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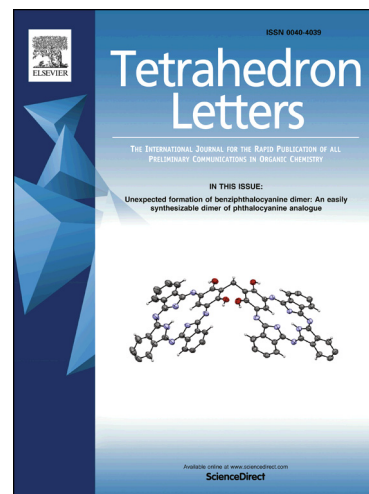
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Metal-free oxidative self-coupling of aldehydes or alcohols to symmetric carboxylic anhydrides

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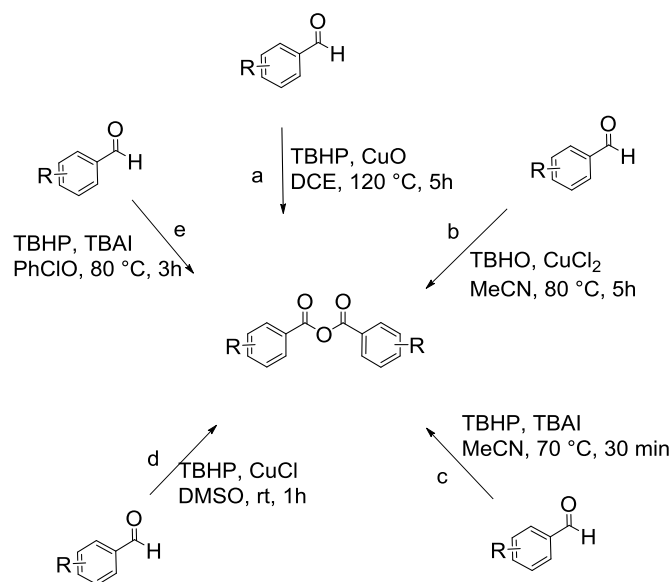
ABSTRACT

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.

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1. 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-triazines⁶ 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*-Butylhydroperoxyde (TBHP) as an oxidant, nano CuO as a catalyst and occurs at 120 °C for 5h. 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 substituents 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.



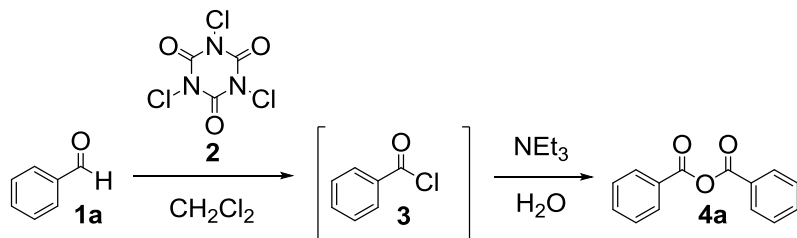
Scheme 1 Strategies to carboxylic anhydrides from aldehydes

This approach is a convenient and efficient way to form new bonds 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 H₂O and after 2 hours the desired benzoyl anhydride **4a** was formed in 45% yield (Table 1, entry 1). When 0.75 mmol of H₂O was used the product **4a** was obtained in 60% yield (Table 1, entry 2).

While 1.00 mmol of H₂O was used the product **4a** was obtained in 75% yield (Table 1, entry 3). Further increasing the amount of H₂O to 1.50 mmol and 10.0 mmol, provided, respectively **4a** in 32% yield and in trace (Table 1, entries 4 and 5).

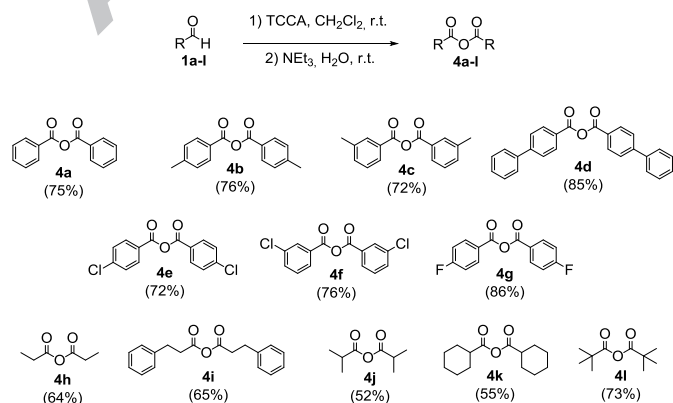
Table 1. Screening of reaction conditions



