

Selective cleavage of ketals and acetals under neutral, anhydrous conditions using triphenylphosphine and carbon tetrabromide

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A convenient method for the selective removal of ketal and acetal protection under mild, neutral, anhydrous conditions using PPh₃ and CBr₄ is described.

The deprotection of ketals and acetals, in particular the 1,3-dioxolanes, to the corresponding carbonyl compound is a transformation of considerable importance in organic synthesis. Regeneration of the aldehyde or ketone is normally accomplished by aqueous acid hydrolysis.¹ In the case of compounds possessing acid-sensitive functionality, a number of alternative methods, some of which use non-aqueous conditions, have been developed. These include the use of phosphorous iodides,² alkylsilanes,³ transition metals and other Lewis acids,⁴ oxidative methodology⁵ and other generally less acidic techniques;⁶ each of which have their own respective strengths. However, all of the systems developed to date show some practical or synthetic limitations including the use of inaccessible or sensitive reagents, harsh or aqueous reaction conditions, or utility with a limited range of substrates. Here we report a mild and neutral method for the selective deprotection of ketals and acetals under non-aqueous conditions using the readily available and handled reagents triphenylphosphine and carbon tetrabromide.

Some recent work in our laboratory has resulted in the total synthesis of the sesquiterpene (+)-taylorione.⁷ During the course of the synthetic sequence, we attempted a dibromo-olefination of aldehyde **1** using a modified Corey procedure.⁸ Rather unexpectedly, the initial reactions led to products with either partial or complete loss of the ketal protection (*e.g.* Scheme 1). Despite being able to ultimately overcome this difficulty in our synthetic pathway,[†] the initial problems associated with this step raised the possibility of using this combination of reagents to effect the deprotection of ketals and acetals in a more general sense.

Optimisation of this reaction for the removal of dioxolane protection led to the development of a general procedure. The method employed involved dropwise addition of a solution of PPh₃ (2 equiv.) to a mixture of ketal/acetal and CBr₄ (2 equiv.) in the same solvent (THF or CH₂Cl₂) at 0 °C under N₂.[‡] Reactions were allowed to proceed at 0 °C or warmed to room temperature and were monitored by GC or TLC. When complete, workup involved filtering through a silica pad to remove precipitated triphenylphosphine oxide and purification by flash column chromatography on silica.[§]

As shown in Table 1, the developed techniques successfully deprotect aromatic, α,β -unsaturated and aliphatic ketals, and aromatic and α,β -unsaturated acetals when CH₂Cl₂ or THF is used as solvent. Furthermore, this protocol shows tolerance of

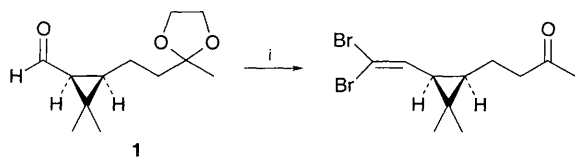
functionality sensitive to standard methods. In the case of entry 9, analogous deprotection using toluene-*p*-sulfonic acid (*p*-TSA) in aqueous MeOH¹ or, the less easily handled, TiCl₄ in Et₂O^{4h} gave the ketone in lower yields (66 and 79% respectively) with contamination caused by decomposition of starting material.

A particularly noteworthy feature of our initial technique is that aliphatic ketals undergo deprotection whereas aliphatic acetals do not (compare entries 6, 9 and 10 with entries 7 and 8).[¶] In order to further demonstrate this discrimination, a mixture of the protected aliphatic aldehyde, undecanal, and the protected ketone, decan-3-one, were subjected to the general procedure in THF and pleasingly it was found that the ketal was deprotected in the presence of the protected aldehyde with almost complete selectivity (Scheme 2). Control experiments on the same mixture of protected aldehyde and ketone indicated that, under standard acid-catalysed conditions (*p*-TSA, MeOH, acetone, H₂O at either room temperature or reflux) both acetal and ketal were deprotected to their corresponding carbonyl compounds as expected. This highly selective discrimination between ketal and acetal is, to the best of our knowledge, unique to this methodology.

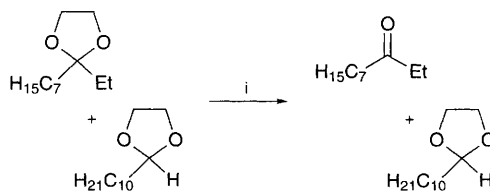
The proposed mechanism for the deprotection reaction involves coordination of the electrophilic phosphonium adduct of CBr₄ and PPh₃ to one oxygen of the dioxolane group. Subsequent successive displacement by 2 equiv. of bromide ion liberates the respective carbonyl compound in addition to the observed by-products, triphenylphosphine oxide and 1,2-dibromoethane.

