Organocatalytic Aerobic Oxidative Cleavage of Cyclic 1,2-Diketones

Sivaji Gundala, Claire-Louise Fagan, Eoghan G. Delany, Stephen J. Connon*
Trinity Biomedical Sciences Institute, School of Chemistry, The University of Dublin, Trinity College, Dublin 2, Ireland
Fax +353(1)6712826; E-mail: connons@tcd.ie

Received: 03.05.2013; Accepted after revision: 27.05.2013

Abstract: The first organocatalytic aerobic oxidative cleavage of cyclic 1,2-diketones is reported. The reaction occurs in either aqueous or alcoholic media and is promoted by a simple *N*-heterocyclic carbene catalyst derived from a 1,2,4-triazolium ion. No strong oxidants are required. The application of the process in a one-pot synthesis of a cyclic anhydride is also possible.

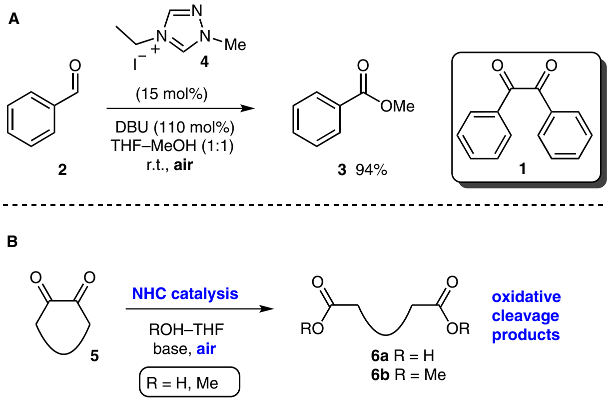
Key words: oxidation, biaryls, carboxylic acids, catalysis, esters

The oxidative cleavage of 1,2-diols is a time-honoured synthetic tool of enormous importance. By contrast, the corresponding oxidative cleavage of 1,2-diketones to yield carboxylic acids has received considerably less attention. There are a number of methods available for this transformation involving the use of stoichiometric oxidants such as Oxone,[1] calcium perchlorate,[2] CuCl/pyridine/O_2,[3] and sodium percarbonate/alkaline H_2O_2.[4,5] The photochemical aerobic oxidation of phenanthrene on silica gel is possible, but yields multiple products.[6]

To the best of our knowledge, no catalytic version of this reaction is known, although a single example of the oxidative esterification of a 1,2-diketone catalysed by dichloroethoxyoxyvanadium in ethanol (under an O_2 atmosphere) has been reported.[7,8]

Very recently, we[9,10] (among others[11,12]) have been engaged in the development of *N*-heterocyclic carbene (NHC)-catalysed oxidative esterification processes involving aldehyde substrates. In the course of these studies, we detected (and confirmed the intermediacy of) benzil (**1**) in the aerobic oxidative esterification of benzaldehyde (**2**) to methylbenzoate (**3**) catalysed by the carbene derived from the triazolium ion **4** in the presence of stoichiometric DBU and methanol (Scheme 1, A).[10,13] This led us to propose that if one exposed a cyclic 1,2-diketone **5** (instead of an aldehyde) to similar conditions it could bring about an organocatalytic oxidative cleavage reaction to give either dicarboxylic acids (*i.e.*, **6a**) or diesters (*i.e.*, **6b**), depending on the protic nucleophile used (Scheme 1, B).

To test this hypothesis, phenanthrene-9,10-dione (**7**) was reacted with either methanol or water in air in the presence of precatalyst **4** and DBU (Table 1). In a 1:1 mixture of THF and MeOH at ambient temperature we were pleased to obtain the ring-opened diester **8**, albeit in low yield (Table 1, entry 1). Increasing the reaction concentration to either 0.5 M or 1.0 M had only marginal influence on efficiency (Table 1, entries 2 and 3), and thus for operational convenience 0.2 M was selected as the concentration of choice for further studies. Increasing the loading of base improved the product yield to 41% (Table 1, entry 4), however, the use of elevated reaction temperatures had no effect (Table 1, entries 5 and 6). It appears that diacid formation (these reactions are carried out in air, so the intervention of adventitious water is difficult to prevent) is problematic in these experiments.



