Journal of Sciences, Islamic Republic of Iran 15(4): 333-337 (2004)
University of Tehran, ISSN 1016-1104

Microwave-Assisted Efficient and Chemoselective Acetalization of Aldehydes with Trimethyl Orthoformate

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Abstract

Efficient and chemoselective protection of aldehydes to the corresponding dimethyl acetals have been carried out by mixture of trimethyl orthoformate and methanol in the presence of a catalytic amount of TMSCl or $AlCl_3$ under microwave irradiation. Under these conditions, acetalization of ketones does not take place and they remain intact under reaction conditions. The results are compared with the reaction of an aldehyde with trimethyl orthoformate in the presence of a mild Lewis acid.

Keywords: Acetalization; Trimethyl orthoformate; Aldehyde; Microwave irradiation

Introduction

The protection of aldehydes to the corresponding acetals is one of the most widely protecting methods in synthetic organic chemistry [1-4]. Acetals can be prepared conveniently by numerous methods [5,15]. All of these methods have merits but there are some limitations that lead to lower yields in some cases.

Although, many conventional catalysts including protic acid and Lewis acid have been reported for the acetalization of aldehydes [16,17], however, many of these methods have problems such as difficulty in handling the reagents and poor chemoselectivity [18,19].

Application of microwave irradiation for rapid organic synthesis coupled with first solvent-free reactions have found widespread use due to the reduction in reaction time and the increased selectivity that can be attained [20-28]. In continuation to our current work on microwave-assisted organic reactions [29-32], herein, we describe a very simple, fast and general protocol for the protection of aldehydes with trimethyl orthoformate and methanol under microwave irradiation. Under these conditions, various aliphatic and aromatic aldehydes are converted to their corresponding acetals in the presence of trimethylsilyl chloride, TMSCl, or anhydrous $AlCl_3$. Upon treatment of an aldehyde (1.0 equiv) with trimethyl orthoformate (1.0 equiv) and methanol (2 mL) in the presence of TMSCl or $AlCl_3$ (0.2-0.4 equiv), the corresponding acetal was produced in excellent yield and very short reaction time (less than 2 min) under microwave irradiation (Scheme 1). The results are shown in Table 1.

In order to show the chemoselectivity of this method, we studied a competitive reaction for the acetalization of aldehydes, in the presence of ketone. Thus, a mixture of an aldehyde and a ketone (1:1 ratio) was allowed to react with trimethyl orthoformate and methanol, in the presence of a catalytic amount of TMSCl or $AlCl_3$ under this method. After 2 min of microwave irradiation, the aldehyde was converted to its corresponding acetal, while the ketone remained unchanged (Scheme 2). The same result was obtained for α,β-unsaturated aldehyde.

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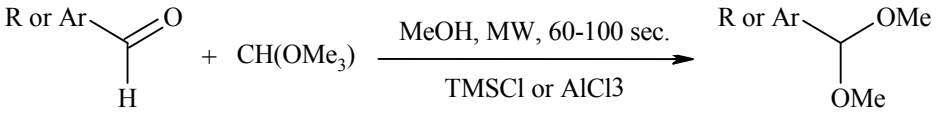
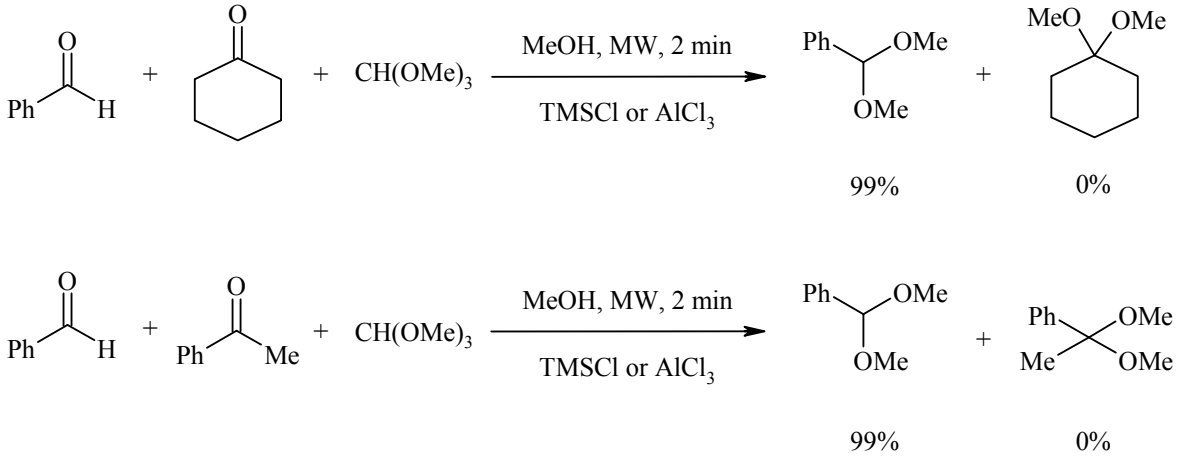


