CHEMISTRY LETTERS, pp. 901-904, 1989.

Simple and Chemoselective Deprotection of Acetals Using Aqueous Dimethyl Sulfoxide

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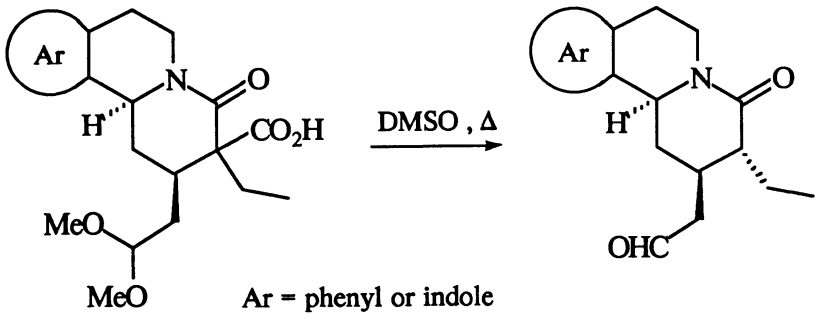
Deprotection of acetals was achieved in aqueous dimethyl sulfoxide under neutral reaction condition. Selective cleavage of acyclic acetals bearing various types of acid labile protecting groups was also reported.

Protection and deprotection of carbonyl group is an inevitable problem on the synthesis of poly-functionalized compounds.

Although a number of deprotecting procedure for acetals, one of the most common carbonyl protecting groups, have been reported,[1] chemoselective deprotection of acetals bearing the acid labile functional groups in the same molecule has been a long-pending problem.

We previously observed[2] that the decarboxylation reaction of the β-keto acid (1) at heating in dimethyl sulfoxide (DMSO) was accompanied by cleavage of the acetal group affording the aldehyde (2). In order to clarify the utility of this deacetalization as a general procedure, we reinvestigated this reaction in detail, and here report a simple and chemoselective deacetalization using aqueous DMSO under neutral condition.



1 2

First, the deprotection reactions of acetophenone dimethyl acetal under

ζDeceased October 11, 1988.

various conditions were carried out and the results are summarized in Table 1. These data showed that this deacetalization in DMSO-H_2O-dioxane afforded acetophenone in high yields, and inhibition was not observed even by addition of pyridine (entries 6 and 7). This fact indicated this reaction not to be an acid catalyzed hydrolysis, although DMSO exhibits a slight acidity in aqueous media. When an excess of water was employed, a catalytic amount of DMSO was required in this reaction (entry 3). Whereas, this deacetalization was not taken place in the absence of either DMSO or water (entries 4 and 5). Interestingly DMSO behaves as a catalyst for acetal exchange reaction when water was replaced by ethylene glycol (entry 8). At present, it is premature to present a detailed mechanistic rationale for the observed deprotection reaction, which can however be considered to be DMSO catalyzed hydrolysis on the basis of the above results.

Table 1. Deacetalization of acetophenone dimethyl acetal in DMSO - H_2O - dioxane system

2mmol

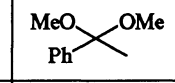
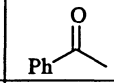
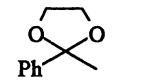
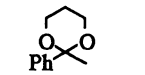
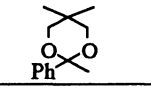
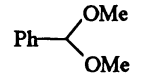
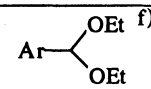
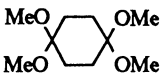
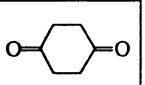
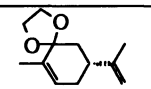
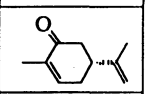
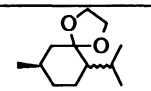
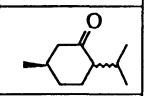
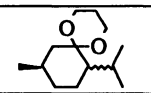
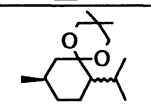
Entry	DMSO[a] (mmol)	H_2O (mmol)	Dioxane[a] (ml)	Temp / °C	Time / h	Yield / %
1	5	5	4	reflux	1.5	93.3
2	5	2	4	reflux	1.5	90.8
3	0.5	10	4	reflux	8	91.3
4	—	10	4	reflux	20	no reaction
5	50	—	—	110	20	trace
6	0.44 + Py 2.4	55	4	reflux	21	85.8
7	4 + Py 2.4	55	4	reflux	4	91.7
8	4	$(CH_2OH)_2$[b] 10	4	reflux	3	85.4[c]

a) DMSO and dioxane were purified by distillation over calcium hydride and lithium alminum hydride, respectively. b) Water was replaced by ethylene glycol. c) Product is acetophenone ethylene acetal.

