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A Mild and Efficient Method for Selective Cleavage of Ketals and Acetals using Lithium Chloride in Water - Dimethyl Sulfoxide

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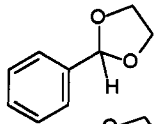
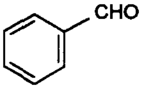
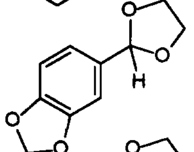
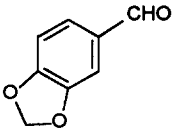
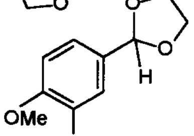
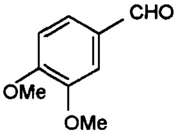
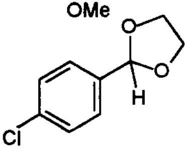
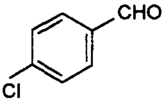
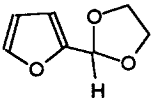
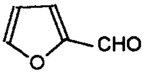
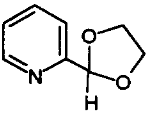
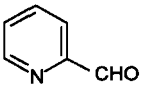
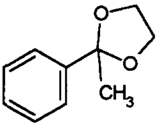
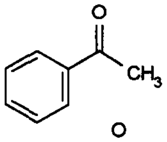
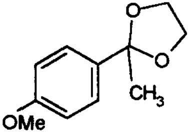
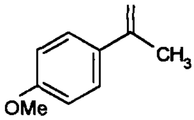
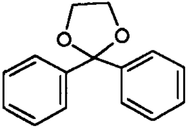
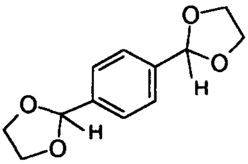
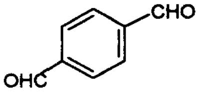
Abstract: A mild and efficient neutral aqueous method for selective cleavage of acetals and ketals to the corresponding carbonyl compounds has been established by using LiCl in H_2O-DMSO at elevated temperature. While aryl and α,β-unsaturated ketals and acetals underwent smooth cleavage, diaryl, non-aryl and isolated ketals and acetals remained unaffected under the reaction conditions.

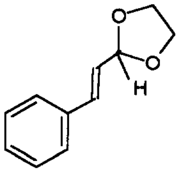
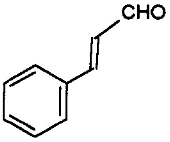
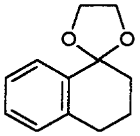
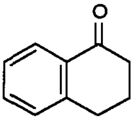
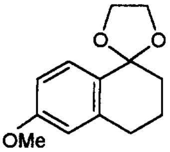
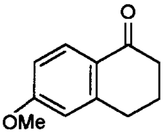
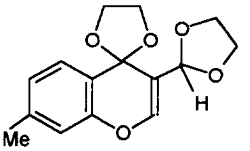
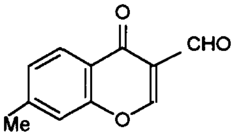
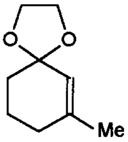
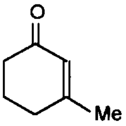
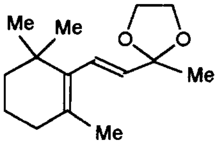
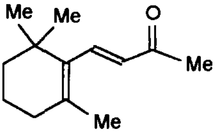
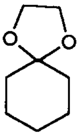
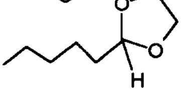
The great significance of selective introduction and removal of protecting groups in organic synthesis is well established. The success of the methodology largely depends on the stability of the protecting groups towards different acidic or non-acidic reagents and how easily they can be installed and removed. Protection of carbonyl groups into ketals or acetals, in particular the 1,3-dioxolanes, as well as their cleavage to the corresponding carbonyl compounds, is well recognized as a useful method[1] specially during the total synthesis of complex natural products. There are many methods for the conversion of ketals and acetals into the corresponding carbonyl compounds,[2] but a mild and neutral method that would effect the selective cleavage in the presence of other sensitive functional groups is still desirable. Moreover, to our knowledge, selective deprotection amongst different types of ketals and acetals is sparcely reported in the literature.[2a] We report herein a mild, efficient and highly selective method for the cleavage of ketals and acetals by using an excess of LiCl in H_2O-DMSO at elevated temperature furnishing the corresponding carbonyl compounds in good yields. While aryl and α,β-unsaturated ketals and acetals underwent smooth cleavage under the present reaction conditions, diaryl, non-aryl and isolated ketals and acetals remained unaffected.