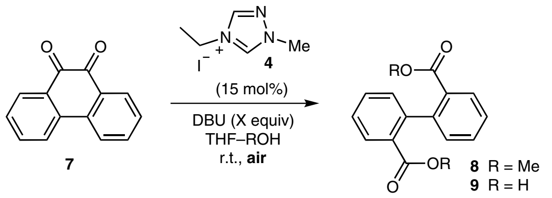
Scheme 1 A: A previously observed oxidative esterification reaction of benzaldehyde involving the intermediacy of benzyl. B: The proposed organocatalytic oxidative cleavage of α-diones.

We next investigated the corresponding transformations involving water as the nucleophile. Speculating that reactions involving THF–H_2O in a 1:1 ratio would not be optimal from both carbene-generation and substrate-solubility standpoints, we began by retaining the conditions previously used in the methanolysis experiments in a 5:1 THF–H_2O mixture. Under these conditions the diacid **9** was generated in low yield (Table 1, entry 7). Further reduction in the contribution of the protic solvent allowed the eventual preparation of the cleaved diacid in 83% yield in a 20:1 THF–H_2O solvent mixture (Table 1, entries 8 and 9). The use of 2.2 equivalents of DBU is critical for the success of the organocatalytic cleavage reaction: A repeat of the reaction with less base resulted in lower product yield (Table 1, entry 10). It would seem likely that the requirement for elevated base loadings is related to the need to prevent protonation of the carbene catalyst by the dicarboxylic acid product.[14]

With an efficient protocol in hand, our attention turned to substrate scope (Table 2). While the aqueous protocol leading to carboxylic acids proved the most effective in

SYNLETT 2013, 24, 1225–1228
Advanced online publication: 04.06.2013
DOI: 10.1055/s-0033-1338494; Art ID: ST-2013-R0416-C

Table 1 NHC-Mediated Oxidative Cleavage of **7**: Preliminary Experiments



Entry	Product	X	Temp	Concn (M)	THF/ROH	Yield (%)[a]
1	**8**	1.1	r.t.	0.2	1:1	26
2	**8**	1.1	r.t.	0.5	1:1	28
3	**8**	1.1	r.t.	1.0	1:1	31
4	**8**	2.2	r.t.	0.2	1:1	41
5	**8**	2.2	30 °C	0.2	1:1	41
6	**8**	2.2	40 °C	0.2	1:1	41
7	**9**	2.2	r.t.	0.2	5:1	12
8	**9**	2.2	r.t.	0.2	10:1	24
9	**9**	2.2	r.t.	0.2	20:1	83
10	**9**	1.1	r.t.	0.2	20:1	41

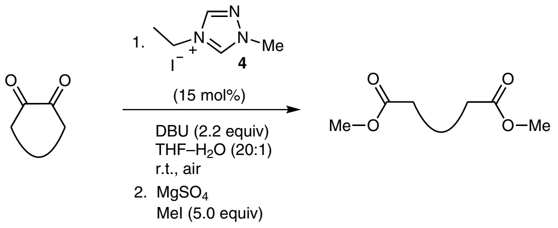
[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.

