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Efficient Method for the Direct Preparation of Aryl Carboxylates from Carboxylic Acids Using Tosyl Chloride Under Solvent-Free Conditions

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A simple, clean and efficient solvent-free procedure for the preparation of aryl carboxylates is described from the direct reaction of carboxylic acids and phenols, in the presence of 1-methylimidazole as base and tosyl chloride (TsCl) as coupling agent. This method can be easily applied for different substituted phenols and carboxylic acids. It can also be applied for the selective acylation when other functional group such as hydroxyl is present on phenol ring.

Keywords: Aryl carboxylate, Carboxylic acid, Tosyl chloride, Solvent-free, 1-Methylimidazole

INTRODUCTION

Esterification of carboxylic acids with alcohols and phenols is of considerable interest. Esters are important in the synthesis and manipulation of natural products [1]. The preparation of esters from their corresponding carboxylic acids is an important and well-known transformation in organic synthesis [2]. In general, the formation of esters from carboxylic acids is carried out with excess loading of alcohol as the solvent in the presence of strong acid activators, *e.g.* sulfuric acid [3]. This reaction cannot usually be applied to the synthesis of esters from phenols. The preparation aryl esters from carboxylic acids require activation of the carboxyl group. Carboxylic acid activation can be achieved either by conversion to more reactive functional groups, such as anhydride [4] and acyl halide [5], or *via* in situ activation by coupling reagents. There are several reagents for the direct esterification of phenols under liquid-phase conditions, such as CCl_4/PPh_3 [6], 2-chloro-1-methylpyridinium iodide [7], *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride [8], PPE [9], TFAA (trifluoroacetic anhydride) [10], DCC [11], BOP [12], Me_2NSO_2Cl [13], diphenyl(1,2-benzisoxazol-3-yl) phosphate [14], montmorillonite-Ti^{4+} [15], $TiO(acac)_2$ [16], $Mn(OAc)_3$ [17], metal triflates in $[bmim]PF_6$ [18], diarylammonium arensulfonate [19], and several other condensing agents [20]. These reported methods are associated with one or more drawbacks including moderate yields, long reaction times, use of relatively expensive reagents, and no agreement with green chemistry protocols by using volatile organic solvents.

The application of solvent-free technique in organic chemistry has been explored extensively within the last decade [21]. Solvent-free conditions often lead to a remarkable decrease in reaction times, increased yields, easier workup, matches with green chemistry protocols, and may enhance the regio- and stereochemistry of reactions [21]. More recently, there has been a report describing the direct preparation of aryl esters from carboxylic acids under solvent-free conditions [22] in which, among different aromatic carboxylic acids available, only benzoic acid has been examined. Moreover, to the best of our knowledge, there is no other report for the direct preparation of aryl carboxylates from carboxylic acids under

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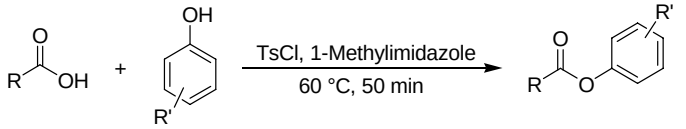


R = Alkyl, Aryl R' = NO_2, OH, OMe, F, Cl, Br, Me, H

Scheme 1

solvent-free conditions. Therefore, there are still opportunities for more versatile and complete study.

Along with our previous works on the direct preparation of amides from carboxylic acids using coupling agents [23a,23b], and in extension of our previous studies on the application of solvent-free technique in organic synthesis [23], we describe here a new procedure for the synthesis of aryl esters *via* direct reaction of phenols with various aliphatic and aromatic carboxylic acids with different electron-donating and electron-withdrawing substituents under solvent-free conditions (Scheme 1).

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were purchased from Merck or Fluka chemical companies. All compounds were identified by comparison of their melting points and/or ^{1}H NMR data with the authentic samples. The ^{1}H NMR (250 MHz) was run on a Bruker Avanced DPX-250, FT-NMR spectrometer. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for the Direct Preparation of Aryl Carboxylates from Carboxylic Acids

To a well-ground mixture of carboxylic acid (1 mmol), phenol (1 mmol) and TsCl (1 mmol) in a 10 ml round-bottomed flask connected to a reflux condenser was added 1-methylimidazole (3 mmol) and the homogeneous reaction mixture was stirred in an oil-bath (60 °C) for 50 min. Subsequently, the reaction mixture was allowed to cool to room temperature and was poured to water (25 ml) and extracted with chloroform (2 × 25 ml). The combined organic layer was then washed with saturated solution of $NaHCO_3$ (2 × 25 ml) and dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on neutral alumina eluted with *n*-hexane to obtain the pure product.

