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Yanhong He^a, Martin Johansson^a & Olov Sterner^a ^a Department of Organic and Bioorganic Chemistry, Lund University, P.O. Box 124, Lund, 22100, Sweden

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Mild Microwave-Assisted Hydrolysis of Acetals Under Solvent-Free Conditions

Yanhong He, Martin Johansson, and Olov Sterner*

Department of Organic and Bioorganic Chemistry, Lund University, Lund, Sweden

ABSTRACT

Acetals are efficiently hydrolyzed with silica gel-supported pyridinium tosylate moistened with water in solvent-free conditions under microwave irradiation. The method is efficient and mild, with acid-sensitive 3-hydroxyacetals and 3-methoxyacetals being hydrolyzed in minutes in good yields.

Key Words: Acetal; Deprotection; Microwave; Solvent-free.

INTRODUCTION

Aldehydes, ketones, and diols (1,2- or 1,3-) are frequently protected as acetals in organic synthesis, and a number of methods for their hydrolysis

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^{*}Correspondence: Olov Sterner, Department of Organic and Bioorganic Chemistry, Lund University, P.O. Box 124, Lund 22100, Sweden; E-mail: olov.sterner@ bioorganic.lth.se.

are known.^[1] Most of these involve either treatment with aqueous acid,^[1,2] acid-catalyzed exchange with acetone,^[3] or nonaqueous media acidified with organic acids.^[4] However, these conditions are normally incompatible with the presence of other acid-sensitive functional groups. Hence, milder techniques that use less acidic conditions^[5] or even neutral conditions have been developed for the deprotection of acetals,^[6,7] and, in addition, a few examples of solvent-free cleavage of acetals have been reported.^[8] During an ongoing synthesis of some terpene analogues, we required a milder and more selective way to deprotect 3-hydroxyacetals to yield 3-hydroxycy-clohexanones (entry 1, Table 1). With conventional aqueous acid hydrolysis, such acetals only yield the corresponding α,β -unsaturated ketone. A procedure for the hydrolysis of acetals with silica gel supported pyridinium tosylate moistened with water in solvent-free conditions under microwave irradiation was, therefore, developed and described here.

RESULTS AND DISCUSSION

Pyridinium tosylate [pyridinium *p*-toluenesulfonate (PPTS)], an inexpensive and safe reagent, has been found to be an excellent catalyst for the cleavage of dioxolane-type of acetals by transacetalization with acetone.^[5] PPTS is a weaker acid (pH 3.0 in 1.0 M aqueous solution) than acetic acid (pH 2.4 in 1.0 M aqueous solution),^[9] suggesting that it should be useful as a catalyst in deprotection of acid-sensitive compounds, although the deprotection of acetals with PPTS in the absence of acetone and under solvent-free conditions has not been reported. In addition, organic reactions on solid support assisted by microwaves^[10,11] especially under solvent-free conditions,^[12] have recently attracted attention because of the enhanced selectivity obtained under the mild reaction conditions. Therefore, we report the deprotection of a number of cyclic and acyclic acetals, shown in Table 1, with silica gel supported PPTS moistened with water under microwave irradiation.

In general, the hydrolysis of the acetals was rapid, and the products were obtained in high yields; in several cases, the pure product was obtained after only aqueous workup. The 1,3-dioxolanes and dialkylacetals of cyclohexanone underwent smooth deprotection, and typically the hydrolysis was finished after a few minutes. Acetals of aromatic aldehydes (entries 8-10) required longer reaction times at lower microwave power to be completely hydrolyzed, but the free aldehydes were also obtained in excellent yields. The acid-labile 3-hydroxyketone (entry 1) was obtained in 90% yield after only 3 min without any trace of cyclohex-2-enone, whereas the acetal group of 1,1,3-trimethoxycyclohexan (entry 6) selectively was hydrolyzed 3-methoxycyclohexanone in 84% yield without elimination of methanol. The benzylidene acetal group (entry 11) was selectively cleaved without affecting the

