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Short communication

# A TFAA–$H_3PO_4$-mediated direct, metal-free and high-speed synthesis of aryl carboxylate esters from phenols

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ABSTRACT

An operationally simple, mild and single-step method for the direct and metal-free synthesis of aryl carboxylate esters is described under a solvent free condition. The reaction of phenols including 2-naphthol (or 1-naphthol) with a variety of carboxylic acids in the presence of TFAA and 85% $H_3PO_4$ provided a range of aryl carboxylate esters in good yields within few minutes.



## 1. Introduction

We describe the TFAA–$H_3PO_4$-mediated direct O-acylation of phenol and 2-naphthol (or 1-naphthol) using a free carboxylic acid, such reaction is often carried out using acid chloride or anhydride.

Aryl carboxylate esters (e.g. ArOCOR, **1**) are of commercial interest because of their usage as components of liquid crystals and polyarylated liquid crystal polymers [1]. Besides, these esters are of medicinal interest as many of these derivatives have been studied as potential prodrug of phenolic drugs [2,3]. Moreover, Aspirin or acetylsalicylic acid, a well-known anti-inflammatory drug belongs to this class (Fig. 1) [4]. The most convenient and straightforward method for the preparation of **1** is esterification of phenols. However, unlike alcohols, –OH group of phenol is less reactive towards esterification and therefore requires activation of the corresponding carboxylic acid used. This can be achieved either *via* conversion of carboxylic acid to more reactive functional groups, such as anhydride [5–7] and acyl halide [8–10], or *via* in situ activation in the presence of coupling reagents. These include trifluoroacetic anhydride (TFAA) [11], 2-chloro-1-methylpyridinium iodide [12], BOP [13], DCC [14], PPE [15], *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride [16], $CCl_4/PPh_3$ [17], diphenyl(1,2-benzisoxazol-3-yl)phosphate [18], $Me_2NSO_2Cl$ [19], montmorillonite-$Ti^{4+}$ [20], metal triflates in [bmim]$PF_6$ [21], $Mn(OAc)_3$ [22], $TiO(acac)_2$ [23], diarylammonium arensulfonate [24], and several other condensing agents [25–30]. Some of these methods however, are associated with several drawbacks such as moderate yields, long reaction times, use of expensive reagents, and the use of volatile and environmentally harmful organic solvents. Moreover, the use of common acylating agent, i.e. moisture sensitive acid chlorides often cause environmental pollution and their preparation typically involve the use of thionyl chloride and oxalyl chloride. Thus, there is a need to develop alternative and practical method for the preparation of **1**. Previously, we have reported the use of TFAA/$H_3PO_4$ as an efficient catalyst system for C-acylation of benzothiophenes [31] and naproxen [32]. Herein we report a mild, single-step and metal-free process for the synthesis of **1** *via* TFAA/$H_3PO_4$-mediated direct O-acylation of phenol and 2-naphthol (or 1-naphthol).

## 2. Results and discussion

In the beginning of our study we examined the reaction of phenol (**2**) with benzoic acid (**3a**, Ar = $C_6H_5$) in the presence of TFAA (4.0 mol) and 85% $H_3PO_4$ (1.0 mol) at room temperature (Scheme 1). The reaction was completed within 5.0 min and the results are summarized in Table 1. Based on earlier reports [33–35] and our previous observation we expected the formation of C-acylated product (path b, Scheme 1) as a major or side product. However, we observed that only O-acylated product (path a, Scheme 1) was

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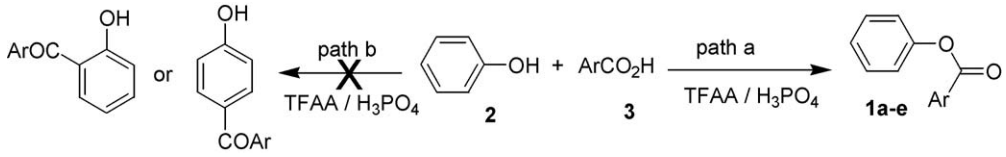



**Scheme 1.** TFAA/$H_3PO_4$-mediated reaction of phenol (**2**) and carboxylic acids (**3**).

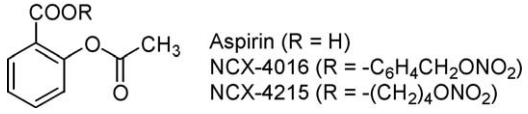
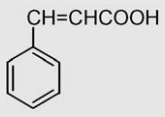
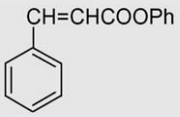
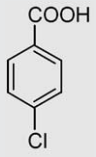
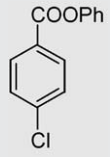
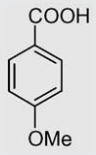
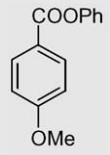
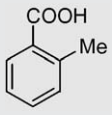
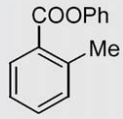
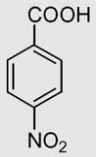
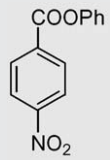