RESULTS AND DISCUSSION

Firstly, we examined the synthesis of phenyl benzoate as a model reaction (Scheme 1). Thus, to a well-ground mixture of benzoic acid (1 mmol), phenol (1 mmol) and tosyl chloride (1 mmol) was added 1-methylimidazole (3 mmol), and the resulting mixture was stirred at room temperature for 60 min. Analysis of the reaction mixture showed the formation of phenyl benzoate (43%) as the sole product. The yield was improved to 80% when the reaction was achieved at 60 °C within 50 min. No significant progress in the yield was achieved by prolonging the reaction time and enhancing the temperature. The effect of different bases on the reaction progress and the composition of products were investigated. The results are depicted in Table 1. As seen, among different bases examined, 1-methylimidazole was the most efficient. A homogeneous mixture was obtained by using this base, and the reaction proceeded efficiently, while, the formation of phenyl tosylate was not observed.

To compare the efficiency of the solvent-free conditions with respect to solution conditions, the model reaction was examined in several solvents (Table 2). As is obvious, the solvent-free method is more efficient.

To investigate the generality and versatility of this method, the reaction was extended to various structurally diverse carboxylic acids and phenols and the results are summarized in Table 3. As is clear from Table 3, the reactions proceeded efficiently and the aryl esters were obtained in good to excellent yields. The results showed that the presence of electron-releasing substituents on both aromatic carboxylic acids and phenols improved the reaction yields (Table 3, entries 2-6, 8 and 9). Esterification of carboxylic acids

Table 1. Effect of Different Bases on the Results of Reaction of Benzoic Acid with Phenol in the Presence of TsCl at 60 °C after 50 min

Entry	Base	Yield (%)[a]	
		$PhCO_2Ph$	PhOTs
1	1-Methylimidazole	80	0
2	NEt_3	32	9
3	NEt_3/SiO_2	30	19
4	DABCO	40	12
5	K_2CO_3	20	46
6	$NaHCO_3$	27	39

[a]Isolated yield.

Table 2. Effect of Various Solvents (10 ml) Upon the Reaction of Benzoic Acid (1 mmol) with Phenol (1 mmol) in the Presence of TsCl (1 mmol) and 1-Methylimidazole (3 mmol) at 60 °C after 50 min

Entry	Solvent	Yield (%)[a]	
		$PhCO_2Ph$	PhOTs
1[b]	-	80	0
2	DMF	17	5
3	DMSO	12	4
4	EtOAc	33	0
5	THF	42	0
6	MeCN	0	70
7	$CHCl_3$	40	0

[a]Isolated yield. [b]Our method.

Table 3. Direct Preparation of Aryl Esters from Carboxylic Acids and Phenols Using TsCl and 1-Methylimidazole at 60 °C under Solvent Free Conditions

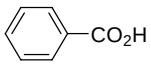
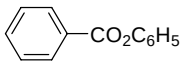
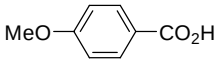
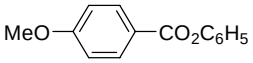
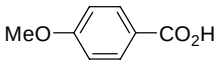
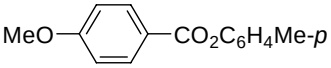
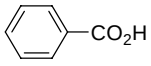
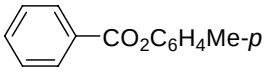
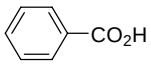
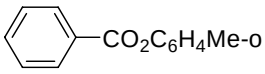
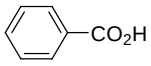
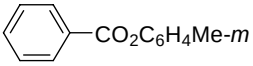
Entry	Acid	Product	Yield (%)[a]	M.p. °C (Lit.)
1			80	68-69 (66-67) [24]
2			90	68-70 (67.5-69) [6]
3			94	65-66 (64-66) [25]
4			93	69-71 (70-71) [6]
5			84	307-309[b] (310) [22]
6			88	52-54 (55) [26]

