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Simple and efficient MW-assisted cleavage of acetals and ketals in pure water

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Abstract—Simple and efficient MW-assisted cleavage of acetal and ketal is proposed in deionized water and in a very short time.

Acetals and ketals are frequently used to protect carbonyl function during complex synthetic pathways, and a wide variety of methods have been developed for their deprotection.[1] In the recent years, the use of mild Lewis acid catalysis has increased very quickly[2] and some triflate derivatives were proposed as reagents in the very mild deprotection procedures of acetals.[3]

As part of our efforts to develop new catalytic methods for valuable protection/deprotection steps of various functional groups,[4] we have already reported the use of Ce(III) and Er(III) trifluoromethane sulfonates as mild and efficient cleaving agents for acetals and ketals.

The principles of Green Chemistry have well emphasized the need to address increasing environmental concerns by adopting more sustainable strategies in fine synthetic processes such as reducing the employment of reagents to catalytic amounts and performing the reactions in neat or environmentally benign solvents (e.g., water, nonclassic solvents, etc.).[5] According to those principles, improvements to the literature methods typically involve time saving, higher yields, greater selectivity, the need for less catalyst,[6] or the employment of a more environmentally benign solvent or reaction medium[7].

Unfortunately, the water—the safest, cheapest, and most abundant solvent available—is only seldom employed to perform organic reactions since they often involve the usage of water sensitive reagents and the species produced can be too much or too little water soluble, so only very few reports are present in the literature regarding the catalyzed hydrolysis of acetals in water.[8]

In exploration of new 'green' applications, water at high temperature was found to be a useful synthetic medium.[9] It behaves as a *pseudo-organic solvent*,[6] its dielectric constant decreases substantially, the solvating power toward organic molecules becomes comparable with that of EtOH or Me_2CO at ambient temperature, and acid or base-catalyzed reactions typically required less catalyst and often proceeded rapidly.[6,7,10] On the contrary, many examples of microwave-assisted reactions in water are available. Here, we present a very simple and efficient MW-assisted cleavage of acetal and ketal in deionized water and in very short reaction times.

In the test experimental procedure, cyclohexanone diethyl ketal **1** was suspended in water (6.0 ml) in the Teflon reaction vessel of a Synthos 3000 microwave synthesizer and the Teflon tube stopped and stirred at 80 °C for 15 min under MW irradiation (1000 W). The evaporation of dichloromethane extracts of water solution furnished the sufficiently pure product.

For all compounds reported in Table 1, EI-MS spectra and full ^1H and ^{13}C NMR data were compared with

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Table 1. MW-assisted deprotection of acetals in pure H_2O

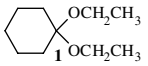
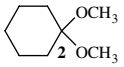
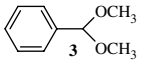
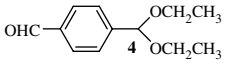
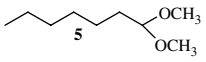
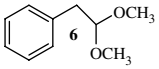
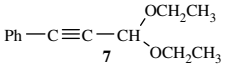
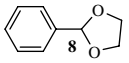
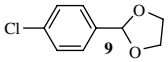
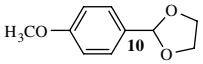
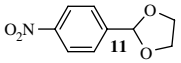
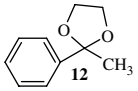
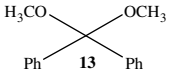
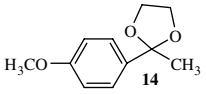
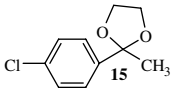
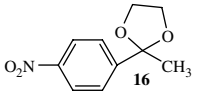
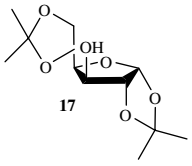
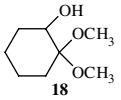
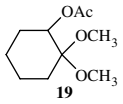
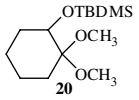
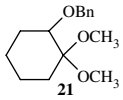
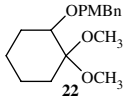
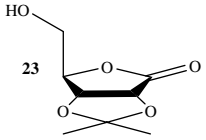
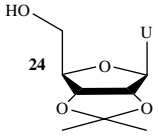
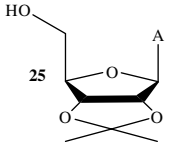
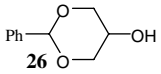
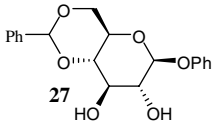
Entry	Substrate	T (°C)	Time (min)	Yield[a] (%)
1	 **1**	80	15	>99
2	 **2**	,,	,,	,,
3	 **3**	,,	,,	,,
4	 **4**	,,	,,	,,
5	 **5**	,,	,,	,,
6	 **6**	80 120	15 30	25 95
7	 **7**	80	15	>99
8	 **8**	100 80 120	300 15 30	Trace 84 >99
9	 **9**	,, 120 150	,, 30 30	25 50 87
10	 **10**	80	15	>99
11	 **11**	,, 120 150	,, 30 30	10 53 88
12	 **12**	80 120	15 30	84 >99
13	 **13**	,,	,,	,,
14	 **14**	120	30	,,
15	 **15**	,, 120 150	,, 30 30	5 30 75
16	 **16**	120 150	30 30	37 78
17	 **17**	120	30	>99[b,c]
18	 **18**	80	15	,,

