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Exploring the *one-pot* C-acylation of cyclic 1,3-diones with unactivated carboxylic acid

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ABSTRACT

The use of DCC, triethylamine, and 4-dimethylaminopyridine in dichloromethane provides a general and standard *one-pot* procedure for the C-acylation of cyclic 1,3-diones with a wide range of carboxylic acids, giving rise to β-triketones in good to excellent yields.

The cyclic β-triketone moiety,[1] also called 2-acyl-cycloalkane-1,3-dione, is part of the skeleton of diverse natural compounds, such as **1**[2] and **2**,[3] with a wide range of biological activities such as antibiotic, antibacterial, and anticancer properties (Fig. 1). Moreover, hundreds of patents[4] describe herbicides containing the β-triketone structure like compound **3**,[5] or deriving from it like tralkoxydim **4**.[6] By analogy with 1,3,5-triketonates,[7] β-triketones are also attractive as they can be envisioned as tridentate ligands for metals. Finally, they can be used as building blocks in the synthesis of various heterocycles.[1] The existence of β-triketones in a completely enolized form explains the possibility of synthesizing such a wide range of heterocycles.

Three methods are reported in the literature for the preparation of 2-acyl-cycloalkane-1,3-dione. The first one consists of exhaustive methylation of phloroglucinol derivatives giving rise to β-triketones moiety.[1] In the more general second route, representing the vast majority of existing protocols, 1,3-diones are initially O-acylated with acyl chloride, anhydrides or carboxylic acid, and in a second step a catalyzed O–C isomerization led to the β-triketone.[1] Various catalysts were employed in this two-step process such as Lewis acids ($AlCl_3$, $ZnCl_2$), bases (imidazole, 4-DMAP), and heat.[1] Alternatively, dehydration reagents such as dicyclohexylcarbodiimide (DCC),[8] chloroamidinium salts,[9] and 1,1-carbonyldiimidazole[10] can also be used for the C-acylation of 1,3-diones with carboxylic acids. The preparation of 2-acyl-cyclohexane-1,3-diones can also be performed under more drastic conditions by using stoichiometric amount of strong bases, such as barium hydride in tetrahydrofuran under reflux, from 1,3-diones and anhydrides.[11] Finally, only recently, Zhou developed the first catalytic C-acylation, of mostly acyclic 1,3-dicarbonyl compounds, however, using $SmCl_3$ as the catalyst, and acyl chlorides as acyl donors.[12]

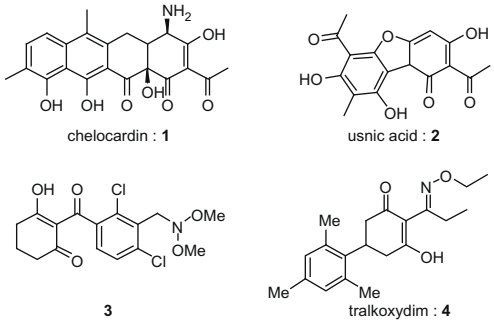

Figure 1. Biologically active compounds and herbicides containing the β-triketone moiety.

In the course of our studies toward the total synthesis of a natural product, we were interested in a *one-pot* C-acylation procedure of cyclic 1,3-diones, with functionalized carboxylic acid as the acyl donor. However, we found that this reaction performed with unactivated carboxylic acids has received scant attention,[8] and no general standard procedure was known for these substrates. Moreover, some reports have also mentioned the difficulties and failures to perform such transformation that needs most of the time specific optimization conditions and much more

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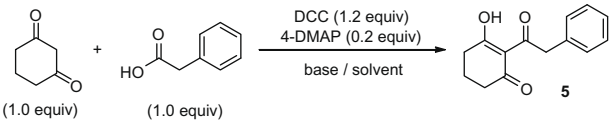
activated precursors such as acyl cyanide.[13,14] Only few reports, most of which are patents, include the acylation of 1,3-diones with unactivated carboxylic acids using DCC as the coupling agent.[5,8,9,15] Moreover, drastic conditions are generally used and the reported procedures always differ from one to the other. The use of DCC was also found for C-acylation of tetronic acids, Meldrum's acids, and β-keto-δ-valerolactones with carboxylic acids,[8,10,16] however, these substrates exhibit reactivities that differ from cycloalkane-1,3-diones. To the best of our knowledge, a general protocol for the preparation of 2-acyl-cyclohexane-1,3-diones using unactivated organic acid as the acyl donor has not been reported so far. As a consequence, the development of an efficient *one-pot* standard procedure to access cyclic β-triketones from 1,3-cyclic diketone and unactivated carboxylic acid is desirable. In this Letter, we describe an efficient simple *one-pot* method for the synthesis of 2-acyl-cyclohexane-1,3-diones with a broad scope of application under mild conditions.