A range of ketals and acetals were prepared from the corresponding carbonyl compounds using the standard procedure [ethanediol, p-TsOH (cat), reflux in benzene using water-separator] and subjected to deprotection using an excess of LiCl in H_2O-DMSO at elevated temperature.[3] The results are summarized in Table 1. All the products were purified by column chromatography over silica gel and the corresponding carbonyl in excellent yields.

Table 1: Selective cleavage of acetals and ketals with LiCl in H_2O-DMSO

Entry	Ketal / Acetal	Reaction temp./ time	Product	Yield(%)^a
1		90^{0}C/18h		75
2		90^{0}C/6h		91
3		90^{0}C/6h		95
4		130^{0}C/8h		93
5		90^{0}C/6h		78
6		90^{0}C/18h		76
7		130^{0}C/8h		75
8		90^{0}C/6h		94
9		130^{0}C/8h	No reaction	-
10		90^{0}C/18h		84

(Table 1 continued)

11		90^{0}C/6h		96
12		90^{0}C/6h		85
13		90^{0}C/6h		90
14		90^{0}C/6h		92
15		130^{0}C/8h		85
16		90^{0}C/6h		86
17		130^{0}C/8h	No reaction	-
18		130^{0}C/8h	No reaction	-

^{a}Yields refer to chromatographically pure isolated products

When a mixture of piperonal acetal and acetophenone ketal was allowed to react with LiCl in H_2O-DMSO at 90^{0}C for 6h, piperonal was isolated in 80% yield while acetophenone ketal was recovered unchanged in 79% yield. Similarly, when a mixture of acetophenone ketal and cyclohexanone ketal was exposed to LiCl in H_2O-DMSO at 130°C for 8h, acetophenone was isolated in 75% yield and the unreacted cyclohexanone ketal was isolated in 82% yield. It was found that both LiCl and H_2O is essential for success of the reaction.

In conclusion, we have established a mild, efficient and highly selective method for deprotection of aryl and α,β-unsaturated ketals and acetals in presence of other ketals and acetals using LiCl in H_2O-DMSO at elevated temperature which will provide an attractive addition to the range of procedures already known for this general transformations.

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References and Notes

1. (a) Reese, C.B. in *Protecting Groups in Organic Chemistry,* McOmie, J.F.W. Ed., Plenum Press: London, **1973**, Chapter 3. (b) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis,* John Wiley and Sons, Inc.: New York, **1967**, Vol. 1, pp. 256. (c) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis,* 2nd Ed. John Wiley and Sons, Inc.: New York, **1991**, pp. 31. (d) Kocienski, P.J. *Protecting Groups,* Thieme, Stuttgart, **1994**.
2. For recent examples see (a) Johnstone, C.; Kerr, W.J.; Scott, J.S. *Chem.Commun.*, **1996**, 341 and references cited therein. (b) Kantam, M.L.; Swapna, V.; Santhi, P.L. *Synth.Commun.*, **1995**, *25*, 2529. (c) Caballero, G.M.; Gros, E.G. *Synth.Commun.*, **1995**, *25*, 395 and references cited therein. (d) Gautier, E.C.L.; Graham, A.E.; McKillop, A.; Starden, S.P.; Taylor, R.J.K. *Tetrahedron Lett.*, **1997**, *38*, 1881.
3. General procedure for the cleavage of ketals and acetals: A mixture of the ketal or acetal (2 mmol), LiCl (10 mmol) and H_2O (2 ml) in DMSO (15 ml) was stirred at the appropriate temperature for the required time as mentioned in Table 1. The reaction mixture was allowed to cool to room temperature, diluted with H_2O (40 ml) and extracted with ether (4 x 25 ml). The organic extract was washed with H_2O (3 x 20 ml) and dried (Na_2SO_4). The solvent was removed and the residue obtained was purified by column chromatography over silica gel [ethyl acetate-light petroleum (boiling range 60°C to 80°C) to afford the carbonyl compounds, which were identified by comparison (TLC, IR and ^{1}H NMR spectra) with the authentic samples.

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