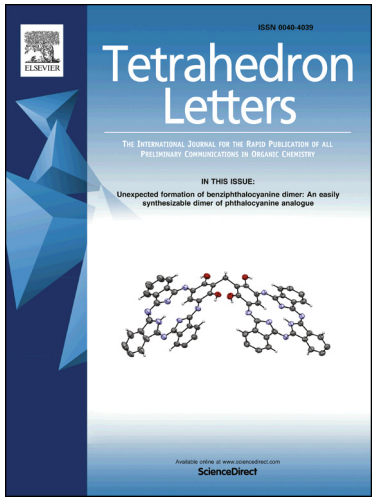

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Efficient cyclodehydration of dicarboxylic acids with oxalyl chloride

Grigory Kantin,[a] Evgeny Chupakhin,[b] Dmitry Dar'in[a] and Mikhail Krasavin [a, b, *]

[a] *Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation*

[b] *Immanuel Kant Baltic Federal University, Kaliningrad, 236016 Russian Federation*

* Corresponding author; phone: + 7 931 3617872, fax: +7 812 428 6939.
E-mail: m.krasavin@spbu.ru

Abstract

Literature examples illustrating the use of oxalyl chloride to prepare dicarboxylic acid anhydrides are surprisingly limited. At the same time, we have discovered a method involving the use of this readily available reagent which allowed the preparation of novel cyclic anhydrides where other, more conventional, methods had failed. Herein, we demonstrate that the method is applicable to a wide diversity of substrates, delivers good to excellent yields of cyclic anhydrides without chromatographic purification and can be considered a synthetic tool of choice whenever dicarboxylic acid cyclodehydration is required.

Keywords

Dicarboxylic acid cyclodehydration, cyclic anhydride, oxalyl chloride, oligomerization side-reaction, *N,N*-dimethyl formamide catalyst.

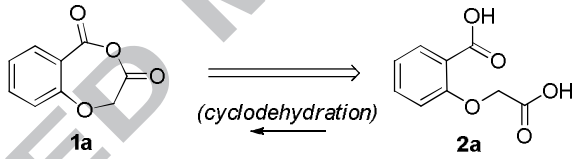
One in need of transforming dicarboxylic acids into the corresponding cyclic anhydrides has a vast arsenal of dehydrating agents whose use is amply exemplified in the literature. These include acetic anhydride,[1] trifluoroacetic anhydride,[2] Boc_2O,[3] carbodiimides (e. g. EDC[4] or DCC[5]), 1,1′-carbonyldiimidazole (CDI),[6] thionyl chloride,[7] phosphorus (V) oxide,[8] cyanuric chloride[9] and many others. However, when these reagents fail to trigger the desired cyclodehydration event, which usually results in the formation of oligomeric product mixtures,[10] a workable alternative must be found among less popular dehydrating agents.

As part of our research program directed towards the design of novel cyclic anhydrides employable in the Castagnoli-Cushman reaction (CCR),[11] particularly after it was reported by Ryabukhin and co-workers[10] and ourselves[12] that the CCR is capable of delivering ε-lactams

from seven-membered cyclic anhydrides, we required hitherto unknown 2*H*-benzo[*e*][1,4]dioxepine-3,5-dione (**1a**) which we hoped to prepare *via* the cyclodehydration of the known[13] dicarboxylic acid **2a** (Fig. 1). However, when the above-mentioned cyclodehydration protocols were attempted and failed (delivering predominantly linear, dehydrative homo-oligomerization products), we sought to screen other, less explored dehydrating agents. Herein, we report the convenient application of oxalyl chloride to prepare chemically diverse cyclic anhydrides from dicarboxylic acids.

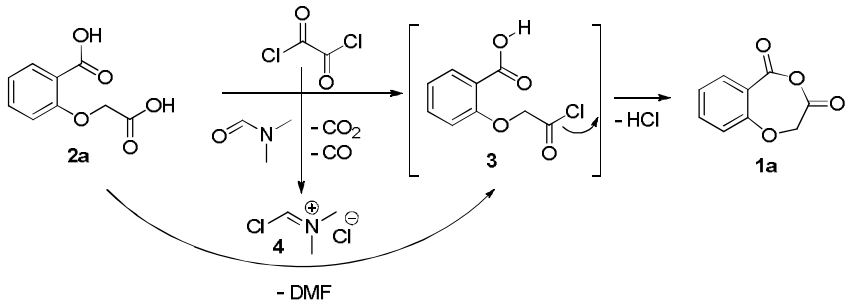
Upon reviewing the literature, we were surprised to find that the employment of oxalyl chloride to dehydrate mono- or dicarboxylic acids was rather limited. Following an example used to dehydrate benzoic acids published nearly 100 years ago,[14] we identified only two other examples: cyclodehydration of fumaric acid (with intermittent addition of hydrochloric acid to form the chlorosuccinic acid motif)[15] and preparation of *N*-benzyliminodiacetic anhydride from the respective dicarboxylic acid.[16] The latter example prompted us to test the applicability of oxalyl chloride as a dehydrating agent for the preparation of **1a** from **2a**.