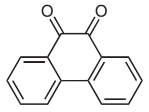
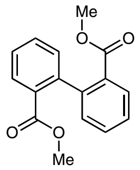
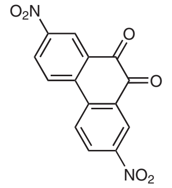
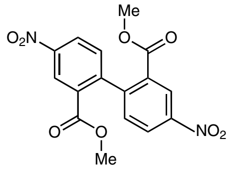
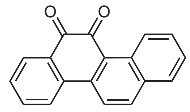
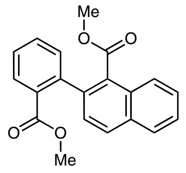
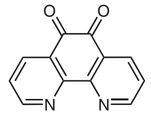
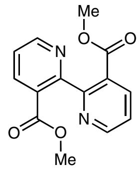
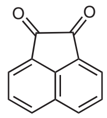
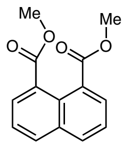
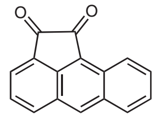
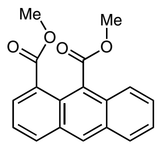
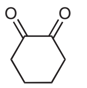
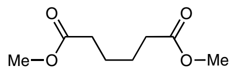
our preliminary studies, we were also interested in extending the methodology to oxidative cleavage to produce diesters. Thus, in these reactions $MgSO_4$ was added to sequester the water from the solvent after the C–C bond-breaking processes involving **7** and **10**–**15** were complete, and the dicarboxylate products were then esterified *via* the addition of MeI.

Under these conditions, **7** could be converted into the biaryldiester **8** in high yield (Table 2, entry 1). The dinitro substrate analogue **10** also underwent smooth transformation to **16** (Table 2, entry 2). Unsymmetrical quinones also undergo the reaction: oxidative cleavage of the chrysene derivative **11** provided **17** with comparable efficiency (Table 2, entry 3). Gratifyingly, the phenanthroline-derived dione **12** produced the bipyridyl diester **18** (of synthetic potential as a starting material for transition-metal ligand synthesis) in 70% yield (Table 2, entry 4). In this instance esterification with an electrophile introduces a chemoselectivity problem, which is readily circumvented through Fischer esterification with MeOH.

Exposure of the tricyclic quinone **13** to the reaction conditions resulted in the isolation of the relatively strained 1,8-naphthalene dicarboxylic acid dimethyl ester (**19**) in slightly reduced yield (Table 2, entry 5), while the corresponding anthrancene derivative **20** could be similarly prepared from **14** in almost identical yield (Table 2, entry 6). Perhaps unsurprisingly (under these basic conditions), oxidative cleavage of the enolisable 1,2-dione **15** proved more challenging: this reaction was not clean, however, the acyclic diester **21** could be isolated in low (yet appreciable) yield (Table 2, entry 7).

Table 2 Substrate Scope

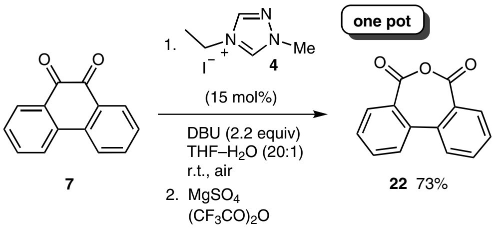


Entry	1,2-Diketone	Product	Yield (%)[a]
1	 **7**	 **8**	82
2	 **10**	 **16**	80
3	 **11**	 **17**	83
4[b]	 **12**	 **18**	70
5	 **13**	 **19**	66
6	 **14**	 **20**	68
7	 **15**	 **21**	18

[a] Isolated yield.

[b] Alkylative esterification replaced with an *in situ* Fischer esterification with MeOH and H_2SO_4 (see Supporting Information for details).

We were also able to exploit this organocatalytic process in the one-pot synthesis of an anhydride from a 1,2-dione (Scheme 2). The α-dione **7** was first oxidatively cleaved in the presence of the carbene derived from **4** in an aqueous medium. When this reaction was complete, addition of magnesium sulfate and trifluoroacetic anhydride led to the cyclisation of the *in situ* formed diacid **9** to afford the anhydride **22** in good isolated yield. To the best of our knowledge, such a one-pot sequence starting from a 1,2-diketone is unprecedented in the literature.