Scheme 1



Scheme 2

Therefore, under the above conditions, very low yield of acetal was obtained from cinnamaldehyde. In general, the yields are higher when TMSCl is used as catalyst in compare with $AlCl_3$. Without using a catalyst, the yields of the reactions will be low. Under these reaction conditions, the yield of the reaction does not change significantly with aromatic aldehydes bearing electron-withdrawing substituents, such as nitro- and chloro-groups, on the aromatic ring or with aliphatic aldehydes.

We also compared our results for the reaction of an aldehyde with trimethyl orthoformate in the presence of a mild Lewis acid. Although the reported yields are about the same, but the reaction times are shorter under microwave irradiation [6].

The reactions were repeated several times in a conventional microwave oven and the same results were obtained.

In conclusion, the results obtained in this study reveal a clean, fast, simple, efficient, and chemo-selective acetalization of aldehydes, in the presence of a catalytic amount of TMSCl or $AlCl_3$, under microwave irradiation with good to excellent yields.

Exprimental

NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured with Perkin Elmer 1600 FTIR spectrometer. Mass spectra were obtained on Fisson 800 Trio, and GC-Mass HP 5973 MSD.

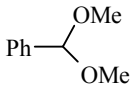
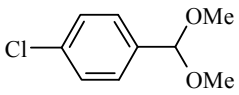
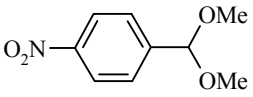
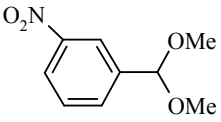
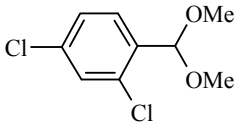
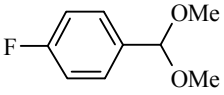
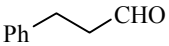
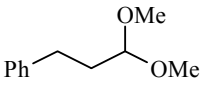
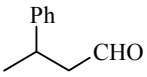
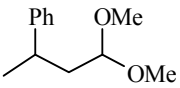
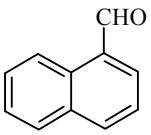
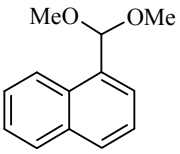
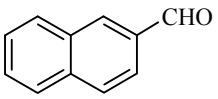
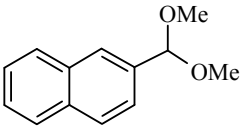
The General Procedure for Acetalization of Aldehydes Mediated by Microwave Irradiation

A mixture of an aldehyde (2 mmol), trimethyl orthoformate (2 mmol), MeOH (3.5 mL) and $AlCl_3$ (0.2 mmol) or TMSCl (0.2 mmol) were placed in a sealed teflon container (screw cap type, 50 cm^3) and subjected to microwave irradiation in a conventional microwave oven with 30% of power for 60 to 100 sec (Table 1) with 1 min interval between each 20 sec. After cooling, the product was diluted with CH_2Cl_2 (20 mL) and washed with water. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to give the pure products. Further purification was carried out by column chromatography on basic alumina eluting with ethyl acetate/hexane, if needed. All compounds were known and characterized on the basis of spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature [3-5].