Secondly, we examined DMSO catalyzed hydrolysis of various acetals in several solvent systems and temperatures as shown in Table 2. In these reactions, again none of the corresponding carbonyl compounds was produced without DMSO in the solvent. Methanol, ethanol, and 2-butanone can be used as co-solvents for this reaction, however, benzene was found to be ineffective, probably because of the biphase system (entry 9). Acyclic acetals were deprotected successfully below 100 °C to give the corresponding carbonyl compounds in high yields (entries 9, 13, 14, and 15). On the other hand, hydrolysis of cyclic acetals such as 1,3-dioxolane and 1,3-dioxane required slightly vigorous reaction conditions, and was achieved at higher temperature (entries 10, 11, 12, 16, 17, 18, and 19).

These results suggested the possibility for selective cleavage of acyclic acetals in the presence of cyclic acetals.

Table 2. Deprotection of acetals in various solvent system
(acetal 2 mmol - H_2O 1 ml - DMSO 4 mmol - solvent 4 ml at reflux)

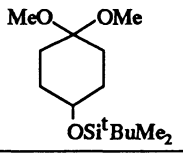
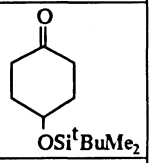
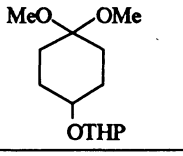
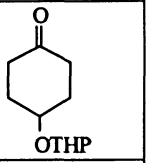
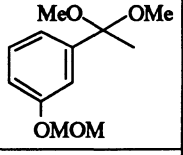
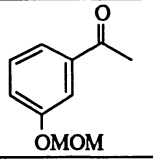
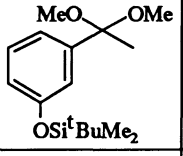
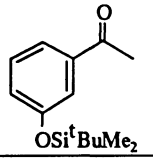
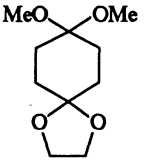
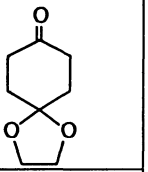
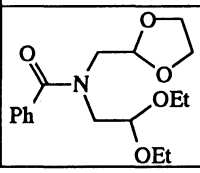
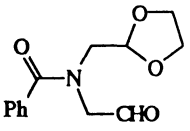
Entry	Acetal	MeOH	EtOH	2-Butanone	Dioxane	2-Methoxy-ethanol	DMSO	Product
9		28 h[a] 89.6%[b]	5 h 85.4%	6 h 89.2%	—[c]	—	—	
10		—	NR[d]	—	NR	A[e]	180 °C 10 h 91.7%	
11		—	A	—	A	—	120 °C 5 h 70.8%	
12		NR	A	—	72 h 89.6%	33 h 79.2%	—	
13		4 h 94.0%	2.5 h 87.3%	—	7 h 82.5%	—	—	PhCHO
14	 [f]	5 h 99.1%	1 h 98.8%	1 h 95.7%	1 h 96.4%	—	—	ArCHO
15		—	—	—	12 h 98.2%	—	—	
16		—	—	—	87 h 85.0%	4 h, 96.7% (2-ethoxy-ethanol)	—	
17		—	—	—	NR	—	180 °C 1.5 h 77.9%	
18		—	—	—	5 d 77.9%	—	180 °C 10 min 90.9%	
19		—	—	—	NR	—	180 °C 20 min 89.9%	

a) Reaction time. b) Yield of isolated product. c) Not examined. d) No reaction.
e) Reaction was not completed for 5 days. f) Ar = p-butylphenyl.

Finally, selective hydrolysis of acyclic acetals in the presence of acid labile protecting groups, such as tert-butyldimethylsilyl, methoxymethyl, and tetrahydropyranyl groups for hydroxy group and 1,3-dioxolanyl group for carbonyl function was attempted to give successfully the corresponding carbonyl compounds in high yields without any deprotection of co-existing protecting groups shown in Table 3.

This deprotection method of acetals has following advantages; 1) neutral reaction condition, 2) no by-products and high-yields, 3) easy isolation of products, 4) safety and low cost of reagents, and 5) excellent chemoselectivity.

Table 3. Chemoselective deacetalization in DMSO - H_2O system

Entry	Acetal (mmol)	DMSO (ml)	H_2O (ml)	Dioxane (ml)	Temp °C	Time h	Yield %	Product
20		0.75	0.6	4	reflux	12	84.4	
21		0.75	0.6	4	reflux	14	87.0	
22		0.23	0.5	3	reflux	18	83.9	
23		0.25	0.5	3	reflux	14	86.7	
24		4	0.18	—	150	8	64.7	
25		4	0.18	—	145	2	89.1	

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2) T. Kametani, Y. Suzuki, and M. Ihara, Heterocycles, 13, 209 (1979); T. Kametani, N. Kanaya, H. Hino, S. -P. Huang, and M. Ihara, Heterocycles, 14, 1771 (1980).

(Received March 10, 1989)