**Fig. 1.** Examples of aryl carboxylate ester drug: Aspirin and its NO-donating derivatives.

**Table 1**
TFAA/$H_3PO_4$-mediated O-acylation of phenol (**2**) with carboxylic acids (**3**)[a].

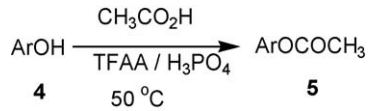
| Entry | Carboxylic acids (**3**) | Products (**1a–e**) | Conditions | Yield%[b] |
|---|---|---|---|---|
| 1. | $PhCO_2H$ **3a** | $PhCO_2Ph$ **1a** | RT; 5.0 min | 92 |
| 2. | **3a** | **1a** | RT; 2 h | 67[c] |
| 3. | **3a** | **1a** | RT; 2 h | 20[d] |
| 4. |  **3b** |  **1b** | RT; 14 min | 87 |
| 5. |  **3c** |  **1c** | RT; 5.0 mn | 89 |
| 6. |  **3d** |  **1d** | RT; 5.0 min | 84 |
| 7. |  **3e** |  **1e** | RT; 5.0 min | 86 |
| 8. |  **3f** |  **1f** | 50 °C; 15 min | 78 |

[a] All the reactions were carried out using **2** (1.0 mol), **3** (1.0 mol) in the presence of TFAA (4.0 mol) and 85% $H_3PO_4$ (1.0 mol) at room temperature.
[b] Yield of isolated product.
[c] The reaction was carried out using 0.1 mol of $H_3PO_4$.
[d] The reaction was carried out in the absence of $H_3PO_4$.

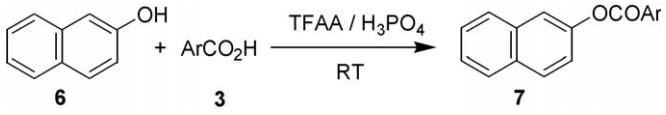
formed exclusively with 92% yield (entry 1, Table 1). While the initial reaction was carried out using 1.0 mol of $H_3PO_4$, we then reduced its amount to 0.1 mol in order to assess its role in the present O-acylation process. A slow progress of reaction was observed but it did not reach to the completion even after 2 h and the product yield was decreased to 67% (entry 2, Table 1). The reaction was also carried out in the absence of $H_3PO_4$ when the product yield was further decreased to 20% (entry 3, Table 1). These observations clearly indicated that the presence of $H_3PO_4$ is essential to complete the O-acylation process successfully.

Having established the optimum condition we then examined the reactivity of phenol (**2**) towards other carboxylic acids. Accordingly, a number of carboxylic acids were reacted [36] with **2** and yields of the corresponding products are shown in Table 1. As evident from Table 1 that the carboxylic acid may contain an olefin (**3b**) or a mild electron donating group such as chloro (**3c**) and methyl (**3e**) or a strong electron donating group, e.g. methoxy (**3d**) (entries 4–7, Table 1). We have observed that the success of the TFAA/$H_3PO_4$-mediated O-acylation reaction of phenol was partially dependent on the nature of group present on the benzene ring of the carboxylic acid employed. This was supported by the fact that *p*-nitro benzoic acid did not provide the desired product at room temperature. However, the desired product was isolated in 78% yield when the reaction was carried out at an elevated temperature (50 °C) for 15 min (entry 8, Table 1).

To extend the scope and generality of this methodology we then examined the reaction of substituted phenols (**4**) with acetic acid (Scheme 2) and 2-naphthol (**6**) with carboxylic acids (Scheme 3). The reactions of **4** with acetic acid required an elevated temperature, i.e. 50 °C to obtain the optimum yields of products (entries 1–3, Table 2) perhaps due to the less reactivity of acetic acid towards the present O-acylation process in compared to aromatic acids **3a–e**. However, the reaction of **4a** with benzoic acid proceeded well at room temperature affording the desired product in 78% yield (entry 4, Table 2). Similarly, the reaction of 2-naphthol (**6**) and 1-naphthol with acetic acid required an elevated temperature (entries 3 and 4, Table 3) to give the desired product **7c** and **7d** in 96 and 87% yield, respectively. Overall, the O-acylated products (**5a–d** and **7a–d**) were isolated in good yields indicating