Table 1 (*continued*)

Entry	Substrate	*T* (°C)	Time (min)	Yield[a] (%)
19		,,	,,	,,
20		,,	,,	,,
21		,,	,,	,,
22		,,	,,	,,
23		,,	,,	,,
24		100 120	300 30	— >99
25		,, 150	,, ,,	20 32
26		80 120	 ,,	89[d] >99[d]
27		80 120	,, ,,	48[c] >99[c]

[a] All products were purified by chromatographic column when necessary and identified by comparison of their spectral data with those of authentic compounds and the literature reported data only.
[b] The reaction was performed in refluxing water.
[c] D-Glucose was collected.
[d] The yield was determined by HPLC using the standard addition method.

those of pure samples or with spectra already reported in the literature. Based on the results reported in Table 1, we adopted a simple experimental procedure that involves stirring the solution of acetal or ketal substrates in deionized water in the Teflon reaction vessel of a Synthos 3000 microwave synthesizer, tapping Teflon tube and stirring at 80–150 °C for 15–30 min under MW irradiation (1000 W).

Dialkyl acetals and ketals derived from aromatic as well as aliphatic carbonyl compounds underwent smooth deprotection at room temperature without relevant differences (Table 1, entries 1–7 and 13). No substantial differences in reactivity between dimethyl and diethyl ketals were registered, and both cyclohexanone dimethyl and diethyl ketals were removed very quickly (Table 1, entries 1 and 2).

In the case of phenylacetaldehyde dimethyl acetal **6**, only 25% of deprotection was registered at 80 °C for 15′ and more drastic conditions were required to complete cleavage. Cyclic acetals and ketals required more prolonged reaction times to be quantitatively deprotected. So 2-phenyl-1,3-dioxolane **8** is deprotected in

30 min at 120 °C, meanwhile its parent derivative, benzaldehyde dimethylacetal, gave the corresponding aldehyde in only 15′ at 80 °C (Table 1, entries 3 and 8). Noteworthy, in our previous report about $Er(OTf)_3$-catalyzed method,[3b] 2-phenyl-1,3-dioxolane **8** required 12 h of reaction to almost quantitative cleavage, meanwhile, the same reaction, performed in traditional conditions, gave only undetectable quantity of deprotected product after 5 h (Table 1, entry 8). The cleavage of cyclic acetals and ketals of aromatic carbonyl compounds was shown to be strongly dependent on the presence of electron-withdrawing groups on the aromatic ring. In fact, quantitative hydrolysis of 2-(methoxyphenyl) 1,3-dioxolane **10** (Table 1, entry 10) was registered at 80 °C in 15′, but acceptable yield of 4-chlorobenzaldehyde from 2-(chlorophenyl) 1,3-dioxolane **9** (Table 1, entry 9) was obtained only by raising up to 150 °C the reaction temperature in 30′ and nearly the same result was observed for 2-(4-nitrophenyl)-1,3-dioxolane **11** (Table 1, entry 11). Remarkably, the latter substrate has previously shown to be extremely resistant to the action of lanthanoid triflates used as Lewis acid catalysts, and also after very prolonged reaction times (6–7 days, 30–50 mol % of catalyst), acetal **11** was collected completely unreacted.[3]

In contrary to the previously reported trend in which the aromatic cyclic ketals are more labile than the corresponding acetals,[3] the presence of electron-withdrawing groups on the aromatic ring of substrate is still much more limiting in the case of aromatic cyclic ketals. So, 2-methyl-2-phenyl-1,3-dioxolane **12** and its 4-methoxy analog **14** were easily completely deprotected in 30′ at 120 °C (Table 1, entries 12 and 14), but 2-(chlorophenyl)-2-methyl 1,3-dioxolane **15** and 2-methyl-2-(nitrophenyl) 1,3-dioxolane **16** showed to be still more resistant than their acetal analogs **9** and **10** (Table 1, entries 15 and 16).

