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Acetal and Ketal Deprotection using Montmorillonite K10: The First Synthesis of *syn*-4,8-Dioxatricyclo[5.1.0.0^{3,5}]-2,6-octanedione

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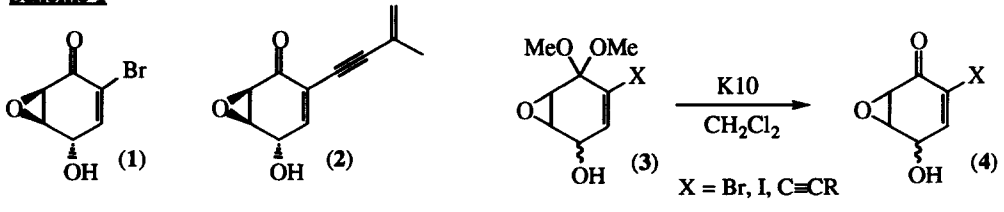
Abstract: Montmorillonite K10 in dichloromethane at room temperature conveniently and efficiently converts acetals and ketals into the corresponding carbonyl compounds. The title dione (diepoxy-1,4-cyclohexanedione) has been prepared for the first time using this procedure.

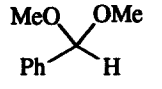
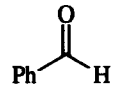
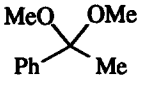
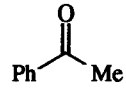
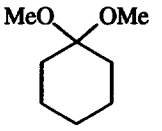
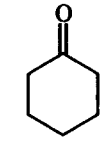
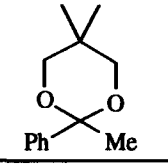
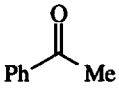
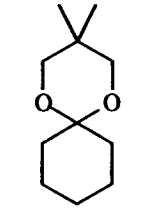
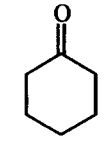
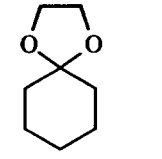
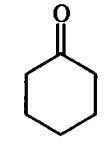
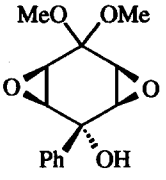
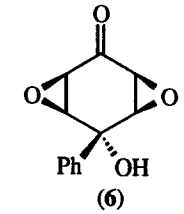
There are many published procedures for the conversion of acetals and ketals into carbonyl compounds[1] but such is the synthetic importance of this form of protection/deprotection that the development of new, improved methods continues to attract attention.[2] In recent total syntheses of the naturally occurring anti-cancer agents bromoxone (**1**)[3] and harveynone (**2**)[4] we required a mild procedure for effecting the transformation of sensitive ketals of type (**3**) into ketones (**4**). After an extensive search, we found that the use of montmorillonite K10[5] in dichloromethane provided a mild and efficient means of accomplishing this process. This commercially available and inexpensive, acidic, activated clay has been employed to effect acetalisation processes[6] but, to our knowledge, its effectiveness for carrying out the reverse process has not been described in the literature.[7-9] As with all deprotection methods employing heterogeneous reagents,[9] the reaction is operationally straightforward and the reagent is easily removed by filtration when the transformation is complete. This *Letter* describes reactions carried out to define the scope and limitations of this deprotection procedure.

Scheme 1



The Table illustrates representative results.[10] Methyl acetals of an aldehyde, an acyclic ketone and a cyclic ketone were deprotected in almost quantitative yields (entries i - iii). Cyclic acetals were also removed efficiently (entries iv - vi), although it should be noted that larger amounts of K10 were required to obtain efficient conversions in reasonable times.

Table Deprotection of acetals and ketals using montmorillonite K10[a]

Entry	Substrate	Conditions	Product	Yield (%)
(i)[b]		CH_2Cl_2, RT, 5 min		95
(ii)[c]		CH_2Cl_2, RT, 5 min		100
(iii)		CH_2Cl_2, RT, 40 min		95
(iv)		CH_2Cl_2, RT, 30 min		95
(v)		CH_2Cl_2, RT, 2 h		76
(vi)		CH_2Cl_2, RT, 2 h		71
(vii)[d,e]	 (5)	CH_2Cl_2, reflux, 1 h[c]	 (6)	92

[a]Carried out on *ca.* 1 mmol scale using *ca.* 250 mg K10 for acetals and 1-2 g for ketals; in several examples the "crude" product was pure according to analysis by NMR spectroscopy

[b]Product contaminated by a trace of benzoic acid

[c]Also successful in acetone, diethyl ether and THF; all of the reactions were complete within 5 min according to TLC analysis

