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Ecofriendly Fast Batch Synthesis of Dioxolanes, Dithiolanes, and Oxathiolanes without Solvent under Microwave Irradiation

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Abstract:

2,2-Dimethoxypropane and 3,3-dimethoxypentane react with 1,2-ethanediol, thio, and oxathio analogues to give the corresponding protected carbonyls in high yield under mild solvent-free conditions. These environmentally benign conditions under microwave irradiation are applied to a large-scale synthesis.

Introduction

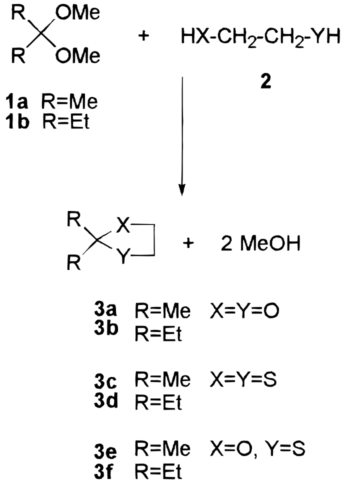
In a recent paper,[1] we have reported various methods for solvent-free protection of carbonyl groups under focused microwave irradiation. The best procedure to prepare dioxolanes was shown to be the exchange with 2,2-dimethyl-1,3-dioxolane (DMD) over montmorillonite clay K10 under microwave irradiation for 10−30 min in a Synthewave 402 apparatus.[2] Although this is a two-step process (synthesis of the dioxolane and then exchange), it gives better yields without solvent as compared to the literature methods which use benzene or toluene.

So, owing to the need for large quantities of DMD and to its relatively high price, we decided to look for a less expensive large-scale, solvent-free synthesis of this compound and some related derivatives in order to check their reactivity in exchange reactions.

The synthesis of DMD was previously described by Dauben et al.[3] according to the following procedure: acetone and ethylene glycol in equimolecular amounts were added with a catalytic amount of *p*-toluene sulfonic acid and refluxed in benzene during 30 h in a modified Dean−Stark separator. After workup and distillation through a glass helices-packed column, the yield was 65%.

Results and Discussion

According to our previous studies related to synthesis in dry media under microwave irradiation,[1,4] we tried to set up an easier, cleaner, and faster procedure.



Scheme 1. **Preparation of 2,2-dimethyl and 2,2-diethyl-1,3-dioxolanes, dithiolanes, and oxathiolanes**

This was achieved with DMD as a model on a 10 mmol scale starting from acetone dimethyl ketal **1a** and ethylene glycol **2** ($X = Y = O$, 1 equiv) in the presence of 0.1 g of montmorillonite clay K10 under microwave irradiation during 30 min in a Synthewave 402 apparatus.[5] The temperature was monitored at 70 °C by continuous adjustment of the emitted power between 0 and 150 W.

After filtration of K10, the workup is quite tedious, because DMD **3a** and methanol distilled together. This problem was solved by extraction with chloroform, washing with water, and then distillation through a glass helices-packed column (bp 91−92 °C, conversion 96%, isolated yield 75%).

1b is not commercially available, and we carried out the synthesis from 3-pentanone (10 mmol) and methyl orthoformate (10 mmol) with clay K10 (0.1 g) under microwave irradiation (15 min at 60 °C, 150 W). The conversion was quantitative, and we got the resulting ketal **1b**, which was further reacted without purification with glycol **2** ($X = Y = O$) under the conditions described for DMD to give 2,2-diethyl-1,3-dioxolane (**3b**, DED) in 88% yield after distillation (bp 139 °C) (Scheme 1). These reactions were extended on a 10 mmol scale to ethanedithiol and 2-hydroxy ethanethiol for the preparation of the corresponding five-membered rings.

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(5) This apparatus operates with a power between 0 and 300 W, having quartz reactors (8 cm high; 4, 2.5, or 1.5 cm diameter) fitted with a stirring device and monitored either in power or in temperature.

(6) Patent ref 2. This apparatus operates with an adjustable power between 0 and 800 W and may be monitored either in power or in temperature. The cylindrical quartz reactor (10 cm diameter) has a useful volume of 800 mL. The cover allows mechanical stirring, reflux, and, eventually addition during the reaction.

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Figure 1. **Photograph of Synthewave 1000 apparatus as it is used.**

To scale-up these syntheses, we used a Synthewave 1000 apparatus[6] fitted with a 1-L quartz reactor, a mechanical stirrer, and a glass helices-packed column (15 cm long, 1 cm diameter), as shown in Figure 1.