Entry	Substrate	PPTS (mol%)	Microwave power	Time/ min	Product	Yield (%) ^a
1	С С он	10	50% of (1300w, 220v, 50 Hz)	3	С	90
2		10	50%	3	Å	81
3	Ś	10	50%	3	Å.	89
4		10	50%	1	Ļ	88
5	δ	10	50%	3	$\dot{\bigcirc}$	82
6		10	50%	1		84
7	Хорон	10	50%	3	но Нон	97
8		10	10%	20	Сно	88
9	(Jy)	10	30%	3	Сно	90
10	CCOH	10	10%	15	СССНО	90
11 ¹⁹	HXO HOLOSPh	20	50%	8	HOLOG SPh	91
12 ²⁰		100	50%	10	OH OBz HOLLOSPh OBz	73

Table 1. Microwave-assisted deprotection of acetals/ketals under solvent-free conditions.

^aRefers to yield of isolated product after chromatography (when required).

galactosidic linkage. The isopropylidene group attached to secondary hydroxyls of a sugar (entry 12) was more resistant to hydrolysis, requiring longer reaction times, but the diol was still obtained in acceptable yields.

In conclusion, the simple protocol for the deprotection of acetals presented here is both selective and efficient. The reaction is performed with an inexpensive and safe reagent under solvent-free conditions; the reaction is carried out in minutes and the product does often not even have to be purified by chromatography.

EXPERIMENTAL

The NMR spectra (in CDCl₃) were recorded with a Bruker DRX300 spectrometer at 300 MHz (¹H) and at 75 MHz (¹³C), a Bruker DRX400 spectrometer (at 400/100 MHz) and a Bruker DRX500 spectrometer (at 500/125 MHz). All flash chromatography was performed on 60 Å 35–70 μ m Matrex silica gel (Grace Amicon), and with mixtures between ethyl acetate and heptane as eluent. TLC analyses were made on Silica Gel 60 F₂₅₄ (Merck) plates and visualized with anisaldehyde/sulphuric acid and heating. The inorganic and organic reagents were all of commercial guaranteed grade and used without further purification. Acetals (entry 1–5, 7, 9–12) were prepared according to the literature procedures.^[13–20] 2-Furaldehyde diethyl acetal (entry 8, Table 1) was purchased from Janssen Chimica (Belgium). A typical procedure for the acetal hydrolysis performed in this investigation is given below. PPTS was prepared according to Ref.^[9]

Deprotection of acetals with silica gel supported PPTS moistened with water under microwave irradiation, exemplified with entry 5, Table 1.

A solution of PPTS (50 mg, 0.20 mmol) in H₂O (1 mL) was added to 8-methyl-1,4-dioxaspiro[4,5]decane (312 mg, 2.0 mmol) absorbed on silica gel 60 (1 g). The mixture was transferred into a sealed tube and exposed to microwave heating (placed in a household microwave oven operating at 50% of 1300 W) (650 W, 220 V, 50 Hz) for 3 min. After cooling to r.t., 5 mL of water was added, and the mixture was extracted with three times 10 mL diethyl ether. The combined organic phases were washed with brine and dried (MgSO₄). The solvents were removed, and the residue was purified by column chromatography (silica gel, hexane/EtOAc, 5:1) to yield 184 mg (82%) of 4-methylcyclohexanone.

1,1,3-trimethoxycyclohexane (entry 6) was prepared by refluxing a solution of 2-cyclohexen-1-one (1.50 g, 15.6 mmol) and TsOH \cdot H₂O (296 mg, 1.56 mmol) in CH₃OH (30 mL) for 4 hr. After cooling to r.t., NaHCO₃ (Sat. 8 mL) was added, and the mixture was extracted with three times 15 mL diethyl ether. The combined organic phases were washed with water and

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then brine and dried (MgSO₄). The solvents were removed, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 4:1) to yield 1.67 g (62%) of 1,1,3-trimethoxycyclohexane, identical to that previously reported.^[21]

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