

Microwave-assisted Rapid Ketalization/ Acetalization of Aromatic Aldehydes and Ketones in Aqueous Media†

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Aromatic aldehydes and ketones are readily acetalized or ketalized under microwave irradiation in the presence of water as a solvent.

Acetal formation is the most widely used protecting method for carbonyl compounds.¹ This reaction is usually catalyzed by protic acids,² Lewis acids,³ pyridinium salts⁴ as well as heterogeneous catalysts such as molecular sieves,⁵ montmorillonite K-10,⁶ sulfated zirconia,⁷ Envirocat EPZG,⁸ alumina/KSF,⁹ natural kaolinitic clay,¹⁰ zeolite Y,¹¹ zeolite HSZ-360¹² and resin supported FeCl₃.¹³

Acetalization proceeds with azeotropic removal of water using a Dean–Stark apparatus and toxic solvents such as benzene and toluene.

Several publications have described the use of commercially available microwave ovens for acetal formation by inorganic catalysts (FeCl₃, TiCl₄, ZnCl₂),^{14,15} KSF clay,^{16,17} Envirocat EPZG, EPZ10 and EPIC.¹⁸

From perspectives including considerations for the environment, safety and economics, efforts are being directed toward decreasing the use of organic solvents in chemical laboratories and industrial processes.^{19,20}

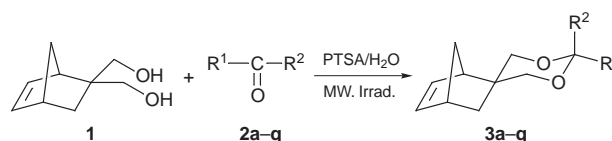
On the other hand, few solvents are suitable for organic reactions above 200 °C.

Water as a nontoxic, inexpensive and readily available solvent could be an effective medium for organic reactions at high temperature, due to the decrease of its dielectric constant and polarity which leads to increased water solubility of organic compounds.²¹ Recently, Siskin *et al.* reported several classical organic reactions in superheated water²¹

while An *et al.* have applied high temperature aqueous media for condensation, isomerization, decarboxylation, hydrolysis, Claisen rearrangement, addition of water to alkenes, alkynes, dehydration of alcohols, multiproduct reactions, Rupe and Meyer–Schuster rearrangements.²²

Although an aqueous environment may not seem convenient for elimination of water from organic substrates, such a transformation proceeded well at high temperatures for the formation of cyclohexene from cyclohexanol.²¹

This paper describes the synthesis of a series of new acetals and ketals based on spiro-1,3-dioxane-5-norbornene by (i) a classical method using PTSA catalyst and (ii) a microwave assisted reaction in aqueous media. The importance of second method is that acetalization unexpectedly occurs in aqueous media. New acetals **3a–q** are prepared from 2,2'-bis(hydroxymethyl)norborn-5-ene **1**²³ and a variety of carbonylated compounds **2** (Scheme 1).



Scheme 1

Table 1 Formation of acetals **3** from **1** and carbonyl compounds **2**

Product	R ¹	R ²	mp/°C	M.W. irradiation						
				Classical conditions			In water		Without water	
				t/min	Yield ^a (%)	t/s	Water (mL)	Yield ^a (%)	t/s	Yield ^a (%)
3a	4-nitrophenyl	H	124	75	90	60	1	90	300	65
3b	3-nitrophenyl	H	60	60	80	60	0.5	80	300	50
3c	2-nitrophenyl	H	63	150	85	80	0.5	90	300	55
3d	4-nitrophenyl	Me	140	240	70	120	0.5	75	300	45
3e	2-hydroxyphenyl	H	110	150	85	150	0.5	85	300	40
3f	4-hydroxyphenyl	H	150	90	80	75	0.5	75	300	30
3g	2-hydroxyphenyl	Me	103	300	50	—	—	—	—	—
3h	4-hydroxyphenyl	Me	140	150	65	—	—	—	—	—
3i	4-cyanophenyl	H	87	105	90	130	2	90	300	50
3j	2-cyanophenyl	H	−8	60	90	130	1	80	300	45
3k	4-chlorophenyl	H	105	75	85	30 ^b	0.5	80	300	55
3l	4-bromophenyl	H	87	60	85	30 ^b	0.5	85	300	55
3m	4-hydroxy-3-methoxyphenyl	H	102	90	80	60	0.5	70	300	40
3n	2-pyrrolyl	H	98	240	20	30	0.5	20	30	^c
3o	2-furyl	H	58	80	25	25	0.5	50	30	10
3p	2-hydroxy-1-naphthyl	H	144	60	80	60	0.5	75	300	40
3q	phenyl ^d	H	39	120	60	90	0.5	75	300	45

