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Synthesis of 1,4-ketoaldehydes and 1,4-diketones by Mo-catalyzed oxidative cleavage of cyclobutane-1,2-diols†

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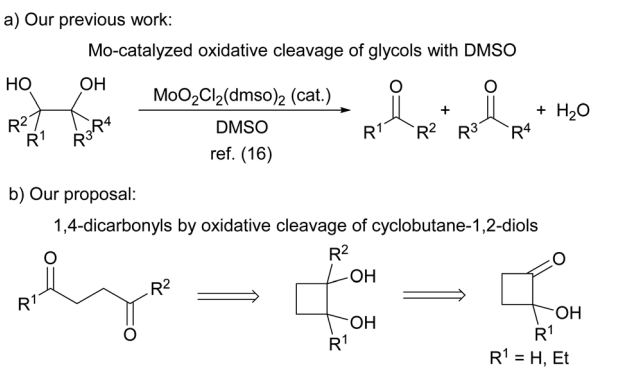
A new two-step procedure for the synthesis of 1,4-dicarbonyls has been developed involving an efficient and clean Mo-catalyzed oxidative cleavage of cyclobutane-1,2-diols with DMSO, which is used as solvent and oxidant. The required starting glycols were prepared by nucleophilic additions of organolithiums and Grignard reagents to easily available 2-hydroxycyclobutanones.

1,4-Dicarbonyls are valuable structural motifs in organic synthesis that are typically employed to prepare five-membered heterocycles and functionalized cyclopentenones.[1] In addition, they are common skeletons in natural products possessing interesting biological activities.[2] For that reason, several synthetic approaches have been developed for accessing these building blocks, ranging from classical procedures,[3] such as the conjugate addition of acyl anions to Michael acceptors, like the Stetter reaction,[4] the acylation of homoenolate equivalents,[5] the reaction of enolates with α-haloketones,[6] or the oxidative coupling of enolates,[7] to more recent routes involving metal-catalyzed cross-coupling reactions of different carbonyl derivatives,[8] conjugate addition of acyl radicals,[9] carbene insertion into 1,3-dicarbonyls,[10] hydrocarbonylation reactions,[11] as well as different photocatalyzed processes,[12] or the organocatalytic redox isomerization of allylic alcohols.[13]

On the other hand, the oxidative cleavage of 1,2-diols is a fundamental synthetic transformation, early developed by Criegee and Malaprade a century ago.[14] Since then, several protocols have been developed trying to improve the efficiency and selectivity of the process and to reduce the drawbacks associated with the use of hazardous reagents and/or conditions.[15] In this field our group has reported the employment of DMSO as both solvent and oxidant for the selective oxidative cleavage of a wide variety of glycols under dioxomolybdenum (VI)-catalysis (Scheme 1a).[16] These metallic complexes are readily available and have been successfully used by our group and others as efficient catalysts for different processes involving O-atom transfer reactions.[17] In addition, DMSO is an inexpensive and widely used solvent with low relative toxicity,[18] obtained as a byproduct of the wood industry, which has also been employed as a mild oxidant and as oxygen, one-carbon, or thiomethyl/methiomethyl source in a variety of organic transformations.[19]

In this context, we envisaged that a simple and straightforward route to access 1,4-dicarbonyl derivatives would be the oxidative cleavage of cyclobutane-1,2-diols (Scheme 1b). This conceptually simple approach has not been previously reported, and only related examples have been scarcely developed, such as the preparation of *ortho*-keto-functionalized benzaldehyde derivatives from α-siloxybenzocyclobutanone.[20] Therefore, to the best of our knowledge, the use of 2-hydroxycyclobutanones for the synthesis of aliphatic 1,4-dicarbonyls has not been previously described.[21] These derivatives have been used mainly by Secci *et al.* for the development of chemoselective methodologies applied to the preparation of different carbo- and heterocyclic scaffolds.[22] Herein, we report a new



Scheme 1 Dioxomolybdenum(VI)-catalyzed oxidative cleavage of glycols with DMSO (previous work) and proposed synthesis of 1,4-dicarbonyls (this work).

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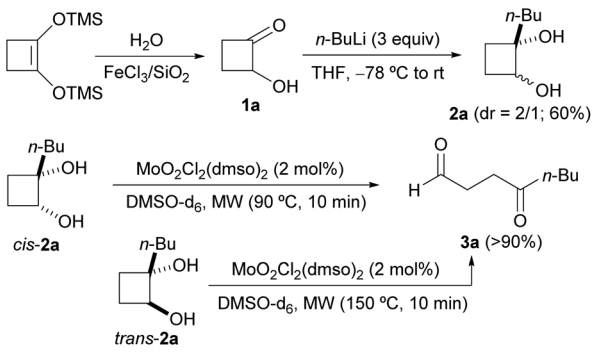
protocol for the preparation of 1,4-dicarbonyls based on the Mo-catalyzed oxidative cleavage of cyclobutane-1,2-diols with DMSO.

