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On the synthesis of β-keto-1,3-dithianes from conjugated ynones catalyzed by magnesium oxide

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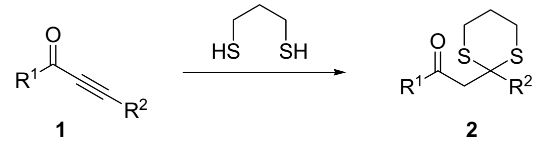
Abstract

MgO was used for the first time as a heterogeneous basic catalyst to synthesize β-keto-1,3-dithianes, potentially useful synthetic intermediates, from conjugated ynones and ynoates.

β-Keto-1,3-dithianes **2** are highly functionalized three-carbon units, which are of much importance as potentially useful synthetic intermediates.[1] For example, the 1,3-dithiane substituent may, if desired, be hydrolyzed to a carbonyl group and hence provides an attractive and useful strategy for ketone protection in general. Alternatively, it may be converted into a methylene group by reductive desulfurization.[2] Alkylation with this three-carbon unit has also been utilized in several syntheses.[3] Procedures reported for the preparation of β-keto-1,3-dithianes **2** include α-alkylation of carbonyl compounds with 1,3-dithiane or its derivatives,[2,4] nucleophilic addition of 1,3-dithiane to epoxides followed by oxidation,[3] conjugate reduction of α-oxo ketene dithio acetals[5] and double Michael addition of 1,3-propanedithiol to α,β-acetylenic ketones **1** (Scheme 1).[6] Systems related to the mono-protected 1,3-diones **2** have also been prepared by dithiane alkylation using haloacetaldehyde acetals,[7] in a reverse sense by β-keto-ester dianion alkylation using 2-chloro-1,3-dithiane[8] and various exchange reactions.[9] However, these syntheses are homogeneous and in most cases relatively complicated; certainly, most of the existing procedures are not especially environmentally friendly.



Scheme 1. The generalized conversion of ynones **1** into β-keto-1,3-dithianes **2**.

In recent years, there has been increasing emphasis on the design and use of environmentally friendly solid acid and base catalysts to reduce the amount of toxic waste and by-products arising from chemical processes prompted by stringent environmental protection laws.[10] Hence, reusable heterogeneous catalysts will have a distinct advantage but only if they can match the performance of homogeneous catalysts.

To date, there has been only one report regarding the synthesis of β-keto-1,3-dithianes **2** by Michael additions induced by a heterogeneous catalyst,[11] when solid alumina was used. This was readily reused; however, a large excess (7 equiv) was required. There has been no other report of using a heterogeneous basic catalyst to synthesize β-keto-1,3-dithianes **2**. Magnesium oxide (MgO) is a typical basic

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oxide (Hammett constant $H = +26.0$)[12] and has the lowest solubility among the alkaline earth oxides (MgO, BaO, CaO and SrO) and so can potentially be reused, as it will not be lost due to leaching into the reaction mixture. Furthermore, MgO is inexpensive and easily obtained so that it could be applied to large scale manufacture. In view of our success in using MgO as a basic catalyst in both Knoevenagel and especially Michael additions, it appeared that this catalyst might be useful for triggering the 'double' Michael addition of 1,3-dithianes to propargylic carbonyl systems **1** to give β-keto-1,3-dithianes **2**. In this Letter, we report the successful outcome of using this inexpensive and easily obtained heterogeneous basic catalyst for this purpose (Scheme 1).

The catalysts used in this study were obtained by calcination of the precursors (450 °C, static air, 2 h) with a heating ramp of 10 °C/min (Table 1), except MgO-AD and MgO-RIB. MgO-AD was the commercially available MgO from Aldrich. MgO-RIB was obtained by igniting Mg ribbon in air.

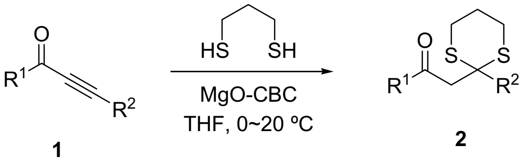
Initial trial reactions to test the various catalysts involved the addition of the particular MgO sample (2.5 equiv or 1.0 equiv) in one portion to a stirred solution of 4-phenyl-3-butyn-2-one **1a** (1 mmol) and propane-1,3-dithiol (1 mmol) in THF (2 ml) cooled in ice-water. The cooling bath was then removed and the mixture stirred at ambient temperature and reaction progress followed by withdrawing samples (about 0.5 ml), which were filtered and the filtrate divided into two parts. One part was directly analyzed by GC or GC–MS. The other part was evaporated and the residue analyzed by ^{1}H NMR and ^{13}C NMR using $CDCl_3$ as solvent. The conversions observed are summarized in Table 1.

A series of substrates were then tested using MgO-CBC as the catalyst, as this showed one of the highest surface areas, clearly a key factor in the activity of this class of catalyst. After the reaction, the solution was filtered through silica gel to remove the catalyst and the solvent evaporated. No further purification was usually necessary. The results (Scheme 2) show that MgO-CBC is a very active catalyst for the synthesis of β-keto-1,3-dithianes **2**. Substrates **1a**–**g** underwent clean additions with propane-1,3-dithiol by this procedure to give the corresponding β-keto-1,3-dithianes **2**. The experimental procedure is very simple and the reactions are fast and clean.