^aIsolated yield based on the starting carbonyl compounds. ^b12% w/w catalyst applied. ^cPolymerization occurred. ^dThis product had already been synthesized by a classical method.²³

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As shown in Table 1 acetals have been prepared by both classical and microwave-assisted methods. The latter method was conducted either in the presence or absence of water. The resulting acetals are obtained in excellent

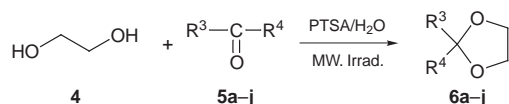
Table 2 Formation of acetals **6** from diol **4** and carbonyl compounds **2**

	Product		M.W. Irradiation in water	
	R ³	R ⁴	t/s	Yield(%)
6a	phenyl	H	120	82
6b	4-nitrophenyl	H	120	98
6c	4-chlorophenyl	H	120	96
6d	4-hydroxyphenyl	H	120	30
6e	4-methylphenyl	H	120	80
6f	phenyl	Me	240	80
6g	4-nitrophenyl	Me	180	85
6h	4-methoxyphenyl	Me	180	30
6i	4-chlorophenyl	Me	180	75
6j	2-furyl	H	—	— ^a

^aPolymerization occurred.

yields except for **3n** (R¹ = 2-pyrrolyl) due to polymerization. For **3o** (R¹ = 2-furyl) some polymer was formed under classical conditions, but in high temperature aqueous media, polymerization occurs to a lesser extent. For **3g,h** (R¹ = 2- or 4-hydroxyphenyl) no reaction occurred under microwave irradiation. For **3k,l** (R¹ = 4-chloro- or 4-bromo-phenyl) PTSA catalyst was 1% and 12% w/w in the classical and microwave-assisted reactions, respectively.

Some complementary studies were also performed using ethylene glycol **4**, under the same microwave conditions in aqueous media (Scheme 2) and results are summarized in Table 2.

**Scheme 2**

As is evident from Table 1, the absence of water led to a considerable decrease of yield, requirement for increased reaction time, and partial thermal decomposition of the materials. This deficiency is obviously attributed to the absence of water, which can act as a heat transfer agent as well as a low polarity solvent at high temperature. As expected, Tables 1 and 2 indicate that electron-withdrawing groups in most of the carbonyl compounds, favour acetal/ketal formation.

In conclusion, the microwave irradiated method has been found to be useful for ketal/acetal formation in aqueous media. In addition to classical method, this is an excellent alternative method because of ease of work-up, high yields, short reaction times and use of non-toxic inexpensive solvent.

Experimental

Experiments under microwave irradiation were carried out in a non-modified domestic microwave oven (White-Westinghouse, 1400WAT). The structures of all compounds were determined by FTIR spectroscopy (FTIR spectrometer, MATTSON 1000), ¹HNMR and ¹³CNMR DEPT spectra (FTNMR Bruker, AC 80). 2,2-bis(hydroxymethyl)norborn-5-ene was synthesized and the other reagents were purchased from Merck, Fluka and purified by crystallization or distillation before use.

General Procedure for Ketalization/acetalization under Classical Conditions.—**1** (5.2 mmol) carbonyl compound **2** (5 mmol), 1% w/w PTSA and sodium dried toluene (50 ml) in a 100 ml flask were refluxed using a Dean-Stark apparatus. After completion of reaction, the solvent was evaporated and the product **3** recrystallized from ethanol-water.

