

AN EFFICIENT SYNTHESIS OF 1,3-DIOXANE-4,6-DIONES CATALYZED BY BORIC ACID

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Abstract

Several kinds of 1,3-dioxane-4,6-diones have been synthesized from malonic acid and ketones using boric acid as catalyst, acetic anhydride as condensing reagent at room temperature. The present method does not involve any hazardous organic solvents, it gives some notable advantages such as mild reaction conditions, short reaction time, less catalyst dosage and high yields. Further study showed that H_3BO_3 was reused for four times without any noticeable decrease in the catalytic activity.

Keywords

1,3-dioxane-4,6-dione, boric acid, malonic acid, ketones.

Introduction

1,3-dioxane-4,6-diones and their derivatives have been the common intermediate products in organic synthesis and extremely promising synthones, which have been used to obtain a great variety of heterocyclic compounds, including biologically active substancesⁱ. In particular, 2,2-dimethyl-1,3-dioxane-4,6-dione is an important reagent for synthesizing lipid-lowering drugs "Lipitor"ⁱⁱⁱ. Therefore, the preparation of 1,3-dioxane-4,6-diones is of much current importance.

More recently, lots of methods for the synthesis of 1,3-dioxane-4,6-diones have been reported in the literature. Generally, they are synthesized by reaction of malonic acid and ketones in the presence of strong proton acids such as concentrated sulphuric acidⁱⁱⁱ, phosphoric acid or p-TsOH^{iv} and Lewis acids, such as $La(OTf)_3$ ^v. However, many of these methodologies have not been entirely satisfactory, owing to such drawbacks as low yields, long reaction time, more catalyst dosage, environmentally unfavorable solvents, emerging the problems of corrosivity, tedious work-up and effluent pollution. Thus, a mild, efficient, and environmentally friendly method using economical catalyst is desirable.

In recent years, boric acid (H_3BO_3) has gained special attention as catalyst in organic synthesis because of excellent solubility in water, effective activity, mild conditions and many times reusable. Recently, boric acids as catalyst has been greatly applied in various organic transformations such as esterification of hydroxycarboxylic acids^{vi}, aza Michael^{vii}, thia Michael^{viii} addition, bromination^{ix}, chemoselective oxidation^x, preparation of homoallylic acetates^{xi} and Biginelli reaction^{xii}. We now report here a simple, efficient and practical method for the preparation of 1,3-dioxane-4,6-diones using boric acid as catalyst (Scheme 1),.

Scheme 1

Experimental

Material and Apparatus

Malonate, acetone, cyclopentanone, cyclohexanone, acetophenone, acetic anhydride, methyl ethyl ketone and dichloromethane were all of reagent grade and without further purification. The melting points of the various compounds were measured by XT-4 digital micro melting point instrument. IR spectra were taken on a Nicolet-360 FT-IR spectrometer by incorporating samples in KBr disks. ¹H NMR spectra were recorded with a Bruker AVance400 MHz spectrometer with CDCl_3 as the solvent and TMS as the internal standard.

General procedure for synthesis of 1,3-dioxane-4,6-diones catalyzed by H_3BO_3

Malonate 1 (0.05 mol, 5.2 g), acetic anhydride 0.06 mol, boric acid 0.3 mol%, ketones 2 (0.05 mol) were taken in a round bottom flask, then the mixture was stirred at room temperature. After the completion of the reaction (TLC), the mixture was diluted with 30 mL dichloromethane. Then filtered, filter cake as boric acid was directly used for the next reaction. The filtrate was distilled with 50 mL water. The organic layer was washed with water (20 mL \times 2). The organic layer was dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure to give pure (3a-3e) in excellent yields.

Selected spectral data of products

2,2-dimethyl-1,3-dioxane-4,6-dione 3a: IR (KBr, cm^{-1}) 2951, 2850, 2911, 2813, 1793, 1751, 1450, 1387, 1245, 1206, 1075, 975; ¹H NMR (CDCl_3), δ ppm: 1.78 (s, 6H, 2 CH_3), 3.64 (s, 2H, CH_2).

2-methyl-2-ethyl-1,3-dioxane-4,6-dione**3b**: IR(KBr, cm⁻¹)2965, 2923, 2862, 2845., 1791, 1753, 1465, 1456, 1385, 1286, 1243, 1203, 1087, 1042, 976; ¹H NMR(CDCl₃),

δppm: 1.08(t, 3H, CH₃), 1.76(s, 3H, CH₃), 2.01(q, 2H, CH₂), 3.65(s, 2H, CH₂).

2-methyl-phenyl-1,3-dioxane-4,6-dione**3c**: IR(KBr, cm⁻¹)3040, 2974, 2910, 2871, 2836, 1785, 1751, 1608, 1502, 1453, 1296, 1190, 1093, 1046, 985, 749, 648. ¹H NMR(CDCl₃),

δppm: 1.97(s, 3H, CH₃), 3.01(d, 1H, CH), 3.44(d, 1H, CH), 7.41-7.53(m, 5H, Ph).

