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C–C Coupling

Formation of 1,4-Diketones by Aerobic Oxidative C–C Coupling of Styrene with 1,3-Dicarbonyl Compounds**

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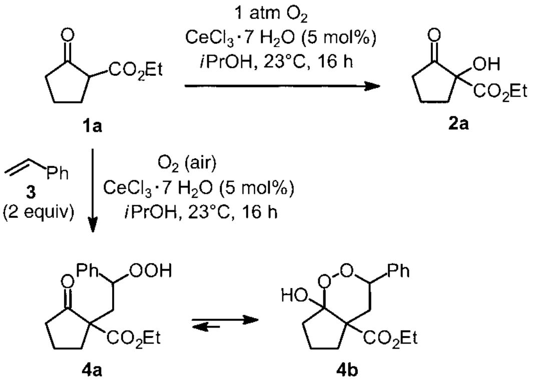
1,4-Dicarbonyl compounds[1] are versatile precursors for the synthesis of various heterocyclic structural motifs, for example, furan,[2] thiophene, and pyrrole derivatives.[3] The conversion of α-halo ketones with enolates represents a classic route to 1,4-dicarbonyl compounds (Feist–Bénary synthesis of furan derivatives).[4] A modern concept utilizes the umpolung of aldehydes, for example, by application of the Stetter reagent[5] or 1,3-dithiane derivatives.[6]

Recently, we reported the cerium-catalyzed α hydroxylation of 1,3-dicarbonyl compounds **1** (Scheme 1).[7] With respect to economical and ecological considerations, the use of molecular oxygen is superior to other reagents applied in this type of conversion. Based on the assumption of radical intermediates along the hydroxylation pathway, the conversion has been performed in the presence of olefins such as styrene (**3**), and indeed, hydroperoxides **4** were obtained as the major products. Compounds **4** were isolated as hemiacetals such as **4b** with an endoperoxide 1,2-dioxane ring.[8]



Scheme 1. Cerium-catalyzed α hydroxylation of β-oxoester **1a** with O_2 and oxidative C–C coupling with styrene **3**.

Surprisingly, these crystalline endoperoxides have a remarkable stability indicated by defined melting points between 50 and 150 °C, but, unfortunately, they were obtained as hardly separable mixtures of diastereoisomers. Thus, purification and characterization are difficult, resulting in a

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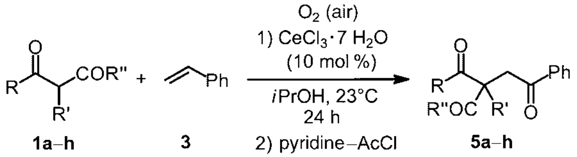
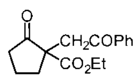
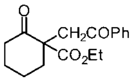
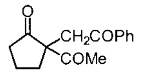
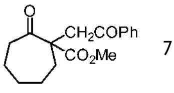
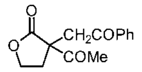
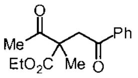
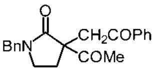
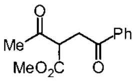
restricted application for further synthetic purposes. We were therefore interested in the conversion of 1,2-dioxanes into diastereomerically unique products, either by oxidation, reduction or by disproportionation of the peroxide unit.[9] After considerable experimentation with a number of transition-metal-assisted transformations,[10] we focused our interest on the Kornblum–DeLaMare fragmentation mediated by a pyridine/acetyl chloride system.[11] Owing to the difficult purification of the diastereomeric endoperoxide mixtures, we investigated a sequential one-pot procedure for oxidative C–C bond formation and Kornblum–DeLaMare fragmentation. Herein we report an optimized protocol as the result of these studies.

1,3-Dicarbonyl compounds **1a–h** were converted with styrene (**3**) under $CeCl_3{\cdot}7H_2O$ catalysis (10 mol%) in 2-propanol at ambient temperature under an atmosphere of air as the oxidant (Table 1). Under higher partial pressures of O_2 the formation of undesired α-hydroxylated products **2** is favored.

Table 1: Formation of 1,4-dicarbonyl compounds **5** by a two-step one-pot reaction consisting of cerium-catalyzed C–C coupling with **3** and subsequent Kornblum–DeLaMare fragmentation.[a]



1a–h **3** **5a–h**

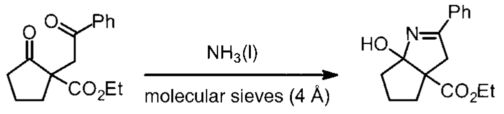
	Product	Yield [%][b]		Product	Yield [%][b]
5a		71	**5e**		50[c]
5b		62	**5f**		71
5c		87[c]	**5g**		68
5d		72	**5h**		72

[a] See Experimental Section for reaction conditions. [b] Overall yield over two steps. [c] 5 mol% of $CeCl_3{\cdot}7H_2O$.