We worked on a 2-mol scale in a two-step process according to Scheme 2 without any solvent.

During the first step, the resulting methyl formate was continuously distilled so that, at the end of the process, we got nearly pure ketal (NMR) **1b**, R = Et (**1a** is commercialy available and was used directly in the second step). Then, after addition of the substituted ethane **2**, the irradiation was continued during 30 min with continuous distillation of methanol.

Under these conditions, we got the various protected carbonyls **3**, together with 10% methanol, which was further removed by distillation to give pure **3a**−**f** (see Table 1).[7−14]

Scheme 2. **Two-step process for preparation of dioxolanes, dithiolanes, and oxathiolanes**

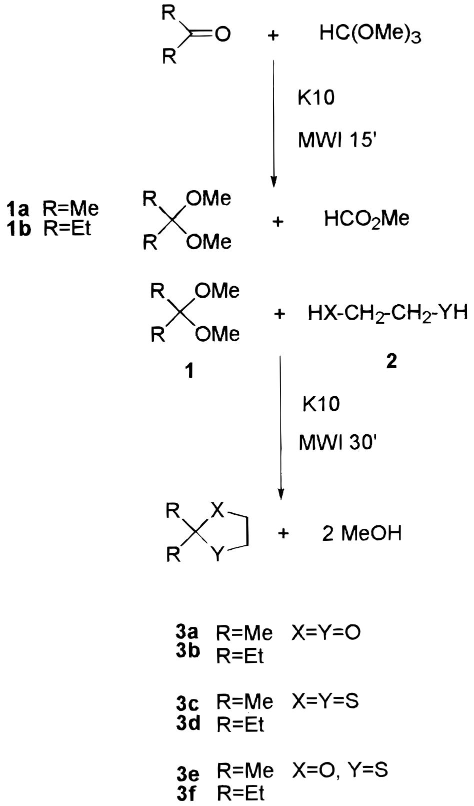

Table 1. **Conditions and results for the synthesis of 3**

3	R[a]	X	Y	temp, °C	isolated weight, g	isolated yield, %	literature[b]
a	Me	O	O	70	154	75	3, 7, 8
b	Et	O	O	80	231	88	8
c	Me	S	S	70	240	90	9−11
d	Et	S	S	80	269	83	
e	Me	O	S	70	203	86	
f	Et	O	S	80	252	86	

[a] When R = Me, only the second step is realized, and irradiation lasts 30 min. When R = Et, the two steps are carried out, 15 min for the first and 30 min for the second. [b] Reactions are usually run in solution at a small scale and require 5−16 h to give equivalent or much lower yields, except for in ref 11, where a quantitative yield is reported.

In fact, the 2-mol scale was easier than the 10-mmol scale, owing to the possibility of continuous distillation under irradiation in the Synthewave 1000 with a packed column, which is not possible in the smaller Synthewave 402. It is noteworthy that the conditions (time, temperature) were exactly the same going from the 10-mmol scale to the 2-mol scale.

In summary, we have developed a new technique for the synthesis of dioxolanes, dithiolanes, and oxathiolanes which is fast, environmentally friendly, and easily scaled up.

Experimental Section

In a typical experiment, we prepared **3b** in the following way: 3-pentanone (2 mol, 172.26 g), methyl orthoformate

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(2 mol, 212.24 g), and clay K10 (20 g, purchased from Prolabo−France, *d* = 300−370 g·L^{-1}, specific area = 220−270 m^2·g^{-1}, Na$^+$ exchanged without further activation) were placed in the 1-L quartz reactor of the Synthewave 1000 apparatus under mechanical stirring. The assigned temperature of 60 °C was reached in 2 min and maintained during 13 min by continuous adjustment of the power between 0 and 150 W. During this time, the resulting methyl formate was distilled. Then, ethylene glycol (2 mol, 124.14 g) was added and irradiation started again in order to reach 80 °C in 1 min. This temperature was maintained during 29 min. During this time, methanol was distilled. The remaining product, which still contained 10% methanol, was then filtered to remove K10 and distilled over a glass helices-packed column to give **3b** (bp 139 °C, 231 g, 88% yield).

The same procedure was applied for the syntheses of **3d** and **3f**. In the cases of **3a,c,e**, only the second step was realized at an assigned temperature of 70 °C.

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