The standard procedure was first optimized for the C-acylation of cyclohexane-1,3-dione with phenylacetic acid to obtain 2-(2-phenylacetyl)cyclohexane-1,3-dione **5** (Table 1). *One-pot* reactions were done by using DCC and a catalytic amount of 4-DMAP, the best catalyst reported for the O–C isomerization. Firstly, we tested triethylamine and after 3 h of reaction, **5** was obtained in 29% along with some O-acylated product in 62%, the kinetic product (entry 1). This result proved that the O–C isomerization was not complete and performing the reaction during 14 h permitted to increase the yield to 88% (entry 2). Moreover, a control experiment without 4-DMAP led to the exclusive formation of the O-acylated product, demonstrating the role of 4-DMAP in the O–C isomerization process. Two other bases, diisopropylethylamine and potassium carbonate, were also tested without any improvement (entries 3 and 4). Acetonitrile and 1,2-dichloroethane were also tried as potential solvents for the reaction. In MeCN, the yield of **5** was slightly decreased to 72% (entry 5) compared to DCM (Entry 2). DCE was relatively equivalent to DCM and **5** was obtained in a comparable yield (entry 6).

Finally, with the aim to get a quantitative yield while shortening the reaction time, we decided to exploit the benefit of microwave irradiation. Unfortunately, the yield of **5** was not better (entry 7). The screening of the reaction parameters allowed identifying the optimized conditions for the synthesis of β-triketones: DCC (1.2 equiv), 4-DMAP (0.2 equiv), and Et_3N (1.2 equiv) in DCM at room temperature for 14 h. We next studied the generality of the procedure and investigated the scope of the reaction for a panel of cycloalkane-1,3-dione, which were reacted with 2-*meta*-tolylacetic acid, as a model unactivated acid, under the optimized conditions (Table 2). As a general trend, all the C-acylations[17] proceeded smoothly and without any complications for the preparation of C6-membered β-triketones. In most of the cases, they

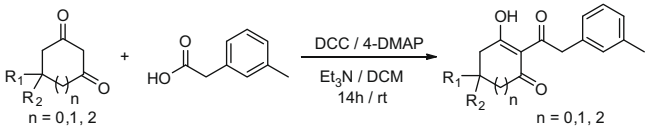
Table 1
Optimization of the conditions on the synthesis of **5**

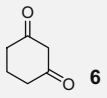
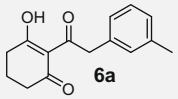
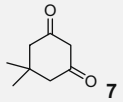
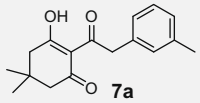
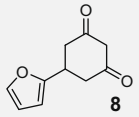
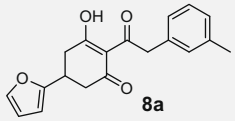
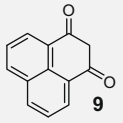
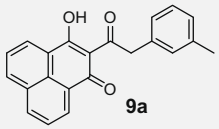
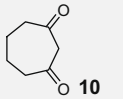
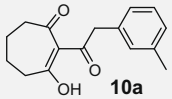
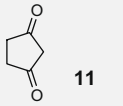
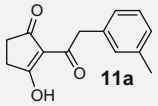
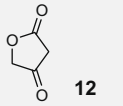
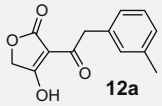


Entry	Base (1.2 equiv)	Solvent	Time	Temperature	Yield[a] (%)
1	Et_3N	DCM	1.5 h	rt	29
2	Et_3N	DCM	14 h	rt	88
3	DIPEA	DCM	14 h	rt	69
4	K_2CO_3	DCM	14 h	rt	57
5	Et_3N	MeCN	14 h	rt	72
6	Et_3N	DCE	14 h	rt	83
7	Et_3N	DCM	0.1 h	90 °C[b]	73

[a] Isolated yields.
[b] Reaction performed under microwave irradiation.

Table 2
Exploring the scope of the reaction on various cyclic 1,3-diones



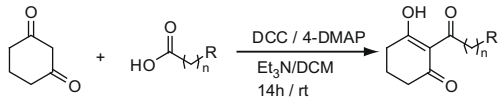
Entry	1,3-Dione	Product	Yield (%)
1	 **6**	 **6a**	85
2	 **7**	 **7a**	100
3	 **8**	 **8a**	100
4	 **9**	 **9a**	86
5	 **10**	 **10a**	37
6	 **11**	 **11a**	/
7	 **12**	 **12a**	82