2-Hydroxycyclobutanone **1a**, easily accessed from commercially available 1,2-bis(trimethylsilyloxy)cyclobutene,[23] was selected as starting material for synthesizing cyclobutane-1,2-diol derivatives. Its treatment with an excess of *n*-BuLi provided glycol **2a** in good yields as a mixture of diastereoisomers, which could be isolated independently after column chromatography, and stereochemically assigned from the ready formation of a cyclic acetal from the *cis*-diol stereoisomer (Scheme 2).[24] Then, each diastereoisomer, *cis*-**2a** and *trans*-**2a**, was evaluated in the Mo-catalyzed oxidative cleavage reaction with DMSO-d_6 under microwave irradiation.

After a brief optimization[25] we could establish the conditions for obtaining the corresponding γ-ketoaldehyde **3a** in very high yields in both cases, after short reaction times (Scheme 2). Not surprisingly, the temperature required for the cleavage of *trans*-**2a** was considerably higher than for *cis*-**2a**. In addition, the oxidative cleavage of *cis*-**2a** can also be carried out under conventional heating (90 °C) for 1 h with similar yield.

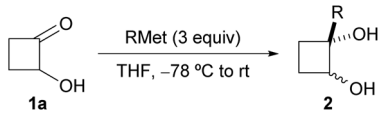
Then, we prepared a wide variety of cyclobutane-1,2-diols **2** from both organolithium and Grignard reagents, which were obtained in good yields as mixtures of *cis*- and *trans*-diastereoisomers, being *cis*-**2** the major isomer in all cases (Table 1). Surprisingly, only the reaction with benzylmagnesium chloride proceeded with high diastereoselectivity (entry 6). In most cases both diastereoisomers could be isolated independently. Different organometallics were used successfully, including (cyclo)alkyl (entries 1–5), benzyl (entry 6), (hetero)aryl (entries 7–9), and alkynyl ones (entries 10–13), as well as a lithium enolate (entry 14).

Due to the milder conditions required for the oxidative cleavage of *cis*-**2** and their easy isolation, these diastereoisomers were used as starting materials for the synthesis of the corresponding γ-ketoaldehydes **3** (Table 2). Reactions were carried out in DMSO-d_6 under microwave irradiation (90 °C, 10 min) and very high yields were achieved for all the essayed substrates, which were obtained in pure form without further purification and properly characterized in the deuterated solvent.[25] No significant effect of the R group was observed in the Mo-catalyzed oxidative cleavage. Apart from simple aliphatic



Scheme 2 Synthesis of cyclobutane-1,2-diol **2a** and its oxidative cleavage with DMSO.

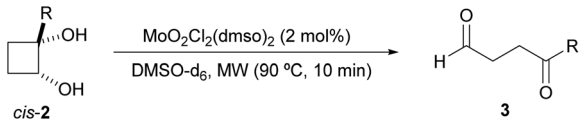
Table 1 Synthesis of cyclobutane-1,2-diols **2**[a]



Entry	RMet	2	dr[b]	Yield[c] (%)
1	*n*-BuLi	**2a**	2/1	60
2	MeLi	**2b**	3/1	55
3	EtMgBr	**2c**	2/1	63
4	*i*-PrMgCl	**2d**	1.2/1	58[d]
5	*c*-C_6H_{11}MgCl	**2e**	1.2/1	63
6	$PhCH_2MgCl$	**2f**	>20/1	61[d]
7[e]	PhLi	**2g**	3/1	55
8	2-$MeOC_6H_4Li$	**2h**	3/1	57[d]
9	5-Me-2-ThLi[f]	**2i**	2/1	42
10	BuC≡CLi	**2j**	2/1	67
11	PhC≡CLi	**2k**	2/1	66
12	3-ThC≡CLi[g]	**2l**	2/1	61
13	$PhOCH_2C{\equiv}CLi$	**2m**	2/1	55
14	$LiCH_2CO_2t$-Bu	**2n**	2/1	54[d]

[a] Reactions conducted using 2-hydroxycyclobutanone **1a** (2 mmol) and the corresponding organometallic (6 mmol) in THF (4 mL) from −78 °C to RT. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Combined isolated yield of *cis*- and *trans*-**2** based on starting material **1a**. Both diastereoisomers were isolated independently unless otherwise noted. [d] Only the corresponding *cis*-**2** was isolated. [e] Similar yield and diastereoselectivity were obtained using PhMgBr. [f] 5-Methyl-2-thienyl lithium. [g] 3-Thienylethynyl lithium.