Figure 1. Cyclic anhydride **1a** that failed to form upon cyclodehydration of **2a** using most common protocols.



To our delight, treatment of **2a** with oxalyl chloride (1.2 equiv.) in dry toluene for 10 h (with periodic ^{1}H NMR analysis of reaction mixture aliquots) led to the complete conversion to **1a**. Since we expected the conversion of **2a→1a** to involve the formation of monoacyl chloride **3**, we tested the same reaction in presence of catalytic DMF and found that it led to reaction completion in only 3 h, likely due to the known[17] acceleration mechanism involving formation of the Vilsmeier-Haack reagent (**4**) which is the acting catalytic species (Fig. 2).

Figure 2. Likely mechanism of **2a→1a** conversion.



Following simple evaporation of toluene, analytically pure **1a** was obtained in 99% yield. Notably, the same reaction attempted at reflux in dichloromethane, chlorobenzene or 1,2-dichloroethane led to much poorer (<50%) conversions as evidenced by ^{1}H NMR analysis of the reaction mixture aliquots.

Encouraged by these findings, we applied the same protocol (Scheme 1)[18] to a range of diverse dicarboxylic acids **2b-v** and found it to deliver good to excellent yields of the respective cyclic anhydrides **1b-v** (Table 1).[19] The identity of all known anhydrides **1** was established using ^{1}H NMR spectroscopy and high-resolution mass-spectrometry (HRMS). All newly described anhydrides **1** were fully characterized, including ^{13}C NMR spectroscopy (ESI). In some cases, electrospray ionization used in obtaining HRMS data did not allow detection of the molecular ion of poorly ionizable compounds **1**. In these cases, HRMS was run in methanol and the exact molecular weight was reported for the respective methyl monoester, i. e. the ring-opening product of anhydride **1** with methanol (ESI).

Scheme 1. Cyclodehydration of dicarboxylic acids **2a-v-**.

