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Metal-free oxidative self-coupling of aldehydes or alcohols to symmetric carboxylic anhydrides

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ABSTRACT

A metal-free synthesis of symmetrical anhydrides has been developed starting from aldehydes, both aliphatic and aromatic or primary benzylic alcohols. The reaction occurs at room temperature and makes use of trichloroisocyanuric acid (TCCA) as an oxidant providing the desired carboxylic anhydrides in satisfactory yields.

Introduction

Carboxylic anhydrides are an important class of very reactive organic compounds and, due to their reactivity find many applications as intermediates in organic synthesis, especially in the preparation of peptides and drugs. Classical syntheses of carboxylic anhydrides involve the treatment of carboxylic acids with dehydrative coupling agents, such as phosgene,[1] thionyl chloride,[2] sulfonyl chloride,[3] phosphoranes,[4] isocyanates,[5] 1,3,5-triazines[6] and carbodiimides.[7] Due to many drawbacks inherent in these traditional procedures,[8] recently many efforts have been directed to find alternative approaches. A rising approach involves the use of different starting materials such as aldehydes. The first example (path a, Scheme 1) of symmetric carboxylic anhydrides synthesis from aromatic aldehydes was proposed by Patel and co-workers,[9] and makes use of *tert*-Butylhydroperoxide (TBHP) as an oxidant, nano CuO as a catalyst and occurs at 120 °C for 5 h. Very recently other syntheses of symmetric anhydrides from aldehydes, both copper-catalyzed (paths b and d Scheme 1) and metal-free (paths c and e Scheme 1) were reported in literature.[10] These methodologies make use of TBHP as an oxidant and, with the exception of Ray's paper (path d, Scheme 1), occur at elevated temperatures. The major drawback related to earlier methodologies is their restricted reaction scope: only few aromatic aldehydes with a limited number of substituent are compatible with these procedures giving often the desired anhydrides in poor yields. In particular, in relation to our recently reported oxidative cross-coupling synthesis of carboxylic anhydrides,[11] we have tested the possibility of transforming aldehydes into symmetrical carboxylic anhydrides by an oxidative self-coupling procedure.

This approach is a convenient and efficient way to form new bond with high atom efficiency, minimization of by-product formation and reduction of the number of steps required. We chose to use trichloroisocyanuric acid (TCCA) as an oxidizing agent by virtue of its low cost, its commercial availability and low toxicity. We began our investigation by treating 1.1 mmol of benzaldehyde **2a** (Table 1) with 1.1 mmol of TCCA in dichloromethane (3.25 mL) at room temperature. The reaction was monitored by TLC until the disappearance of the aldehyde which was quantitatively converted into the corresponding benzoyl chloride **3**. To this reaction mixture were added 2.0 mmol of triethylamine and 0.50 mmol of H_2O and after 2 h the desired benzoyl anhydride **4a** was formed in 45% yield (Table 1, entry 1). When 0.75 mmol of H_2O was used the product **4a** was obtained in 60% yield (Table 1, entry 2).

While 1.00 mmol of H_2O was used the product **4a** was obtained in 75% yield (Table 1, entry 3). Further increasing the amount of H_2O to 1.50 mmol and 10.0 mmol, provided, respectively **4a** in 32% yield and in trace (Table 1, entries 4 and 5).

After the reaction conditions were optimized, the reaction scope was examined (Scheme 2). Firstly the reactivity of aryl aldehydes

