mercaptan or n-butyl mercaptan, it has been found that treatment of MOM ethers with 2 equiv of n-butyl mercaptan in the presence of 2 equiv of magnesium bromide in ether for 36 h afforded the corresponding alcohols in high yields (entry 15, 18). However, MEM ether was recovered invariably even after prolonged reaction time (entry 19).[11,12]

We have also found that hydrazoic acid and thiolacetic acid react readily with various acetals to produce α-alkoxyazides (3b) and α-alkoxyalkyl thioacetates (3c) in high yields, respectively. The former compounds have been reported to be useful intermediates in the reductive amination of carbonyl compounds.[13]

As shown in Table 1, when dimethyl acetals of aldehydes were treated with a stoichiometric amount of hydrazoic acid or thiolacetic acid in the presence of 1.0 equiv of magnesium bromide in ether at room temperature, the corresponding α-methoxyazides or α-methoxyalkyl thioacetates were obtained in high yields within 10 min. In a similar manner, several dimethyl acetals of aliphatic or aromatic ketones were converted to the corresponding α-alkoxyazides equally well (entry 9, 11).[14]

Table 1. Conversion of Acetals into Monothioacetals, α-Alkoxyazides, and α-Alkoxyalkyl Thioacetates with $MgBr_2$.[a]

Entry	Acetal	Nucleophile	Time, min	Product	Yield, %[b]
					
1	R = Me	PhSH	10	X = SPh	86
2		HN_3	10	X = N_3	82
3		CH_3COSH	10	X = $SCOCH_3$	99
4	R = Et	PhSH	10	X = SPh	91
					
5		HN_3	10	X = N_3	89
6		CH_3COSH	10	X = $SCOCH_3$	90
7		CH_3COSH	10		97
8		PhSH	10		80
9		HN_3	10		75
					
10		PhSH	10	X = SPh	78
11		HN_3	10	X = N_3	80
12		PhSH	10		81
13		PhSH	10		93 (92)[c]
	$CH_3(CH_2)_7CH_2OMOM$			$CH_3(CH_2)_7CH_2OX$	
14		PhSH	30	X = CH_2SPh	75 (18)[c]
15		n-BuSH[d]	36 h	X = H	93
					
16		PhSH	30	X = CH_2SPh	86 (9)[c]
17		n-BuSH	30	X = CH_2SBu-n	75 (11)[c]
18		n-BuSH[d]	36 h	X = H	85
19	$PhCH_2CH_2OMEM$	PhSH	5 h	$PhCH_2CH_2OMEM$	93

[a]All reactions were carried out with a stoichiometric amount of nucleophiles and magnesium bromide in ether at room temperature. [b]Isolated yields. [c]Yields of the parent alcohols. [d]2 equiv of n-BuSH were used.

We have firmly established that magnesium bromide is a very mild and highly efficient reagent for the conversion of acetals into monothioacetals, α-alkoxyazides and α-alkoxyalkyl thioacetates. Together with the stability of TBDMS and MEM ethers toward this reagent, the operational easiness and mildness of magnesium bromide seem to make the present method very attractive.

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