Table 2 Mo-catalyzed oxidative cleavage of *cis*-cyclobutane-1,2-diols **2**[a]



Entry	2	R	Product	Yield[b] (%)
1	**2a**	*n*-Bu	**3a**	92 (86)[c]
2	**2b**	Me	**3b**	94
3	**2c**	Et	**3c**	92
4	**2d**	i-Pr	**3d**	89
5	**2e**	*c*-C_6H_{11}	**3e**	92 (87)[c]
6	**2f**	$PhCH_2$	**3f**	90 (86)[c]
7	**2g**	Ph	**3g**	93 (88)[c]
8	**2h**	2-$MeOC_6H_4$	**3h**	91
9	**2i**	5-Me-2-Th	**3i**	88
10	**2j**	C≡CBu	**3j**	94
11	**2k**	C≡CPh	**3k**	93
12	**2l**	C≡C-(3-Th)	**3l**	92
13	**2m**	$C{\equiv}CCH_2OPh$	**3m**	90
14	**2n**	CH_2CO_2t-Bu	**3n**	89

[a] Reactions conducted using 0.3 mmol of the corresponding *cis*-diol **2** in DMSO-d_6 (0.6 mL) with [$MoO_2Cl_2(dmso)_2$] (2 mol%) under microwave irradiation (90 °C, 10 min). [b] The crude products were pure, as observed by ^{1}H NMR analysis. Yield determined using dibromomethane as internal standard. [c] Isolated yield after extraction.

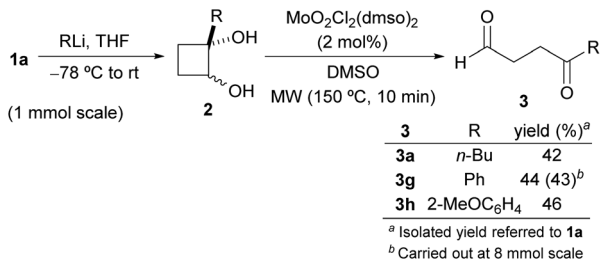
γ-ketoaldehydes **3a–f**, (hetero)aromatic derivatives **3g–i** could also be prepared (entries 7–9) and, more interestingly, alkynones **3j–m**, further functionalized with an aldehyde group, were also efficiently synthesized (entries 10–13). Interestingly, tricarbonyl derivative **3n** was prepared from glycol **2n** (entry 14). Finally, a selection of dicarbonyls **3** were also isolated by simple extraction (entries 1 and 5–7).

Moreover, the synthesis of γ-ketoaldehydes **3** could also be carried out without purification of glycols **2** (Scheme 3). So, the crude products obtained from the reaction of **1a** with selected organometallics were reacted under the Mo-catalyzed conditions. As both diastereoisomers of the corresponding cyclobutane-1,2-diols **2** were present in the crude, the oxidative cleavage with DMSO was performed at 150 °C. After workup, the corresponding ketoaldehydes **3a**,**g**,**h** were isolated in good overall yields after column chromatography (Scheme 3). In addition, the preparation of **3g** was also performed from **1a** (8 mmol) in 43% overall yield.

Next, we decided to check the suitability of this methodology for the preparation of 1,4-diketones. To achieve this goal, a 2-substituted-2-hydroxycyclobutanone would be required as starting material. This type of compound can be prepared by the Norrish–Yang intramolecular photocyclization of 1,2-diketones.[26] Following this methodology, 2-ethyl-2-hydroxycyclobutanone **1b** was synthesized from commercially available 3,4-hexanedione (Scheme 4).[27] However, its reaction with organolithium reagents did not selectively afford the expected diols **4**, as mixtures of diastereoisomers, but also led to formation of glycols **5**. These diol derivatives seem to come from a competitive rearrangement of the alkoxide **1b**-Li affording lithium 1-propionylcyclopropan-1-olate that undergoes a subsequent nucleophilic addition. Although this undesired pathway is minor,[28] glycols **4** and **5** could not be independently isolated by standard column chromatography, except for the case of using lithium phenylacetylide, which allowed the isolation of pure *cis*-**4a**. Gratifyingly, this cyclobutane-1,2-diol derivative underwent efficiently the oxidative cleavage with DMSO, under dioxomolybdenum(VI)-catalysis, giving rise to alkynyl diketone **6a** (Scheme 5). In addition, we could also isolate diol **5e**, arising from the reaction of **1b** with PhLi, but when we submitted it to the oxidative cleavage under Mo-catalysis at 150 °C no reaction took place.