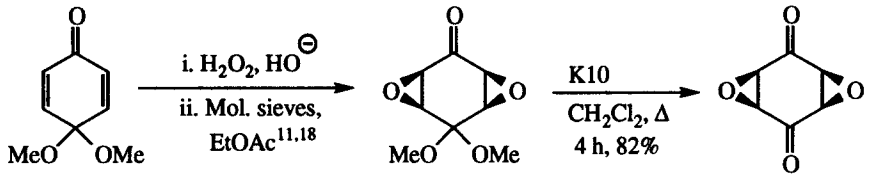
[d]This reaction will go at RT if a large excess of K10 is employed (*ca.* 0.1 mmol scale, 500 mg K10, 5 h, RT, 80%)

[e]For details of deprotection of diastereoisomeric *syn*-hydroxy epoxide see footnote 13

These successes prompted us to explore the deprotection of the complex acetal (**5**, entry vii). In earlier studies,[11] we examined a wide range of reagents for the conversion of (**5**) into ketone (**6**) without any success. Treatment of acetal (**5**) with montmorillonite K10, however, gave a smooth conversion into (**6**): this discovery establishes a new route to novel analogues of the diepoxycyclohexanone antibiotic, aranorosin.[12,13]

We have a long-standing interest in the synthesis of highly oxygenated cyclohexanes and naturally occurring epoxy and diepoxy cyclohexanones.[3,4,11,12,14] As part of this programme, diepoxide (**9**) was identified as a valuable starting material for the synthesis of a range of known and novel inositols, amino cyclitols and related compounds.[15] A number of substituted diepoxy-1,4-cyclohexanediones are known[16] and it is remarkable, therefore, that the parent compound (**9**) has not been reported. The obvious approach to the synthesis of (**9**), *via* epoxidation of 1,4-benzoquinone, was unsuccessful under a range of conditions.[17] We therefore examined the deprotection of diepoxide (**8**), readily prepared[18] as the *syn*-isomer by epoxidation of commercially available quinone monoacetal (**7**) as shown in Scheme 2.

Scheme 2



(**7**) (**8**) *syn*-(**9**)

The use of aqueous acid gave low yields, the water-solubility of (**9**) causing problems. Amberlyst 15 proved much more successful,[17] a 59% yield being obtained when the reaction was carried out in aqueous acetone at room temperature for 24 hours. However, the preferred procedure (Scheme 2) involves the use of montmorillonite K10 in dichloromethane under reflux (82% yield). The title compound (**9**) was obtained as a crystalline solid (m.p. 167-169°C) and the *syn*-nature of the epoxides confirmed by single crystal X-ray crystallography.[19]

We are currently exploring further the synthetic utility of the montmorillonite K10 deprotection procedure. We are also investigating the properties of diepoxide *syn*-(**9**), a remarkable cyclohexane derivative with every carbon bonded to oxygen, and its applications in natural product synthesis.[20]

Representative Procedure: Preparation of Ketone (6) (Table, entry vii)

Ketal (**5**) (175 mg, 0.66 mmol) was dissolved in dichloromethane (25 mL) and montmorillionite K10 (Aldrich, 200 mg) was added. The mixture was then heated under reflux and monitored by TLC. Once the starting material had been consumed (*ca.* 1 h), the yellow solution was cooled to RT and filtered through Celite to remove the K10. The Celite was washed with dichloromethane (3 x 20 mL) and the solvent removed from the combined filtrates under reduced pressure to give a yellow solid. Purification by recrystallization (ether-petrol, bp 40-60°C) gave *ketone (6)* (133 mg, 92%) as a white solid, m.p. 145-148°C; R_f 0.6 (Et_2O); υ_{max} (cm^{-1}) 3474, 1712, 1232, 912; ^1H NMR (270 MHz, $CDCl_3$) 2.85 (1 H, s, OH), 3.58 (2 H, dd, *J* 1, 2.5 Hz, AA'BB' system), 3.75 (2 H, dd, *J* 1, 2.5 Hz, AA'BB' system), 7.52-7.62 (3 H, m), 7.90-7.93 (2 H, m); ^{13}C NMR (67 MHz, $CDCl_3$) 199.4, 139.8, 129.05 (x 2), 125.3, 69.5, 65.3, 55.6; MS (CI): m/z 236 [$(M + NH_4)^+$, 100%]; [Found: 236.0926. $C_{12}H_{10}O_4$ requires $(M + NH_4)^+$, 236.0922 (1.4 ppm error)].

Acknowledgements

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