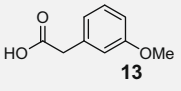
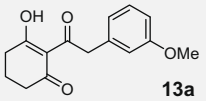
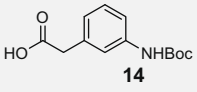
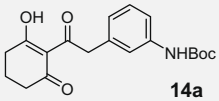
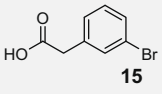
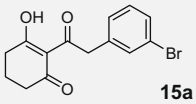
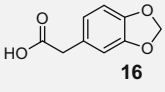
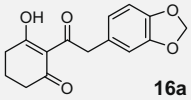
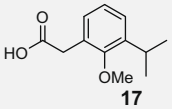
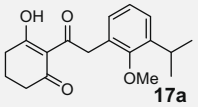
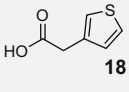
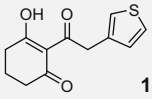
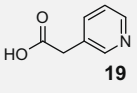
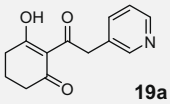
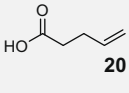
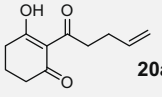
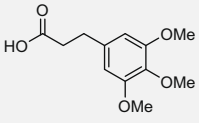
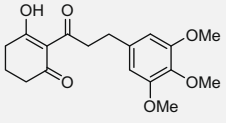
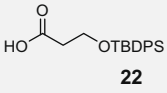
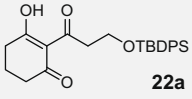
were obtained in good to excellent yields. 5-dimethyl and 5-furyl-cyclohexan-1,3-diones **7** and **8** behaved similar to **6** (entry 1), giving quantitatively β-triketones **7a** and **8a** (entries 2 and 3). 3-hydroxy-1*H*-phenalen-1-one **9** led to the formation of **9a** in a good yield of 86% (entry 4). The methodology was next extended to 7- and 5-membered ring 1,3-diketone. The reaction proceeded moderately with cycloheptan-1,3-dione **10**, giving **10a** in 37% yield (entry 5).

This limitation is ascribed to the low reactivity of **10** in DCM and increasing the temperature of the reaction did not permit to get a better yield. No reaction occurred with the cyclopentan-1,3-dione **11** due to a significant lack of reactivity (entry 6), while tetronic acid **12** provided efficiently **12a** in 82% of yield (entry 7). These results demonstrate that the ring size of the cyclic 1,3-diones has a significant influence on the C-acylation efficiency. While C6-membered substrates afforded the β-triketones satisfactorily, C7-membered 1,3-dione was less reactive and C5-membered 1,3-dione did not react at all. We were then interested in exploring the reactivity of different carboxylic acid substrates in the reaction with cyclohexane-1,3-dione (Table 3). Firstly, we studied the influence of the substitution on the aromatic part of the acidic component. To our delight, acids **13**, **14**, and **15** gave the corresponding β-triketones **13a**, **14a**, and **15a** in good yields (84–90%) (entries 1, 2, and 3), in accordance with the previous result for **6a**.

Increasing the number of substituents did not affect the reaction. Indeed, acids **16** and **17** led to β-triketones **16a** and **17a**, respectively, in good yields (entries 4 and 5). It is important to note that the reaction conditions tolerate various functionalities such as

Table 3
Exploring the scope of the reaction with various acids



Entry	Carboxylic acid	Product	Yield (%)
1	 **13**	 **13a**	85
2	 **14**	 **14a**	90
3	 **15**	 **15a**	84
4	 **16**	 **16a**	74
5	 **17**	 **17a**	82
6	 **18**	 **18a**	63
7	 **19**	 **19a**	/
8	 **20**	 **20a**	/
9	 **21**	 **21a**	22
10	 **22**	 **22a**	81

bromoaryl, methylether, protected amine, and acetal. 2-(thiophen-3-yl)acetic acid **18** gave also **18a** in an acceptable yield of 63% (entry 6), while 2-(pyridin-3-yl)acetic acid **19** or pent-4-enoic acid **20**, afforded complex reaction mixtures (entries 7 and 8). In general, we observed that the presence of a nitrogen-containing heterocycle or an olefin moiety on the carboxylic acid led to the formation of several by-products difficult to identify. Finally, other functionalized carboxylic acids such as **21** and **22** were tested (entries 9 and 10). The low yield obtained with 3-(3,4,5-trimethoxyphenyl)propanoic acid **21** for the preparation of **21a** could be ascribed to its low solubility in DCM, and increasing the temperature did not improve the efficiency of the reaction. Interestingly, 3-(*tert*-butyldiphenylsilyloxy)propanoic acid **22** gave expected **22a** in 81%, demonstrating the compatibility of silyl protected alcohol under our mild optimized conditions.

In summary, we report herein the first general procedure for the *one-pot* C-acylation of cyclic 1,3-diones with unactivated carboxylic acid, using DCC and a catalytic amount of 4-DMAP, in DCM at room temperature. Scopes and limitations were explored by varying the 1,3-dione moiety as well as the carboxylic acid substrate. From these studies, we can conclude that our procedure has broad scope of application and tolerates many functional groups. Under this optimal procedure, a series of 2-acyl-1,3-cycloalkan-1,3-diones were prepared in good to excellent yields.

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Supplementary data

Supplementary data (general methods, general procedure and data, ^{1}H NMR and ^{13}C NMR spectra of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.111.

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17. *Typical experimental procedure*: The carboxylic acid (2 mmol), DCC (2.40 mmol), Et_3N (2.40 mmol), and 4-DMAP (0.2 mmol) were added to a solution of cyclic 1,3-diones (2 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred for 14 h at room temperature. After dilution with DCM (10 mL) and filtration of the precipitate, aqueous HCl 1 M was added to the filtrate. The aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel and characterized by ^{1}H, ^{13}C, IR, and HRMS analyses.