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Tf_2O-Mediated Direct and Regiospecific *para*-Acylation of Phenols with Carboxylic Acids

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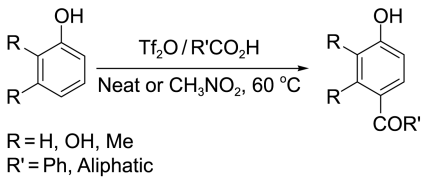
Development of regioselective reactions of aromatic compounds such as phenols is a fundamental goal in both synthetic and theoretical organic chemistry. For example, regioselective acylation of phenols leads to produce *ortho*- or *para*-hydroxyacetophenone (*o*- or *p*-HAP) which are very valuable precursors in the pharmaceutical industry, being this reaction the first step of the Hoechst Celanese manufacturing process of paracetamol.[1] Hydroxyaryl ketones are widely used in perfumery, metallurgy, and pharmaceutics and are versatile intermediates in the synthesis of biologically active compounds.[2]

Friedel-Crafts acylation of phenol derivatives and Fries rearrangement of acyloxy benzenes are major pathways for preparation of hydroxyaryl ketones.[3] Fries rearrangement usually gives *o*-hydroxyaryl ketones using acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$.[4] These methods suffer from one or more drawbacks; for example HF which acts as catalyst and solvent is toxic, corrosive and volatile (bp 15 °C), $AlCl_3$ is corrosive and reacts violently with water, and BF_3 is also very toxic, corrosive and gives an intense reaction with water. However, there are a number of methods that can minimize these problems using the solid catalyst such as zeolites, nafion silica composites or BEA-zeolites.[5] Acylation of phenols with acid halides[6] or acid anhydrides[7] were also reported and a mixture of *o*- and *p*-hydroxyaryl ketones was obtained. In the liquid phase, the acylation reaction of phenol catalyzed by Friedel-Crafts catalysts produced mainly *p*-HAP. However, we did not find any report about the production of *p*-HAP regiospecificly *via* direct acylation of phenol with carboxylic acids. Therefore, development of new methods for obtaining only *p*-HAP *via* direct acylation of phenols can be desirable.

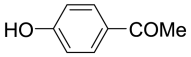
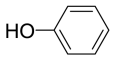
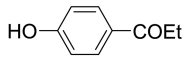
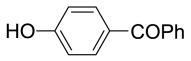
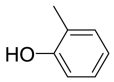
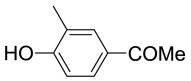
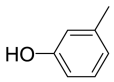
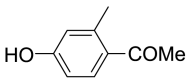
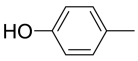
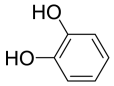
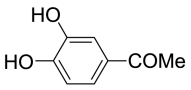
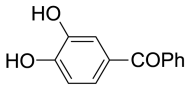
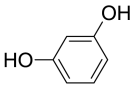
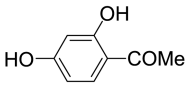
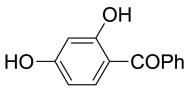
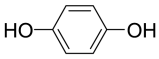
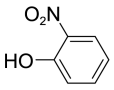
Trifluoromethanesulfonic anhydride (Tf_2O) is commercially available and known for its high ability in conversion of OH group into OTf group as one of the best leaving group in organic transformation.[8] Although Tf_2O is an expensive reagent, but it is widely used in organic reactions.[9] In continuation of our research on acylation reactions[10] and application of Tf_2O in organic reactions, [11] herein we report the *para*-acylation of phenols with carboxylic acids in the presence of Tf_2O (Scheme 1).