The proposed MW-assisted protocol showed its extraordinary activity also in the case of diacetone D-glucose **17** that was converted exclusively to 1,2-isopropylidene-D-glucose in good yield after only 30′ at 120 °C (Table 1, entry 17), meanwhile, only a trace of D-glucose was obtained after prolonged reaction time using higher reaction temperatures. This protocol is compatible with the presence of other functional groups on the substrates such as carbonyl, triple bond, and hydroxyl groups (Table 1, entries 4, 7, 17, and 18); moreover, the method may be proposed to selectively deprotect acetals and ketals in the presence of some other protecting groups (Ac, TBDMS, Bn, and *p*-MBn,) such as is shown for differently protected 2,2-dimethoxycyclohexanols (Table 1, entries 19–22).

Finally, in order to extend the scope of this methodology for acetal and ketal cleavage, some other isopropylidene and benzylidene protected substrates, beside the diacetone D-glucose **17**, were exposed to the action of microwaves under the reported conditions. Thus, 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **23** was straightforwardly removed in only 15′ at 80 °C (Table 1, entry 23), meanwhile more drastic conditions were necessary for 2′,3′-*O*-isopropylideneuridine **24** and only partial cleavage was registered for 2′,3′-*O*-isopropylideneadenosine **25** when only 32% of adenosine was collected after prolonged reaction time at higher temperature (Table 1, entries 24 and 25). Noteworthy, again the attempt failed to perform the isopropylidene cleavage from uridine **24** in refluxing deionized water for prolonged reaction time (Table 1, entry 24). Surprisingly, also the benzylidene acetal, which very often required strong acidic media or demanding conditions to be removed, was easily cleaved by applying the present protocol. So, glycerol and phenyl-β-D-glucopyranoside were obtained in only 30′ at 120 °C (Table 1, entries 26 and 27). The remarkable results obtained in this no-catalyzed acetal cleavage pushed us to explore some aspects of the reaction mechanism performing the same experiments under no-solvent conditions. Noteworthy, two different pure acetals, benzaldehyde dimethyl acetal **3** and 2-phenyl-1,3-dioxolane **8**, resulted partially transparent to microwaves, and their temperature raised up to 70 °C also when the corresponding temperature for deionized water reached 150 °C. No reaction was detected for both acetals, and **3** and **8** were collected unaltered after prolonged reaction time, suggesting that probably the increasing of the ionic product of water under MW-action is the only promoter of the cleavage reaction.[10d]

In conclusion, this simple and efficient MW-assisted cleavage of acetal and ketal performed in pure water fulfills most of the 12 Principles of Green Chemistry and presents, compared with the existing procedures, a series of evident advantages. No catalyst is required and the reaction is carried out under neutral conditions, which are compatible with a wide range of sensitive substrates. Moreover, ample varieties of applicabilities were verified, the protocol being successfully applied to dialkyl such as cyclic acetals and ketals.

The reactions were performed in the modular Microwave synthesis platform Synthos 3000 by Anton Paar.

Deprotection runs were monitored by a GC–MS Hewlett_Packard workstation, formed by a GC-HP 6890 (30-m HPS capillary column, 1 mL/min He as carrier gas) and by an HP 5973 mass detector. ^1H and ^{13}C NMR spectra were recorded with a Brucker WM 300 instrument, at 300 MHz and 75 MHz, respectively. The samples were dissolved in $CDCl_3$. 'Chemical shifts' are given in parts per million (ppm) from tetramethylsilane as internal standard for ^1H NMR and for ^{13}C NMR the central line of $CDCl_3$ (77 ppm) has been used as reference. Coupling constants (*J*) are given in Hertz. All isolated compounds gave satisfactory microanalyses.

Typical procedure: Cyclohexanone diethyl ketal **1**: compound **1** (348.52 mg, 2.0 mmol) was suspended in deionized water (6.0 ml; pH 6.0–6.7) in the Teflon reaction vessel of the Synthos 3000 microwave synthesizer and the Teflon tube stopped and stirred at 80 °C for 15 min under MW irradiation (1000 W). Cyclohexanone (>99%) was determined by GC–MS using the standard addition method. The evaporation of dichloromethane extracts of water solution furnished the sufficiently pure

product. The structural identification of **1a** was confirmed by comparison of its EI-MS and 1H NMR spectral data with those of the literature reported data.

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