This result gave us the opportunity to carry out the oxidative cleavage of crude mixtures of di-tertiary cyclobutane-1,2-diols **4** and glycols **5** (Table 3). After column chromatography we were able to obtain and isolate a selection of pure 1,4-diketones **6** in useful overall yields, considering that they are referred to hydroxyketone **1b**. In this way γ-diketones bearing alkynyl (entry 1), (cyclo)alkyl (entries 2 and 3), benzyl (entry 4) or (hetero)aryl groups (entries 5 and 6), as substituents of one of the carbonyl groups, could be synthesized.

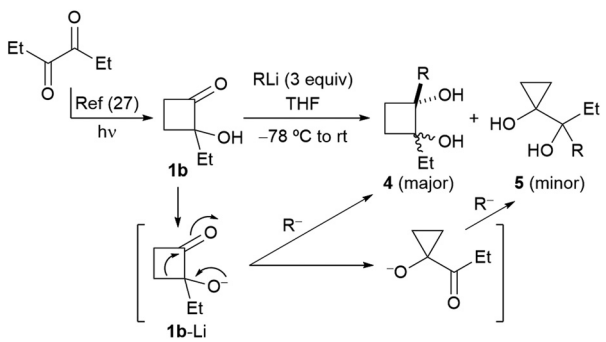
Based on our previous report,[16] the reaction mechanism for the oxidative cleavage of cyclobutane-1,2-diols **2** and **4** was proposed as shown in Scheme 6. Firstly, the catalyst



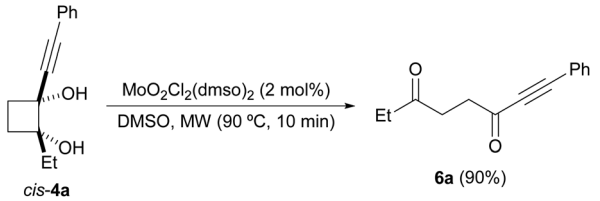
3	R	yield (%)[a]
3a	*n*-Bu	42
3g	Ph	44 (43)[b]
3h	2-MeOC$_6$H$_4$	46

[a] Isolated yield referred to **1a**
[b] Carried out at 8 mmol scale

Scheme 3 Synthesis of 1,4-ketoaldehydes **3** from **1a** (without purification of **2**).

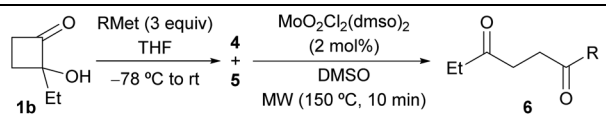


Scheme 4 Synthesis of di-tertiary cyclobutanediols **4** from **1b** and oxidative cleavage of isolated *cis*-**4a**.



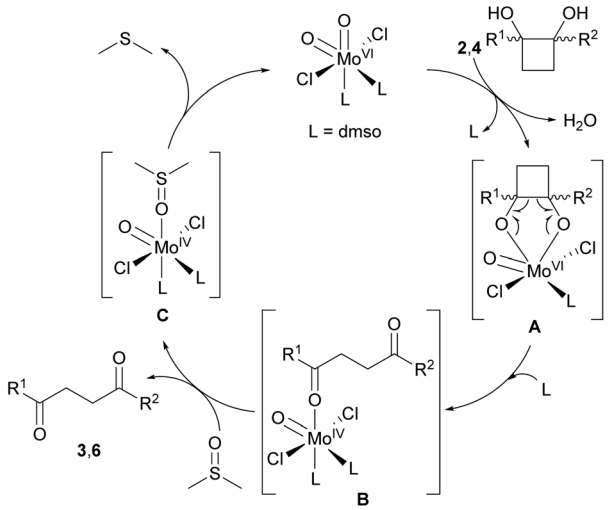
Scheme 5 Oxidative cleavage of *cis*-**4a**: synthesis of alkynyl diketone **6a**.