Our selectivity in these initial reactions can also be explained by the proposed mechanism. In particular, the relative stability of the intermediate oxonium ion would appear to be crucial in dictating the success of any given deprotection (*e.g.* R¹ = alkyl, R² = H does not proceed whereas R¹ = aryl or alkenyl, R² = H deprotect successfully). Additionally, the steric bulk around the protected carbonyl would also appear to be influential in determining reactivity of the ketals/acetals. From Table 1 it can be seen that benzaldehyde forms more quickly than acetophenone whereas benzophenone is not formed at all (entries 1–3).

From our initial set of findings we were only disappointed by the yield observed with protected cyclohexanone (entry 11). In this reaction, after 22 h, the deprotection would proceed no further and gave a 38% yield of the ketone. At this stage, in an attempt to promote this reaction by encouraging transketalisation, acetone was employed as solvent at room temperature. To



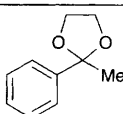
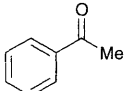
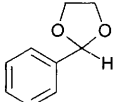
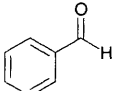
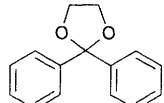
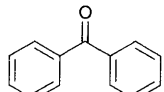
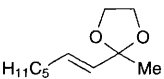
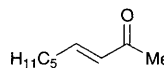
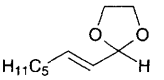
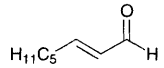
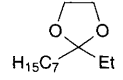
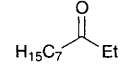
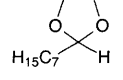
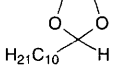
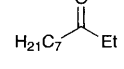
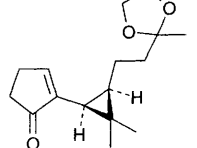
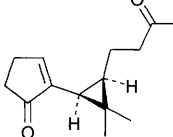
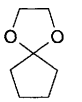

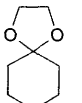

Scheme 1 Reagents and conditions: i, PPh₃ (4 equiv.), CBr₄ (2 equiv.), CH₂Cl₂, 0 °C → room temp. (62%)



Scheme 2 Reagents and conditions: i, PPh₃ (2 equiv.), CBr₄ (2 equiv.), THF, 0 °C (96% of decan-3-one)[¶]

our delight, this switch in reaction medium efficiently enhanced the reactivity of our system.** As can be seen from entry 11, cyclohexanone was deprotected in an excellent 98% yield after only 15 min. Furthermore, when protected benzophenone was

Table 1 Deprotection of ketals and acetals with PPh_3 and CBr_4^a

Entry	Ketal/Acetal	t/h	Product	Yield (%)
1		40 ^b		87
2		20 ^{b,c}		92
3		48 ^b (6)		— (99) ^d
4		25 ^e		62
5		140 ^e		80
6		75 ^{b,c}		82
7		30 ^b	—	—
8		48 ^{b,c}		— (90) ^{d,g}
9		4 ^e		92
10		75 ^e		84 ^g
11		22 ^e (0.25)		38 ^{g,f} (98) ^{d,g}

^a Reactions carried out at room temperature unless otherwise stated.

^b Reaction carried out in THF. ^c Reaction carried out at 0 °C. ^d Reaction carried out in acetone solvent. ^e Reaction carried out in dichloromethane solvent. ^f Starting ketal/acetal makes up mass balance. ^g GC yield.

subjected to the new conditions the parent ketone was also formed in outstanding yield. Finally, to complement the reactions in THF or CH_2Cl_2 and enhance the overall utility of this mild technique, undecanal was formed from the corresponding acetal in 90% yield after only 25 min.

These preliminary results in this area show that a mild, neutral and anhydrous technique using easily handled and accessible reagents has been developed for the removal of 1,3-dioxolane protection from ketones and aldehydes. The solvent dependent selectivity observed for aliphatic ketals over acetals and the general utility of this methodology will make this simple technique an attractive addition to the range of procedures already known for this general transformation.

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Footnotes

[†] The desired transformation, with no ketal deprotection, was subsequently achieved in 84% yield by careful addition of a single equivalent of CBr_4 to a CH_2Cl_2 solution of the aldehyde **1** and 4 equiv. of PPh_3 at 0 °C.⁷

[‡] Reverse addition of CBr_4 to a solution of the substrate and PPh_3 does not appear to adversely affect the deprotection reaction.

[§] All compounds exhibited satisfactory analytical and spectral data.

[¶] Even under forcing conditions (e.g. reflux) in THF the aliphatic acetals were not cleaved. It should be noted that under such conditions the novel substituted furan, tetrahydro-2-(4-bromobutanyloxy)furan, is formed as a reaction byproduct.

^{||} The protected undecanal was recovered in 87% yield. Only 4% of deprotected undecanal was obtained.

** Reaction work up was modified with petroleum ether being added prior to filtration.

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