Entry	H ₂ O (mmol)	Yield ^a %
1	0.50	45
2	0.75	60
3	1.00	75
4	1.50	32
5	10.0	trace

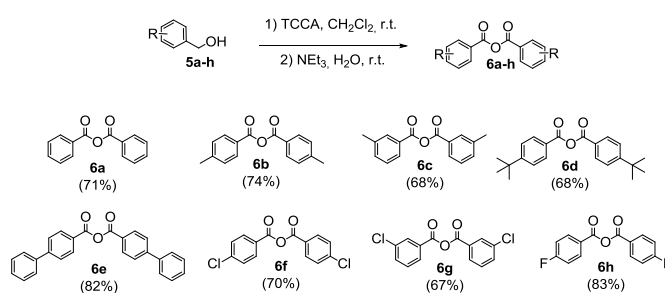
^aIsolated yield.

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



Scheme 2. Evaluation of aldehydes substrate scope

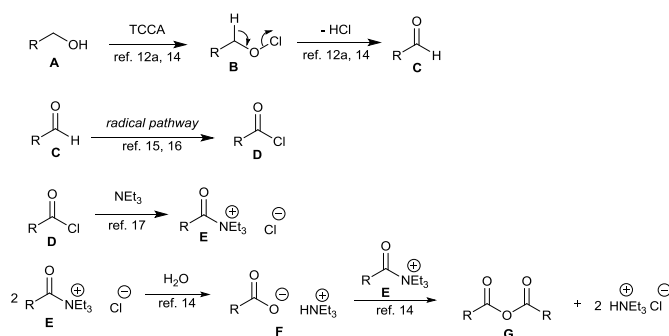
Alcohols are easily accessible and stable compounds. In view of our interest in the use of alcohols¹² and after the successful synthesis of carboxylic anhydrides from aldehydes, we have investigated the possibility to transform primary benzylic alcohols into anhydrides. The same methodology used to convert 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 temperature. The reaction was monitored by TLC until the disappearance of the alcohol which was quantitatively converted into the corresponding benzoyl chloride. To this reaction mixture were added 2.0 mmol of triethylamine and 1.00 mmol of H₂O and after 2 hours the desired benzoyl anhydride **6a** was formed in 71% yield. The methodology was applied to variously substituted benzylic alcohols, affording the corresponding anhydrides (Scheme 3).



Scheme 3. Evaluation of alcohols substrate scope

Benzyl alcohols with aliphatic substituents, as methyl and *tert*-butyl (**6b**, **6c** and **6d** Scheme 3), and phenylic residues (**6e** Scheme 3) were well tolerated providing the desired anhydrides in good yields. The reaction carried out on benzylic alcohols with halide substituents on the aromatic ring furnished the

corresponding anhydrides (**6f**, **6g** and **6h**, Scheme 3).¹³ To the best of our knowledge, the synthesis of anhydrides from alcohols by an oxidative self coupling is unprecedented. A plausible reaction mechanism is described on Scheme 4. On the basis of formerly published papers^{12a, 14} alcohol **A** reacts with TCCA, generating the hypochlorite compound **B**, which loses hydrogen chloride to form the aldehyde **C**. Then aldehyde **C** is converted into the acyl chloride **D**, through a radical pathway.^{15, 16} Then, the acyl chloride **D** reacts with triethylamine to form the acylammonium complex **E**,¹⁷ of which part reacts with water to form the carboxylate **F**.¹⁴ Finally the acylammonium complex **E** and the carboxylate **F** react leading to the formation of the anhydride **G**.¹⁴



Scheme 4. Proposed reaction mechanism

2. Conclusion

In conclusion, we have developed an easy metal-free and versatile oxidative self-coupling of aldehydes or primary alcohols to their symmetrical anhydrides. A variety of both aromatic and aliphatic aldehydes and primary benzylic alcohols were used in this methodology and the corresponding anhydrides were obtained in satisfactory yields. The methodology has an optimal stoichiometric molar ratio of reactants, and makes use of green reagents and mild reaction conditions.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

Metal free self-oxidative coupling to anhydrides from aldehydes or alcohols.

The method appears to be selective and efficient.

The method makes use of green reagents and mild reaction conditions.

The method has an optimal stoichiometric molar ratio of reactants.

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