As **3** is partly consumed by polymerization, the reaction was started with the addition of 2 equivalents followed by a further 1 equivalent of **3** after 4 h. The reaction mixture was stirred for a further 20 h, and then all volatile materials were removed under vacuum, leaving a mixture of crude endoperoxides **4**, polystyrene, and cerium-containing materials. This residue was directly treated with a mixture of pyridine (5 equiv) and AcCl (6 equiv) in CH_2Cl_2 and stirred for 16 h at ambient temperature. Filtration through SiO_2 and chromatography gave unique 1,4-diketones **5** in the range of 50–90% overall yield over two steps (Table 1).

Apart from carbocyclic and open-chain β-oxoesters and 1,3-diketones, heterocyclic compounds were also investigated. As can be seen from Table 1, the best result was realized for lactone **5c** (87% overall yield), whereas of cyclohexanone derivative **5e** was obtained in 50% yield. All other substrates, which include lactam **5d** and carbocyclic and open-chain derivatives, were isolated in 62–72% yield. The reaction sequence could also be extended to the seven-membered ring product **5f** (71%). In contrast to α hydroxylations, even the α-unsubstituted substrate **1h** (R' = H) cleanly reacted in this manner with **3** to give **5h** in 72% yield (Table 1).

To prove the utility of the 1,4-diketones **5** (which bear a quaternary C atom) as building blocks in the synthesis of heterocycles, compound **5a** was treated with liquid NH_3. After chromatographic workup, the novel bicyclic 3,4-dihydro-2*H*-pyrrole derivative **6** was isolated as a single diastereomer in 63% yield (Scheme 2). The molecular structure of **6** was confirmed by X-ray single-crystal analysis (Figure 1)[12] and can be seen as a product of an interrupted Paal–Knorr pyrrole synthesis. The final elimination of water is inhibited by the quaternary center, and the position of the formed double bond is unexpected for this type of reaction.[4a,b]



5a **6** (63%)

Scheme 2. Interrupted Paal-Knorr reaction of the 1,4-dicarbonyl compound **5a** to pyrrole derivative **6**.

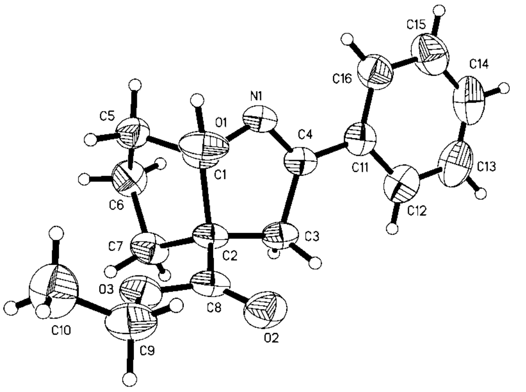


Figure 1. ORTEP view of 3,4-dihydro-2*H*-pyrrole derivative **6** drawn at the 50% probability level.

In summary, 1,4-diketones **5** are readily accessible in a two-step one-pot reaction in 50–87% overall yields. Our synthetic concept, which may be a valuable alternative to other umpolung strategies, combines an oxidative cerium-catalyzed C–C coupling of 1,3-dicarbonyl compounds **1** with styrene (**3**) and a pyridine/AcCl-mediated Kornblum–DeLaMare fragmentation. A follow-up reaction of **5a** with

NH_3 to afford the new dihydro-2*H*-pyrrole derivative **6** demonstrates that 1,4-diketones **5** are suitable precursors for heterocyclic compounds.

Experimental Section

Typical procedure: Styrene (**3**; 2.0 equiv) and the respective 1,3-dicarbonyl compound **1** (1 mmol, 1.0 equiv) were added to a stirred suspension of $CeCl_3{\cdot}7H_2O$ (0.1 equiv) in *i*PrOH (0.65 mL/mmol **1**). After 4 h, more **3** (1.0 equiv) was added, and the reaction mixture was stirred for a further 20 h at room temperature. All volatile materials were removed under vacuum, and the residue was suspended in CH_2Cl_2 (2 mL/mmol **1**). Pyridine (5.0 equiv) and acetyl chloride (6.0 equiv) were added at 0°C, and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was filtered through SiO_2 (petroleum ether/EtOAc 2:1) and subsequently purified by silica-gel column chromatography (petroleum ether/EtOAc 5:1) to give 1,4-diketones **5** as the major products.

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Keywords: dicarbonyl compounds · C–C coupling · cerium · heterocycles · homogeneous catalysis

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[12] CCDC-245445 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).