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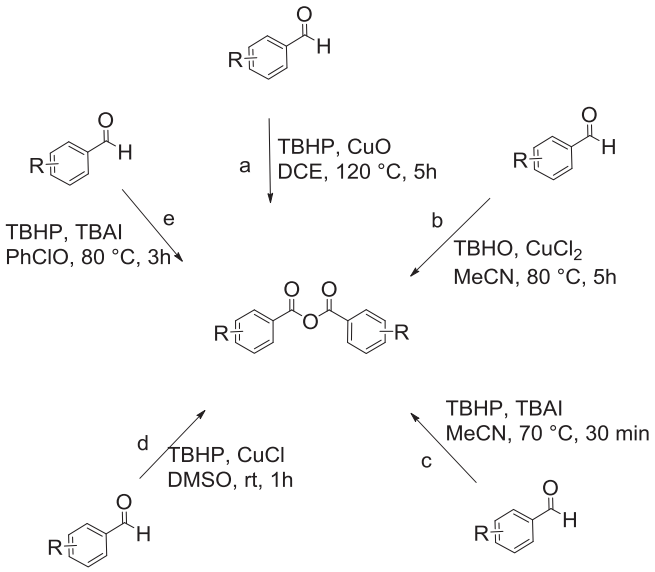
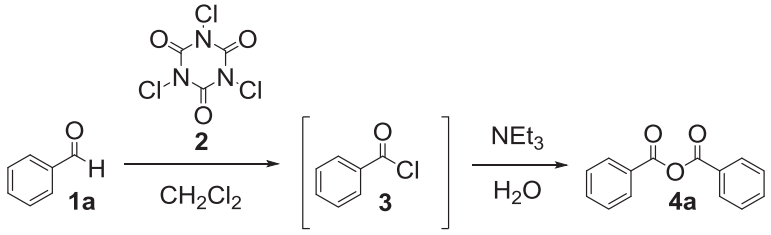


Scheme 1. Strategies to carboxylic anhydrides from aldehydes.

was investigated. Generally, electron-donating substituents, such as methyl and phenyl, regardless of their position on the aryl ring gave the corresponding symmetric anhydrides in 76%, 72% and 85% yield respectively (**4b**, **4c** and **4d** Scheme 2). Halo-substituted aldehydes were successful in this transformation and were converted to the corresponding anhydrides in very good yields (**4e**, **4f** and **4g** Scheme 2). Then aliphatic aldehydes, which typically cannot survive under strong oxidative conditions, were tested furnishing the corresponding symmetrical anhydrides in good yields (**4h**–**4l**, Scheme 2). The synthesis of aliphatic anhydrides from aldehydes by an oxidative self coupling is, to the best of our knowledge, unprecedented. Remarkably, even sterically hindered pivalaldehyde reacted well, giving the pivalic anhydride in good yield (**4l**, Scheme 2).

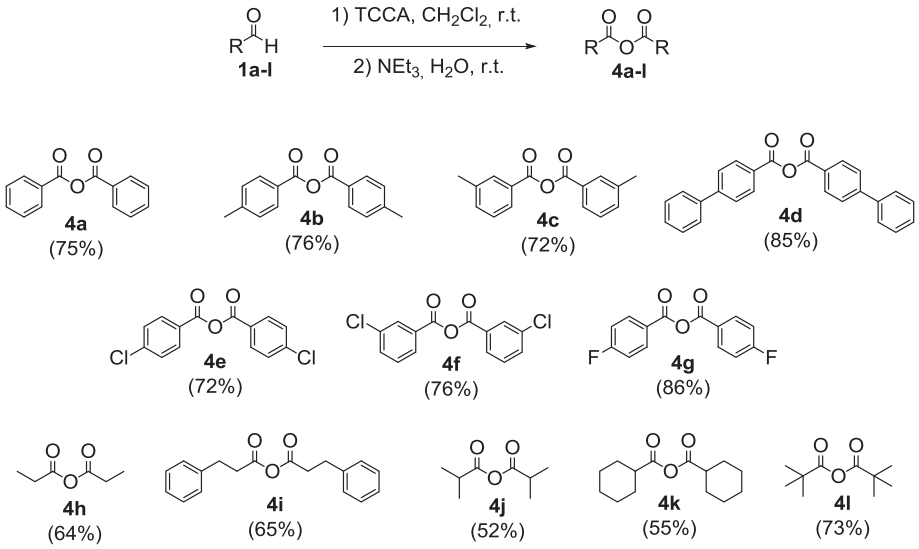
Alcohols are easily accessible and stable compounds. In view of our interest in the use of alcohols[12] and after the successful synthesis of carboxylic anhydrides from aldehydes, we have investigated the possibility to transform primary benzylic alcohols into anhydrides. The same methodology used to convert aldehydes to anhydrides was tested with alcohols. A solution of 1.1 mmol of benzyl alcohol **5a** (Scheme 3) in dichloromethane (3.25 mL) was treated with 1.1 mmol of trichloroisocyanuric acid (TCCA) at room

Table 1
Screening of reaction conditions.



Entry	H_2O (mmol)	Yield[a] %
1	0.50	45
2	0.75	60
3	1.00	75
4	1.50	32
5	10.0	Trace

[a] Isolated yield.



Scheme 2. Evaluation of aldehydes substrate scope.