Table 3 Synthesis of 1,4-diketones **6** from **1b**[a]



Entry	RMet	Product	R	Yield[b] (%)
1	PhC≡CLi	**6a**	C≡CPh	48
2	*n*-BuLi	**6b**	*n*-Bu	42
3	*c*-C$_6$H$_{11}$MgCl	**6c**	*c*-C$_6$H$_{11}$	39
4	PhCH$_2$MgCl	**6d**	CH$_2$Ph	40
5	PhLi	**6e**	Ph	38
6	5-Me-2-ThLi[c]	**6f**	5-Me-2-Th	37

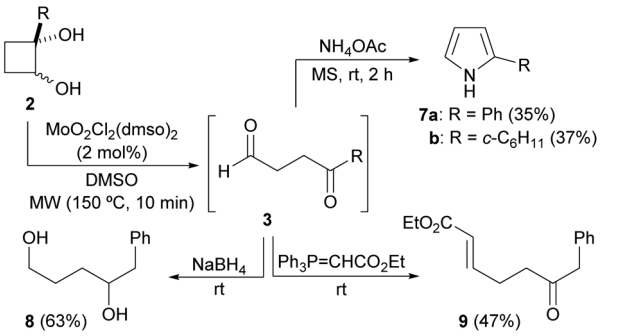
[a] Reactions conducted starting from **1b** (1 mmol) and the corresponding organometallic reagent (3 mmol) in THF (3 mL). The crude mixture is oxidatively cleaved in DMSO (2 mL) under microwave irradiation (150 °C, 10 min). [b] Isolated yield after column chromatography referred to 2-hydroxycyclobutanone **1b**. [c] 5-Methyl-2-thienyl lithium.



Scheme 6 Mechanistic proposal for the Mo-catalyzed oxidative cleavage of cyclobutane-1,2-diols **2** and **4** with DMSO.

$[MoO_2Cl_2(dmso)_2]$ would react with the corresponding cyclobutanediol **2** or **4** leading to diolate complex **A**, releasing a molecule of water. Then, the oxidative cleavage of the glycolate ligand by the Mo(VI) center would lead to the formation of a new oxomolybdenum(IV) species **B**. Finally, the weakly coordinated 1,4-dicarbonyl **3** or **6** would be readily displaced by dimethyl sulfoxide affording the unstable Mo(IV) adduct **C**. Subsequent release of dimethyl sulfide, would eventually regenerate the Mo(VI) catalyst. We further investigated the formation of the proposed diolate complex **A**.[25] According to the ^{1}H-NMR spectra of an equimolecular mixture of diols *cis*- or *trans*-**2a** and the Mo(VI) catalyst in DMSO-d_6, recorded at different temperatures, the suggested complex **A** would likely exist only in the instant of its formation as it could not be detected by NMR. Once the reaction reached the required temperature, *ca.* 40 °C for *cis*-**2a** and 150 °C for *trans*-**2a**, only the final 1,4-dicarbonyl and the starting diol were observed by NMR. This study suggests that the diolate generation is the rate-determining step for the oxidative cleavage.[29] In addition, we carried out the oxidative cleavage of **2a** in the presence of radical scavengers TEMPO and BHT. In both experiments, the addition of these reagents did not have any impact on the reaction outcome. The formation of the ketoaldehyde **3a** was not suppressed, thus suggesting that the transformation does not follow a radical pathway.

Finally, we decided to increase the value of our protocol for the synthesis of 1,4-dicarbonyls by their direct transformation into other derivatives. In such manner, the crude DMSO solution of γ-dicarbonyls **3g,e**, directly obtained after the Mo-catalyzed oxidative cleavage of selected cyclobutane-1,2-diols **2g,e**, was treated with NH_4OAc, in the presence of molecular sieves, allowing the isolation of the corresponding pyrroles **7** in good overall yields considering that they are referred to starting glycols **2** (Scheme 6). In addition, when the crude DMSO solution of **3f** was reacted with $NaBH_4$, 1,4-diol **8** was obtained in high yield (Scheme 6). Finally, a Wittig ylide was added to the same crude γ-dicarbonyl **3f** in DMSO producing ketoester derivative **9** in good yield (Scheme 7).



Scheme 7 Subsequent transformations of DMSO-solutions of crude 1,4-dicarbonyls **3**.

Conclusions

In conclusion, we have designed and developed a two-step process for the synthesis of 1,4-ketoaldehydes and 1,4-diketones from readily available 2-hydroxycyclobutanones. The first nucleophilic addition on the cyclobutanone skeleton controls the substituent of the ketone moiety, whereas the C2-substituent of the starting 2-hydroxycyclobutanone is responsible for the generation of γ-ketoaldehydes or γ-diketones. The dioxomolybdenum-catalyzed oxidative cleavage of glycols, using DMSO as solvent and oxidant, allows the clean and high-yielding production of γ-dicarbonyls, which can be employed in a straightforward manner for subsequent useful transformations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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