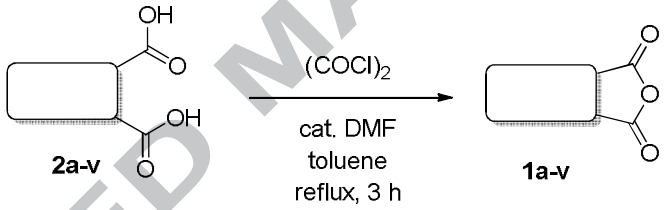
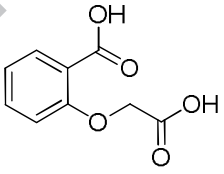
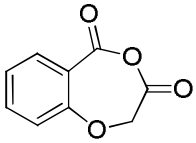
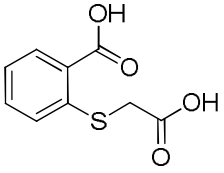
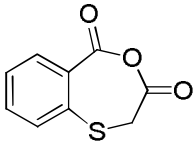
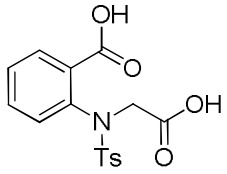
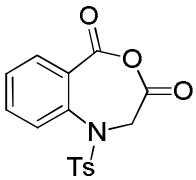
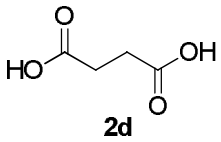
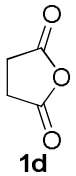
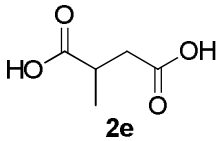
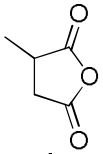
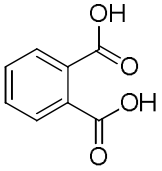
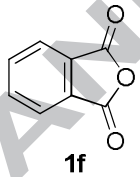
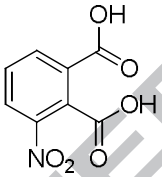
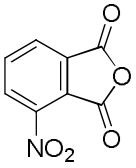
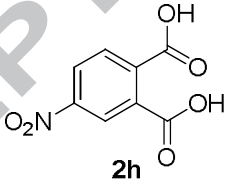
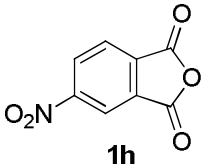
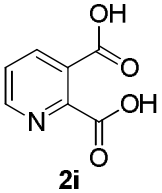
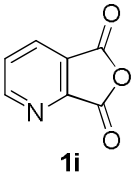
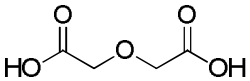
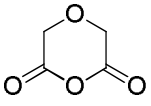
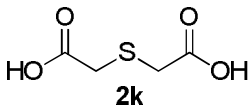
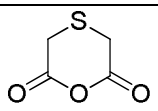
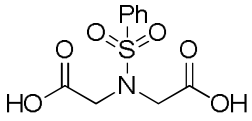
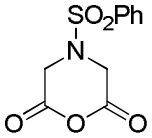
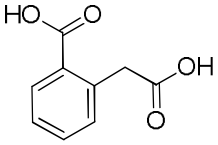
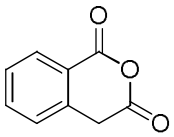
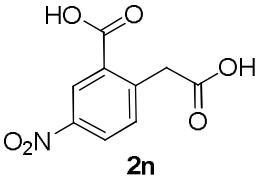
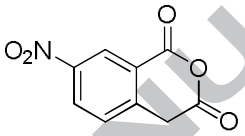
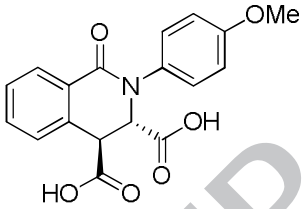
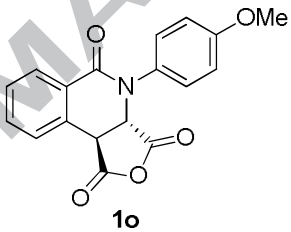
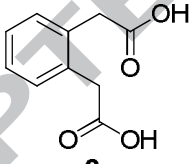
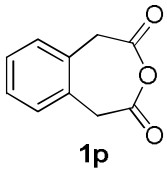
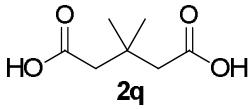
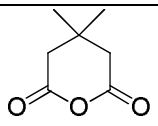
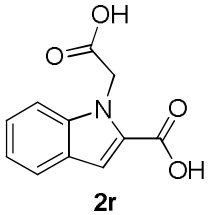
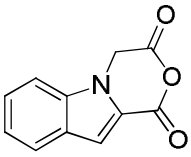
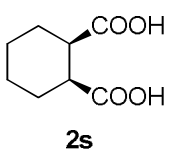
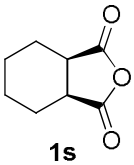
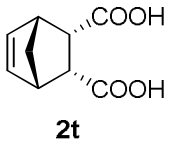
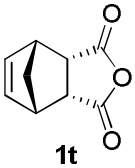
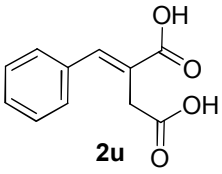
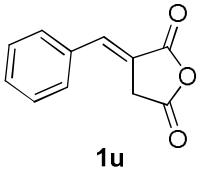
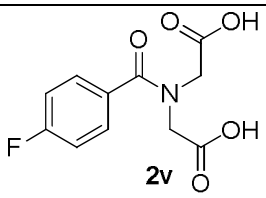
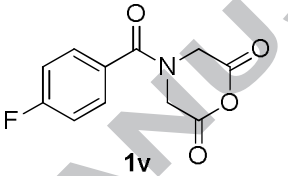


Table 1. Results of cyclodehydration of dicarboxylic acids **2a-v**.[a]

Starting material (**2**)	Product (**1**)	Isolated yield **1** (%)
 **2a**	 **1a**	99
 **2b**	 **1b**	62

 **2c**	 **1c**	81
 **2d**	 **1d**	96
 **2e**	 **1e**	96
 **2f**	 **1f**	93
 **2g**	 **1g**	88
 **2h**	 **1h**	88
 **2i**	 **1i**	91
 **2j**	 **1j**	93

 **2k**	 **1k**	91
 **2l**	 **1l**	85
 **2m**	 **1m**	88
 **2n**	 **1n**	44
 **2o**	 **1o**	80
 **2p**	 **1p**	81
 **2q**	 **1q**	70
 **2r**	 **1r**	72

 **2s**	 **1s**	85
 **2t**	 **1t**	83
 **2u**	 **1u**	79
 **2v**	 **1v**	68

[a] Reagents and conditions: Dicarboxylic acid **2** (1.0 mmol), oxalyl chloride (1.2 mmol), DMF (1 drop), toluene, reflux, 3 h.