Table 3. Continued

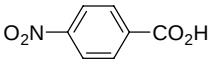
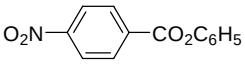
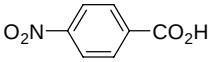
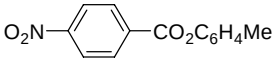
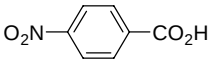
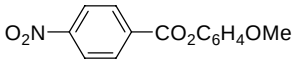
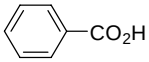
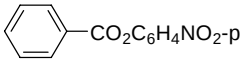
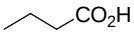
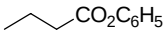
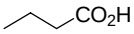
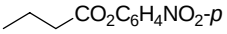
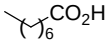
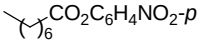
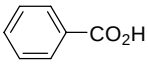
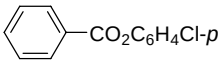
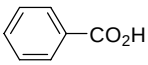
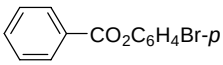
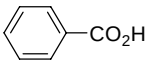
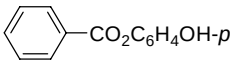
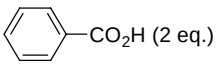
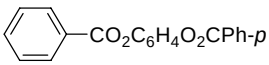
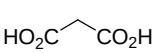
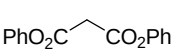
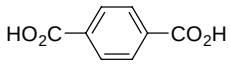
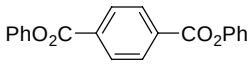
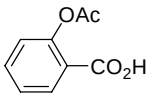
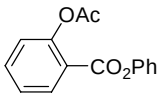
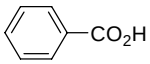
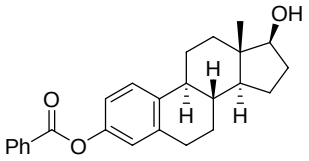
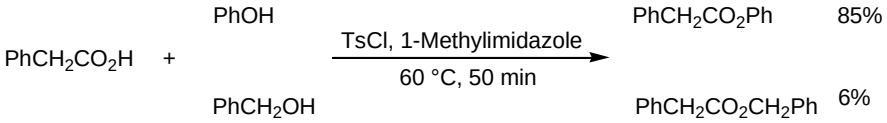
7			72	127-130 (128-129) [27]
8			88	99-100 (98-99) [28]
9			87	114-115 (117) [29]
10			60	143-145 (142-143) [30]
11			95	223-225[b] (227-228) [31]
12			86	184-185[b] (185) [32]
13			87	182-184[b] (183) [32]
14			90	86-88 (84-86) [6]
15			88	101-103 (104) [33]
16			70[c]	163-164 (165) [34]
17			89	202-205 (200-204) [35]
18[d]			87	47-49 (50) [36]

Table 3. Continued

19[d]			82	191-192 (190) [33]
20			78	95-97 (97) [33]
21			75	192-194[e,f] (193) [33]

[a]Isolated yield. [b]B.p. at 760 torr. [c]In this reaction dibenzoyl *p*-hydroquinone (11%) as side product was obtained. [d]In this reaction 2 eq. phenol was used. [e]Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.5; found: C, 79.48; H, 7.35. [f]$[\alpha]_D^{20}$ = +58 (c 2.0, dioxane); Lit. [35] $[\alpha]_D^{20}$ = +55 (c 2.0, dioxane).



Scheme 2

possessing electron-withdrawing substituents with phenol or esterification of benzoic acid with phenols possessing electron-withdrawing groups afforded moderate reaction yields (Table 3, entries 7 and 10).

The application of aliphatic acids, such as butyric and hexanoic acids significantly increased the yield of esterification (Table 3, entries 11-13). The reaction of benzoic acid with phenols possessing halogen substituents, such as *p*-chloro and *p*-bromophenol was also efficient (Table 3, entries 14 and 15). The reaction of *p*-hydroquinone with benzoic acid was afforded *p*-hydroxyphenylbenzoate as the major product (Table 3, entries 16). The reaction of *p*-hydroquinone with 2 eq. of benzoic acid gave the bis-acylated products in excellent yields (Table 3, entry 17). Dicarboxylic acids such as, malonic and terephtalic acids afforded the bis-arylesters as the sole product even if 1 eq. of phenol was applied (Table 3, entries 18 and 19).

When the esterification reaction was carried out with (+)-estradiol and benzoic acid, the corresponding enantiomerically pure product was isolated in high yield (Table 3, entry 21). The reaction for a 1:1 binary mixture of phenol and benzyl alcohol with phenylacetic acid led to the formation of phenyl ester as the major product (Scheme 2).

We suggest that initially a tosyl carboxylate is formed which then reacts with phenoxide anion generated from the reaction of phenol with 1-methylimidazole, providing the aryl ester. To explore the formation of acid tosylate during the reaction, a mixture of benzoic acid, tosyl chloride was reacted with 1-methylimidazole at 60 °C. TLC monitoring indicated the formation of tosyl benzoate as identified with an authentic sample [37]. Moreover, no benzoic anhydride was observed.

CONCLUSIONS

In summary, this present procedure provides an efficient, clean and very simple methodology for the direct preparation

of esters from phenols and various aliphatic and aromatic carboxylic acids in the presence of tosyl chloride as a cheap and available activating agent under solvent-free conditions. This method can be easily applied for different substituted phenols and carboxylic acids. Moreover, it can be applied for selective acylation when other functional group such as hydroxyl is present on phenol ring.

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