Table 1
1,3-Propanedithiol additions to 4-phenyl-3-butyn-2-one **1a** in the presence of various MgO catalysts (1.0 equiv) for 1 h in tetrahydrofuran

Entry	Precursors	S_{BET} ($m^2 g^{-1}$)	Yield (%)
MgO-RIB	Mg ribbon	10	20
MgO-AD	MgO (Aldrich)	25	0
MgO-CAD	MgO (Aldrich)	25	66
MgO-COH	$Mg(OH)_2$ (Fluka)	65	98
MgO-ROH	$Mg(OH)_2$ (Fluka)[a]	277	98
MgO-CBC	$(MgCO_3)_4Mg(OH)_2$ (Fluka)	288	98
MgO-OX	Mg[O(CO)$_2$O]	312	98
MgO-CC	$MgCO_3$ (Acros Organics)	229	98

[a] Calcined at 600 °C for 2 h, refluxed in H_2O for 3 h, then oven-dried.

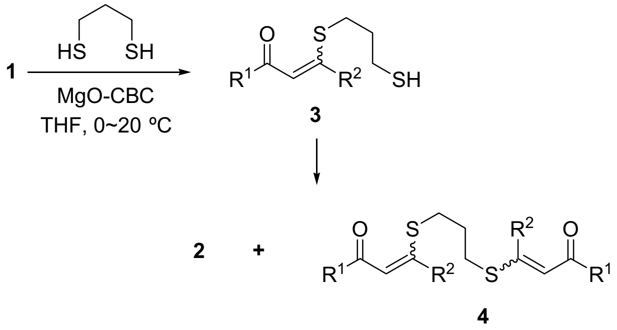


a) R^1 = Me; R^2 = Ph [1 h; 98%]
b) R^1 = R^2 = Ph [1 h; 90%]
c) R^1 = H; R^2 = *n*-pent [3 h; 98%]
d) R^1 = Me; R^2 = $SiMe_3$ [1 h; 95%]
e) R^1 = Me; R^2 = H; [1 h; 90%]
f) R^1 = EtO; R^2 = H [4 h; 95%]
g) R^1 = MeO; R^2 = H [2 h; 88%]
h) R^1 = EtO; R^2 = Me [24 h; 65%]
i) R^1 = MeO; R^2 = Ph [24 h; 30%]

Scheme 2. The addition of 1,3-propanedithiol to ynones and ynoates **1** catalyzed by magnesium oxide.

Ley and co-workers proposed a mechanism[6] for these double conjugate additions of dithiols to propargylic carbonyl systems to generate β-keto-1,3-dithianes **2** when using sodium methoxide as the trigger, which features sequential deprotonation at sulfur, Michael addition and enolate protonation to give both cis- and trans-isomers of the α,β-unsaturated carbonyl intermediates **3**. These are themselves substrates for a second conjugate addition, now an intramolecular process, which gives the desired β-keto-1,3-dithianes **2**. However, this second addition competes with the reaction of substrate **3** with another molecule of ynone to give dimeric side products **4**, which are observed in some cases (Scheme 3).

All five products **2a**–**e** obtained from ynones and ynals **1a**–**e** were essentially free of contamination by either intermediates **3** or 'dimers' **4** and only traces of these were visible in the ^{1}H NMR spectra of products **2f** and **2g**, derived from propynoates **1f**,**g**. This is clearly consistent with these mechanistic proposals, as the propynoates would be expected to be marginally poorer Michael acceptors relative to the ynones. The two final substrates, ethyl 2-butynoate **1h** and its phenyl homologue **1i**, were understandably significantly less reactive, the alkyne substituent doubtless hindering the Michael addition steps significantly relative to propynoates **1f**,**g** (Scheme 2). This, coupled with the generally lower ester reactivity resulted in the requirement for much longer reaction times and the inevitable accumulation of by-products; both 'dimer' **4** and partly reacted



Scheme 3. Double Michael addition prior to final ring closure.

alkenoates **3** were easily identified in the product mixtures. Yields of 60–70% were obtained with ethyl-2-butynoate **1h** as the substrate, but only a 30% yield for methyl phenylpropiolate **1i**.[13] In summary, it is clear that the ynones are more reactive than the corresponding esters, the ynoates in these reactions. Much the same observations were made when NaOMe was used as the triggering base.[6]

The activity of MgO is higher or comparable with that of the previously published homogeneous base catalyst NaOMe.[6] When 4-phenyl-3-butyn-2-one **1a** was tested as the substrate and MgO as the catalyst, 98% yield was reached in $\leqslant$1 h, while for the homogeneous base catalyst NaOMe, 24 h was needed to obtain these high yields, although this time may not have been optimized. Furthermore, as far as the catalyst amount is concerned, the required quantity of MgO (1.0 equiv) is less than that of the homogeneous base catalyst NaOMe (2.5 equiv). The same pattern was observed for ynoate **1f**: the reaction rate was similarly more rapid when MgO was used as catalyst relative to the homogeneous base catalyst NaOMe.

The effect of the MgO preparation method was further investigated. When 2.5 equiv of MgO was used, all the types of MgO, except MgO-RIB and MgO-AD, catalyzed the test reaction (Table 1) to 98% yield within 1 h. When 1.0 equiv MgO was used, MgO-RIB, MgO-AD and MgO-CAD were less active than the others. The low activity of MgO-RIB and MgO-AD may be attributed to the fact that these two catalysts were not degassed before testing. MgO-AD was calcined to obtain MgO-CAD. The conversion increased from 0% to 66% when transferring MgO-AD to MgO-CAD.

This is the first report of the synthesis of β-keto-1,3-dithianes **2** by Michael additions through the use of a heterogeneous basic catalyst. It was proven that the activity of MgO is higher than the previously published homogeneous catalyst NaOMe in some reactions.

Acknowledgements

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