2,2-butylidene-1,3-dioxane-4,6-dione**3d**: IR(KBr, cm⁻¹)2964, 2921, 2866, 1790, 1751, 1468, 1455, 1371, 1299, 1241, 1149, 1136, 1087, 1037, 973; ¹H NMR(CDCl₃),

δppm: 1.49-1.54(m, 2H, CH₂), 1.71-1.77(m, 4H, 2CH₂), 1.98(t, 4H, 2CH₂), 3.64(s, 2H, CH₂).

2,2-pentamethylene-1,3-dioxane-4,6-dione**3e**: IR(KBr, cm⁻¹)2974, 2912, 2879, 1789, 1753, 1453, 1299, 1195, 1164, 1128, 1097, 1044, 984; ¹H NMR(CDCl₃),

δppm: 1.75-1.79(m, 4H, 2CH₂), 2.16(t, 4H, 2CH₂), 3.99(s, 2H, CH₂).

Results and discussion

Initially, we tried to investigate different ketones (0.05 mol) reacted with malonate (0.05 mol) in the presence of the catalytic amount (0.3 mol%) of boric acid at room temperature. They (**3a-3e**) were obtained in excellent yields (**Table 1**). Next, to optimize the reaction condition, the reaction of acetone (**2a**) and malonate was selected as model to investigate the effects of the catalyst at different amount of catalyst on the yield. The best result was obtained by carrying out the reaction with 1:1 mol ratios of acetone:malonate and 0.3 mol% of boric acid at room temperature and under this condition **3a** was obtained in 81% yield after 30 min (**Table 2, entry 3**). Under the above condition, the reaction could not be occurred in the absence of boric acid, which indicated that boric acid plays a crucial role in the process of the reaction (**Table 2, entry 1**). When the 0.1 mol% amount of boric acid was used, the yield of **3a** reached up to 64% at room temperature. Increasing the amount of boric acid from 0.1 to 0.3 mol%, the reaction yields ranged between 64% and 81%, respectively. Therefore, 0.3 mol% of boric acid was enough much to push the reaction forward to complete.

Table 1 Condensation reaction of molanic acid and ketones catalyzed by H₃BO₃^a

Entry	Keton ^e	Product ^b	Time(min.)	Yield(%) ^c	m.p.(°C)	m.p. (lit.)°C
1		3a	30	81	92-94	91-92[9]
2		3b	120	43	—	—

3	3c	180	32	102-104	103-105[9]
4	3d	30	76	95-97	95-97[11]
5	3e	30	74	73-75	73-75[11]

^a Reaction conditions: ketones(0.05 mol),malonate(0.05 mol) ,boric acid(0.3 mol%) ,30°C.

^b All compounds were characterized by spectroscopic technique(IR and ¹H NMR).

^c Isolated yield based upon starting malonic acid.

Table 2 Influence of the amount of catalysts on reaction of acetone (2a) and malonate

Entry	Dosage of catalyst (mol %)	Time (min.)	Yield (%) ^a
2,2-dimethyl-1,3-dioxane-4,6-dione (3a)			
1	none	120	trace
2	0.1	60	64
3	0.3	30	81
4	0.5	30	80
5	1.0	30	76

Reaction conditions: acetone (0.05 mol),malonate(0.05 mol), boric acid as the catalyst,30°C.

^a Isolated yield based upon starting malonic acid.

To further evaluate the overall utility of the current methodology, we compared our results with those of the other methods reported for the synthesis of 2,2-dimethyl-1,3-dioxane-4,6-dione. This comparison is shown in **Table 3**. It is clear from the data that our method reduces reaction time, catalyst dosage and provides higher yields of the product.

Table3 Comparison of the efficiencies of the different catalysts for the synthesis of 3a

Entry	Catalyst	Catalyst dosage(mol %)	Time (min)	Yield (%) ^a	Reference
2,2-dimethyl-1,3-dioxane-4,6-dione (3a)					
1	H ₂ SO ₄	5.5	180	71	[9]
2	P-TsOH	1.7	180	75	[10]
3	La(OTf) ₃	0.3	30	77.5	[11]
4	S ₂ O ₈ ²⁻ /ZrO ₂ -Si O ₂	1.7	180	31	[10]
5	H ₃ BO ₃	0.3	30	81	this work

Reaction conditions: acetone (0.05 mol),malonate(0.05 mol), 30°C.

^a Isolated yield based upon starting malonic acid.

In the interests of green chemistry and developing an environmentally benign process, the reusability of the catalyst was explored using the model reaction system under the optimized conditions. The catalyst itself could be readily recovered from the reaction mixture according to the procedure outlined in the experimental section. The separated catalyst was washed with cold dichlorine methane and subsequently dried at 30 °C under vacuum for 1.0 h before being reused

in a similar reaction. The catalyst could be used at least four times without significant reduction in its activity (81% yield for first use, 80% for second use, 80% for third use and 76% for fourth time).

A plausible mechanism for the formation of the 1,3-dioxane-4,6-diones products using H_3BO_3 as a catalyst has been depicted in **Scheme 2**.

Scheme 2

Conclusion

H_3BO_3 showed high catalytic activity in the synthesis of condensation reaction of molanic acid and ketones at room temperature. This procedure offers several advantages over the other techniques available in the literature, including much shorter reaction times, less catalyst dosage, higher yields and the absence of any hazardous organic solvents. Furthermore, the catalyst could be recycled after a simple work-up, and used at least four times without significant reduction in its catalytic activity.

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