Selected Spectroscopic Data

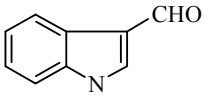
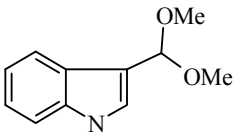
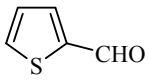
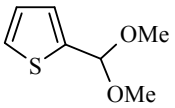
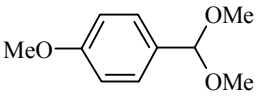
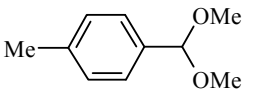
1,1-Dimethyl benzaldehyde, **1**, ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.31 (s, 6H), 5.44 (s, 1H), 7.30-7.38 (m, 3H),

Table 1. Acetalization of aldehyde with trimethyl orthoester under microwave irradiation

Entry	Aldehyde	Product	Time (sec)[a]	Yield (%)[b]
1	PhCHO		3×20	99 (98)
2	4-ClC_6H_4CHO		3×20	92 (88)
3	4-$O_2NC_6H_4CHO$		3×20	98 (91)
4	3-$O_2NC_6H_4CHO$		4×20	99 (95)
5	2,4-$Cl_2C_6H_3CHO$		3×20	98 (91)
6	4-FC_6H_4CHO		4×20	88 (71)
7			5×20	98 (78)
8			5×20	86 (62)
9			5×20	88 (65)
10			3×20	90 (76)

[a] The irradiation time with one min interval between each 20 sec.
[b] The numbers in parenthesis show the yields for acetalization using $AlCl_3$ as catalyst.

Table 1. Continued

Entry	Aldehyde	Product	Time (sec)[a]	Yield (%)[b]
11			3×20	94 (82)
12			3×20	93 (80)
13	4-$MeOC_6H_4CH$		4×20	95 (86)
14	4-MeC_6H_4CH		4×20	92 (78)

7.47-7.48 (m, 2H), IR (KBr): υ, 3021, 2830, 1604, 1516, 1341, 1197 cm^{-1}.

1,1-Dimethyl 4-nitro benzaldehyde, **3**, ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.22 (s, 6H), 5.37 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 8.27 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 5.0 Hz, 1H) IR (KBr): υ, 3057, 2830, 1604, 1516, 1341, 1268, 1197 cm^{-1}.

1,1-Dimethy 3-phenyl propionaldehyde, **7**, ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.87-1.91 (m, 2H), 2.06-2.07 (t, J = 2.1 Hz, 2H), 3.35 (s, 3H), 4.37-4.39 (t, J = 5.7 Hz, 1H), 7.14-7.31 (m, 5H). IR (KBr), υ, 3016, 2951, 1624, 1412, 1318, 1265, 1118, 753 cm^{-1}.

1,1-Dimethy 2-phenyl propionaldehyde, **8**, ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.39 (d, J = 7.1 Hz, 3H), 3.11-3.16 (m, 1H), 3.32 (s, 3H), 3.50 (s, 3H), 4.47 (d, J = 6.8 Hz, 1H), 7.28-7.45 (m, 5H). IR (KBr): υ, 3092, 2973, 2863, 1606, 1412, 1368, 1236, 1134, 675 cm^{-1}.

1,1-Dimethyl thiophenaldehyde, **12**, ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.32 (s, 6H), 5.62 (s, 1H), 6.96-6.98 (m, 1H), 7.03-7.04 (m, 1H), 7.25 (d, J = 5.0 Hz, 1H). IR (KBr): υ, 3057, 2969, 1617, 1537, 1274 cm^{-1}.

Acknowledgments

We are grateful to the Sharif University of Technology Research Council for financial support of this research.

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