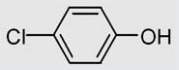
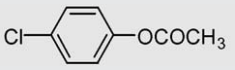
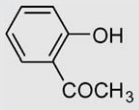
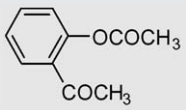
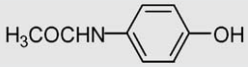
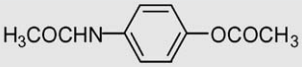
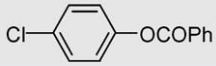



**Scheme 2.** Synthesis of esters (**5**) from substituted phenols (**4**) and acetic acid.



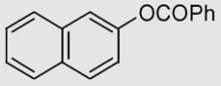
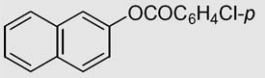
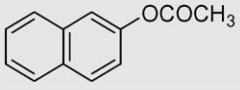
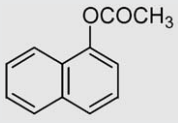

**Scheme 3.** Synthesis of esters (**7**) from 2-naphthol (**6**) and carboxylic acids (**3**).

**Table 2**
TFAA/$H_3PO_4$-mediated O-acylation of substituted phenols (**4**) with acetic acid/benzoic acid[a].

| Entry | Phenols (**4**) | Products (**5**) | Conditions | Yield%[b] |
|---|---|---|---|---|
| 1. |  **4a** |  **5a** | 50 °C; 5 min | 77 |
| 2. |  **4b** |  **5b** | 50 °C; 10 min | 75 |
| 3. |  **4c** |  **5c** | 50 °C; 5 min | 72 |
| 4. | **4a** |  **5d**[c] | RT; 5 min | 78 |

[a] All the reactions were carried out using **4** (1.0 mol), acetic acid (1.0 mol) in the presence of TFAA (4.0 mol) and 85% $H_3PO_4$ (1.0 mol) at room temperature.
[b] Yield of isolated product.
[c] Benzoic acid (**3a**) was used in place of acetic acid.

**Table 3**
TFAA/$H_3PO_4$-mediated O-acylation of 2-naphthol (**6**)/1-naphthol with carboxylic acids (**3**)[a].

| Entry | Carboxylic acids (**3**) | Products (**5**) | Conditions | Yield%[b] |
|---|---|---|---|---|
| 1. | **3a** |  **7a** | 50 °C; 15 min | 86 |
| 2. | **3c** |  **7b** | 50 °C; 15 min | 91 |
| 3. | $CH_3CO_2H$ **3f** |  **7c** | RT 5.0 min | 96 |
| 4. | **3f** |  **7d** | RT 5.0 min | 87[c] |

[a] All the reactions were carried out using **3** (1.0 mol), **6** (1.0 mol) in the presence of TFAA (4.0 mol) and 85% $H_3PO_4$ (1.0 mol) at room temperature.
[b] Yield of isolated product.
[c] 1-Naphthol was used in place of **6**.

that the present process has potential to become a general, inexpensive and alternative method for the preparation of phenolic esters [37,38].

## 3. Conclusion

In conclusion, the methodology presented above illustrates the usefulness of TFAA/$H_3PO_4$ as an efficient coupling agent for the direct O-acylation of phenolic hydroxy group with free carboxylic acid. The methodology does not require the use of expensive reagents or catalysts, inert or anhydrous atmosphere and works well either at room temperature or at 50 °C providing the O-acylated products in good to excellent yields within few minutes. Because of operational simplicity, clean and mild reaction conditions and significantly shorter reaction time the present metal-free process would find wide usage.

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[36] Typical procedure for the synthesis of phenyl carboxylate esters (**1a**–**e**): a mixture of acid (**3**, 1.0 mole), phenol (**2**, 1.0 mole) and 85% orthophosphoric acid (0.1 mole) was stirred under a normal and open atmosphere. To this, TFAA (4.0 mole) was added dropwise and the resulting mixture was allowed to stir at room temperature according to the time indicated in Table 1. The progress of the reaction was monitored by TLC. After the disappearance of the starting compounds the reaction mixture was added to crushed ice (50 g), extracted with diethyl ether (3 × 30 mL), washed with 10% NaOH solution (25 mL) followed by water (2 × 25 mL), dried over anhydrous sodium sulphate and concentrated to afford the desired product.
[37] For a recent review of dehydrative condensation reactions, see: K. Ishihara, Tetrahedron, 65 (2009) 1085–1109.
[38] For an example of esterification using carboxylic anhydrides under auxiliary base- and solvent-free conditions, see: A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, J. Am. Chem. Soc. 129 (2007) 14775–14779.