General Procedure for Ketalization/acetalization under Microwave Irradiation.—A mixture of carbonyl compound **2** (2.5 mmol), **1** (2.6 mmol), 1% w/w PTSA and water (0.5–2 mL) was placed in a

25 mL screw-capped Teflon cylinder and irradiated at high (100%) power for a few minutes. The mixture was cooled to ambient temperature and recrystallized as above.

The same procedure was applied for the synthesis of **6a–j**, but with an excess of ethylene glycol (20 mmol).

Selected Spectroscopic Data.—**3a**: white crystals, IR (KBr), ν/cm^{-1} : 1530, 1347, 1000–1200 (C–O–C), 852 (C–N), 830 (=CH). $\delta_{\text{H}}(\text{CDCl}_3)$ 7.6–8.2 (m, 4H), 6.2 (br, s, 2H), 5.5 (s, 1H), 3.6–3.8 (m, 4H), 3.2 (br, s, 1H), 2.8 (br, s, 1H), 1.5 (br, s, 2H), 1.4 (dd, $J = 12$, 3.6 Hz, 1H), 0.6 (br, d, $J = 12$ Hz, 1H). $\delta_{\text{C}}(\text{CDCl}_3)$ 32(t), 40(d), 42(s), 45(d), 47(t), 75(t), 100(d), 122(d), 127(d), 135(d), 137(d), 139(s), 145(s).

3h: white solid, IR(KBr), ν/cm^{-1} : 3438 (O–H), 1046–1238 (C–O–C), 1515, 1605 (C=C), 838, 715 (=CH). $\delta_{\text{H}}(\text{CDCl}_3)$ 6.7–7.2 (m, 4H), 5.8–6.2 (m, 2H), 6.0 (s, OH), 3.3–3.7 (m, 4H), 2.7 (br, s, 1H), 2.0 (s, 1H), 1.3 (br, s, 2H), 1.4 (s, 3H), 0.9 (dd, $J = 12$, 3.6 Hz, 1H), 0.4 (br, d, $J = 12$, 1H). $\delta_{\text{C}}(\text{CDCl}_3)$ 30(q), 32(t), 40(d), 42(s), 45(d), 47(t), 68(t), 70(t), 100(s), 115(d), 128(d), 133(s), 135(d), 138(d), 158(s).

3i: white solid, IR(KBr), ν/cm^{-1} : 2230 (C≡N), 1030–1215 (C–O–C), 830(=CH). $\delta_{\text{H}}(\text{CDCl}_3)$ 7.5 (m, 4H), 6.1 (m, 2H), 5.4 (s, 1H), 3.6–4.0 (m, 4H), 3.2 (br, s, 1H), 2.7 (br, s, 1H), 1.5 (br, s, 2H), 1.2 (dd, $J = 12$, 3.6 Hz, 1H), 0.5 (br, d, $J = 12$ Hz, 1H). $\delta_{\text{C}}(\text{CDCl}_3)$ 30(t), 40(d), 41(s), 45(d), 48(t), 75(t), 77(t), 100(d), 112(s), 118(s), 127(d), 132(d), 135(d), 138(d), 145(s).

3o: white solid, IR(KBr), ν/cm^{-1} : 3100 (=CH), 1023–1161 (C–O–C), 740–950 (C–H). $\delta_{\text{H}}(\text{CDCl}_3)$ 7.2 (br, s, 1H), 5.8–6.2 (m, 4H), 5.3 (s, 1H), 3.3–3.7 (m, 4H), 3.1 (br, s, 1H), 2.5 (br, s, 1H), 1.4 (br, s, 2H), 1.0 (dd, $J = 12$, 3.6 Hz, 1H), 0.4 (br, d, $J = 12$ Hz, 1H). $\delta_{\text{C}}(\text{CDCl}_3)$ 32(t), 40(d), 41(s), 45(d), 47(t), 74(t), 76(t), 98(d), 108(d), 110(d), 135(d), 137(d), 142(d), 150(s).

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