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Cupric Sulfate Pentahydrate: A Mild and Efficient Catalyst for the Chemoselective Synthesis of 1,1-Diacetates from Aldehydes in a Solvent-Free System

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Summary. Cupric sulfate pentahydrate was found to be an efficient catalyst for the protection of aldehydes as 1,1-diacetates in high yields in a solvent-free system at room temperature. Ketones are not affected under these reaction conditions.

Keywords. 1,1-Diacetates; $CuSO_4 \cdot 5H_2O$; Protection; Acylals; Aldehydes.

Introduction

The protection-deprotection reaction sequence constitutes an integral part of organic synthesis such as the preparation of monomers, fine chemicals, and reaction intermediates or precursors for pharmaceuticals. These reactions often involve the use of acidic, basic, or hazardous reagents and toxic metal salts [1].

Acylals or 1,1-diacetates are synthetically useful as aldehyde protecting groups [2]. They are an alternative to acetals due to their stability in mildly acidic and basic media and ease of chemoselective preparation in the presence of ketones [3]. In recent years, a number of different methods have been reported for the synthesis of 1,1-diacetates and the regeneration of their parent aldehydes [4]. However, many of these methods suffer from one or more drawbacks, such as long reaction times, high catalyst to substrate ratio, use of volatile organic solvents, or large amounts of solid supports, which eventually result in the generation of a large amount of toxic waste, expensive reagents, unsatisfactory yields, and tedious work-up procedures. Nevertheless, it is still desirable to develop alternative and milder conditions for the preparation of acylals and to remove this protecting group.

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In recent years the use of inorganic reagents under solvent-free conditions has rapidly increased, as these reactions often involve milder conditions, easier work-up, and higher selectivity than similar reactions using organic reagents in solution [5, 6].

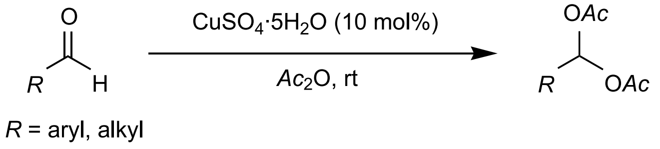
In continuation of our program to develop reactions in solvent-free systems [7–12], herein we report a simple and highly efficient process for the synthesis of 1,1-diacetates.

Results and Discussion

Treatment of an aldehyde with acetic anhydride in the present of 10 mol% of $CuSO_4·5H_2O$ in the absence of solvent at room temperature afforded the corresponding geminal diacetate derivative in very high yields (Scheme 1).

The presence of electron donating and electron withdrawing groups on the aromatic ring makes a difference to the reaction rates for the synthesis of 1,1-diacetates. Substrates having electron-donating groups in the *para* position of the aromatic ring underwent the reactions in a short period of time (Table 1, entries 4 and 5), whereas electron-withdrawing groups lead to higher reaction times (Table 1, entries 7–9).

It is noteworthy to mention that ketones such as acetophenone or benzophenenone did not react under the same conditions (Table 1, entries 12 and 13). This

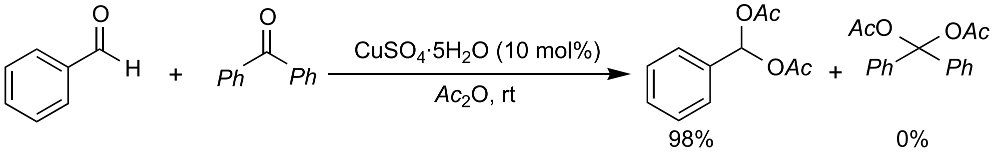


Scheme 1

Table 1. Synthesis of 1,1-diacetates using $CuSO_4 \cdot 5H_2O$

Entry	Substrate	Time / min	Yield[a] / %	mp / °C found	mp / °C reported
1	Isobutyraldehyde	10	85	–[b]	–
2	Butyraldehyde	15	87	–[b]	–
3	Benzaldehyde	15	99	43	44–45 [13]
4	4-Methylbenzaldehyde	20	99	80	81–82 [14]
5	4-Methoxybenzaldehyde	20	99	63	64–65 [15]
6	4-Chlorobenzaldehyde	30	99	81	81–82 [16]
7	2-Nitrobenzaldehye	120	99	89	90 [17]
8	3-Nitrobenzaldehye	90	98	65	64–66 [15]
9	4-Nitrobenzaldehye	150	98	125	125–126 [15]
10	Cinnamaldehyde	15	96	86	84–86 [13]
11	Furfuraldehyde	5	98	53	52–54 [18]
12	Acetophenone	No reaction	–	–	–
13	Benzophenone	No reaction	–	–	–

[a] Yields refer to isolated pure products; [b] oily products were obtained



Scheme 2

proved that a chemoselective protection of aldehydes in the presence of ketones could be achieved with this procedure (Scheme 2).

In conclusion, we developed a convenient and efficient procedure for the synthesis of acylals using catalytic amounts of $CuSO_4 \cdot 5H_2O$ under mild reaction conditions at room temperature. Some of the major advantages of this procedure are very good yields, use of an inexpensive, nontoxic, readily available, and mild *Lewis* acid catalyst, absence of volatile and hazardous solvents, and high chemoselectivity.

Experimental

Melting points were measured by using the capillary tube method with an electrothermal 9100 apparatus. ^1H NMR spectra were recorded on a Bruker DRX-90 AVANCE spectrometer using *TMS* as internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disks on the FT-IR Bruker Tensor 27. All products are known compounds and were identified by comparison of their spectra and physical data with those of Refs. [13–18].

Preparation of Acylals, General Procedure

Cupric sulfate pentahydrate (10 mol%) was treated with 1 mmol aldehyde and 3 mmol acetic anhydride. The slurry mixture was stirred for the indicated time (Table 1) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered off and washed with 5 cm^3 Et_2O. Then the filtrate was washed with 5 cm^3 5% $NaHCO_3$ solution and $2 \times 5\,cm^3$ brine successively, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The crude product was purified over silica gel by column chromatography to provide the pure product.

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