Scheme 2 A novel one-pot oxidative cleavage–cyclisation sequence: chemoselective conversion of a 1,2-diketone into an anhydride

In our previous work in the oxidative esterification of benzaldehyde,[10] we proposed a complex mechanism (supported by, inter alia, both the spectroscopic observation of intermediates and the results of competition experiments) whereby benzil (formed from the aerobic oxidation of benzoin in basic media) can be attacked by both the carbene and the alcohol nucleophile to give an adduct which collapses to form the Breslow intermediate and the carboxylic acid ester. In the absence of evidence to the contrary, these distinct but related oxidative cleavage transformations could be potentially rationalised in a similar fashion. An investigation to probe the mechanism of the oxidative cleavage is under way.

In summary, a new, organocatalytic oxidative cleavage reaction of cyclic 1,2-diones has been developed. The use of water as the nucleophile allows the generation of a diacid in high yield under mild conditions. While the corresponding methanolytic transformation occurs, it is less productive. Coupling an *in situ* esterification with the more efficient acid-generating reaction allows the formation of esters in good yields from a variety of cyclic diketones. The process is promoted by an NHC derived from a readily prepared, simple triazolium ion precursor, and no strong stoichiometric oxidants are required. If trifluoroacetic acid and a drying agent are added to the reaction mixture after formation oxidative cleavage, cyclisation to form the cyclic anhydride occurs in good overall yield.[15]

Acknowledgment

We thank Science Foundation Ireland, The Irish Research Council and the European Research Council for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(14) It is unclear at this juncture why the reactions involving MeOH are reproducibly less efficient than their variants in aqueous media. Investigations into this phenomenon are under way.

(15) **General Procedure for the Esterification of Cyclic Diketones**

To a 25 mL vial equipped with a magnetic stirring bar was charged the triazolium precatalyst **4** (18 mg, 0.07 mmol, 15 mol%). Dry THF (1.25 mL) and deionised H_2O (62.5 μL) were added. DBU (170.0 μL, 1.10 mmol, 220 mol%) was added, and the solution was stirred for 2 min. The aromatic diketone (0.50 mmol) was then added. The vessel was sealed with a plastic lid perforated by 4 holes (ca. 2 mm in diameter). After stirring for 20 h at r.t., $MgSO_4$ (1.40 mmol, 170 mg) and 5.0 equiv of MeI were added, and the resulting mixture was stirred for 12 h. The solvent was then removed in vacuo, and the resulting residue was subjected to flash chromatography to yield the diester product.

Dimethyl Biphenyl-2,2′-dicarboxylate (8)

Prepared according to the general procedure using phenanthrene-9,10-dione (**7**, 104.11 mg, 0.50 mmol). Purified via flash chromatography (*n*-hexane–EtOAc, 9:1), 110 mg (82%) as a pale yellow solid; mp 73–75 °C (lit.[16] 74–75 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.6 Hz, 2 H), 7.51 (app. t, 2 H), 7.40 (app. t, 2 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 3.59 (s, 6 H). HRMS: (ESI$^+$): *m/z* calcd for $C_{16}H_{15}O_4$: 271.0970; found: 271.0984.

Dimethyl 4,4′-Dinitrobiphenyl-2,2′-dicarboxylate (16)

Prepared according to the general procedure using 2,7-dinitro-9,10-phenanthrenequinone (**10**, 149.10 mg, 0.50 mmol). Purified via flash chromatography (*n*-hexane–EtOAc, 9:1), 144 mg (80%) as a white solid; mp 178–180 °C (lit.[17] 182–183 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 2.3 Hz, 2 H), 8.45 (dd, *J* = 2.3, 8.5 Hz, 2 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 3.76 (s, 6 H).

Dimethyl Naphthalene-1,8-dicarboxylate (19)

Prepared according to the general procedure using **13** (91.02 mg, 0.50 mmol). Purified via flash chromatography (*n*-hexane–EtOAc, 9:1), 80 mg (66%) as a pale yellow solid; mp 100–104 °C (lit.[18] 102–103 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 4 H), 7.53 (app t, 2 H), 3.90 (s, 6 H). HRMS: (ESI$^+$): *m/z* calcd for $C_{14}H_{13}O_4$: 245.0814; found: 245.0817.

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