The data shown in Table 1 clearly demonstrate the general applicability of the new cyclodehydration protocol to a wide range of structurally diverse substrates. In most cases, particularly when the product yield was substantially lower than quantitative (e. g. **1b**, **1n**, **1u**), substantial tar formation was noted and attributed to the concomitant formation of oligomeric products from intermolecular dehydration of the starting material. In case of **1n**, the increased acidity of the methylene group could possibly be responsible for degradation of the product due to self-condensation.

In summary, we have identified a workable cyclodehydration protocol for dicarboxylic acids and applied it toward the synthesis of a set of structurally diverse cyclic anhydrides. The method provides high yields of the target products and clearly complements other, more established protocols, particularly when those fail to provide the desired reaction outcome (as was demonstrated for the conversion of **2a→1a** at the onset of this study).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/xxx.

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18. General procedure for the preparation of cyclic anhydrides **1a-v**: Dicarboxylic acid **2** (1 mmol) and oxalyl chloride (1.2 mmol) were combined in dry toluene (5 mL) and a drop of

freshly distilled DMF was added. The reaction vessel was purged with argon and the reaction was heated at reflux with stirring for 3 h. The stirring was stopped and the toluene solution was decanted from the oily residue and filtered. Evaporation of the volatiles provided the analytically pure target product which, if necessary, was transformed into the crystalline form by trituration with diethyl ether. In some cases (see ESI) additional crystallization or trituration with a 1:2 v/v hexane-toluene mixture was used.

19. Characterization data of representative new cyclic anhydrides (for more comprehensive data – see ESI): **1a** - white crystalline solid, mp = 68.5 – 70.0 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.7 Hz, 1H, C<u>H</u>(Ar)), 7.70-7.57 (m, 1H, C<u>H</u>(Ar)), 7.34-7.25 (m, 1H, C<u>H</u>(Ar)), 7.19 (dd, *J* = 8.4, 0.8 Hz, 1H, C<u>H</u>(Ar)), 4.84 (s, 2H, C<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 162.4, 159.6, 158.8, 136.5, 134.5, 124.5, 120.5, 117.7, 71.1; HRMS (ESI), *m/z* calcd for $C_{10}H_{10}NaO_5$ $[M+CH_3OH+Na]^+$ 233.0420, found 233.0426; **1o** - white crystals, mp 204.5 – 207.0 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.32 (d, *J* = 7.6 Hz, 1H, C<u>H</u>(Ar)), 7.73-7.65 (m, 2H, C<u>H</u>(Ar)), 7.63-7.56 (m, 1H, C<u>H</u>(Ar)), 7.51-7.44 (m, 2H, C<u>H</u>(Ar)), 7.03-6.96 (m, 2H, C<u>H</u>(Ar)), 5.23 (d, *J* = 8.7 Hz, 1H, C<u>H</u>(CO_2H)), 4.82 (d, *J* = 8.7 Hz, 1H, C<u>H</u>(CO_2H)), 3.86 (s, 3H, C<u>H</u>$_3$O); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 168.8, 166.6, 161.2, 159.3, 133.7, 133.6, 130.3, 130.1, 128.5, 127.9, 127.8, 126.4, 114.8, 61.5, 55.5, 43.8; HRMS (ESI), *m/z* calcd for $C_{19}H_{17}NNaO_6$ $[M+CH_3OH+Na]^+$ 378.0948, found 378.0953; calcd for $C_{18}H_{13}NaO_5$ $[M+Na]^+$ 346.0686, found 346.0701; **1r** - light brown crystals, mp 218.0-222.0 °C melting with decomposition; ^{1}H NMR (400 MHz, *d*$_6$-acetone) δ ppm 7.83 (d, *J* = 7.93 Hz, 1H, CH(Ar)), 7.64 (d, *J* = 8.24 Hz, 1H, CH(Ar)), 7.57 (s, 1H, CH(Ar)), 7.49 (t, *J* = 7.63 Hz, 1H, CH(Ar)), 7.27 (t, *J* = 7.48 Hz, 1H, CH(Ar)), 5.43 (s, 2H, CH_2); ^{13}C NMR (101 MHz, *d*$_6$-acetone) δ ppm 162.7, 153.9, 137.2, 127.3, 126.6, 123.1, 122.1, 120.1, 110.9, 110.1, 44.4; HRMS (ESI), *m/z* calcd for $C_{12}H_{11}NNaO_4$ $[M+CH_3OH+Na]^+$ 256.0580, found 256.0585.

- Oxalyl chloride promotes cyclodehydration of dicarboxylic acids.
- DMF accelerates the reaction, suggesting intermediacy of a monoacyl chloride.
- The method can be applied to a wide range of structurally diverse carboxylic acids.

Efficient cyclodehydration of dicarboxylic acids with oxalyl chloride

Grigory Kantin, Evgeny Chupakhin, Dmitry Dar'in and Mikhail Krasavin*