Scheme 1

We first investigated the *para*-acylation of phenol (1 mmol) with acetic acid (1 mmol) as model substrates using 1 equivalent of Tf_2O under solvent-free condition at 60 °C. This reaction afforded *p*-hydroxy acetophenone in 80% yield after 10 min (Table 1, entry 1), and no *ortho* isomer was observed. The acylation of phenol with propionic acid was also examined under the same reaction condition and *p*-hydroxy propiophenone was obtained in 80% as a sole product (Table 1, entry 2). However, the reaction of phenol with benzoic acid as an aromatic acid under the same reaction condition did not afford the corresponding product since benzoic acid has high melting point and this physical property prevents to have the homogeneous media in the reaction. Therefore, in this case a suitable solvent such as CH_3NO_2 was used to create a homogeneous media for succession of the reaction and in consequence *p*-hydroxy benzophenone was obtained in 75% yield after 15 min (Table 1, entry 3). To explore the generality of the present method, other phenol derivatives were also treated under this reaction condition, and the results shown in Table 1 confirmed the *para*-selectivity of this procedure for all phenols exclusively. While three isomers of cresols reacted with $MeCO_2H$ activated with Tf_2O, *o*-cresol and *m*-cresol gave the corresponding *para*-acylated products in 83 and 70% yields respectively as expected (Table 1, entries 4,5), whereas *p*-cresol did not produce *para*- or *ortho*-acylated product, and only the corresponding ester (*p*-tolyl acetate) was obtained after appropriate time (Table 1, entry 6). In respect to obtained results for *p*-cresol, it is reasonable that no acylated product was obtained under the above reaction condition when *para* position is occupied. This observation emphasizes the regiospecifity of this procedure for *para*-acylation. In continuation, the reactions of catechol (Table 1, entries 7 and 8) and resorcinol (Table 1, entries 9 and 10) were investigated, and these phenols shown good reactivity to produce the corresponding products, whereas hydroquinone is inactive under the same reaction condition. It is

Table 1. *para*-Acylation of phenols with carboxylic acid activated by Tf_2O

Entry	Phenol	Carboxylic acid	*p*-Hydroxyaryl ketone	Time (min)	Yield (%)[a]	Mp (°C)
1		$MeCO_2H$		10	80	104-105[12]
2		$EtCO_2H$		10	80	143-144[13]
3		$PhCO_2H$		15[b]	75	130-131[12]
4		$MeCO_2H$		10	83	103-104[13]
5		$MeCO_2H$		10	70	123-124[13]
6		$MeCO_2H$		30[c]	0	-
7		$MeCO_2H$		5[b]	90	110-111[12]
8		$PhCO_2H$		10[b]	83	129-130[13]
9		$MeCO_2H$		5[b]	74	142-143[12]
10		$PhCO_2H$		10[b]	71	143-144[12]
11		$MeCO_2H$	-	30[b]	0	-
12		$MeCO_2H$	-	30[b,c]	0	-

[a]Isolated products. [b]Reaction was carried out in 1 mL of CH_3NO_2. [c]Product was only ester.

noted that in the case of phenol with electron-withdrawing substituent, the reaction did not afford *para*-acylated product and only the corresponding ester was obtaind in 40% yield after 30 min.

In this research, we have developed a simple, mild, and convenient method for the preparation of *para*-hydroxyaryl ketones from the direct acylation of phenols with carboxylic acids activated with Tf_2O. In addition, para regiospecifity, high yields of products, short reaction times, and simplicity of work-up are other advantages of this procedure.

Experimental

General experimental procedure: Tf_2O (1 mmol, 0.16 mL) and carboxylic acid (1 mmol) were mixed and stirred at room temperature. The mixture was heated until the temperature was raised to 60 °C, then phenol (1 mmol) was added to the mixture and monitored by TLC. On completion of the reaction, the mixture was washed with aqueous $NaHCO_3$ (10 mL), extracted with EtOAc (2 × 10 mL), and then dried over $MgSO_4$. The residue was purified by chromatography through a short column of silica gel (*n*-hexane/EtOAc: 7/3). All of the compounds prepared are known.

Representative Spectral Data.

4-Hydroxy Acetophenone: IR (KBr): ν_{max} = 3300-3504 (OH), 1660 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 2.64 (s, 3H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.69 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 26.3, 115.6, 129.6, 131.2, 161.3, 198.6.

4-Hydroxy Benzophenone: IR (KBr): ν_{max} = 3550-3200 (OH), 1628 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.95 (d, *J* = 8.5 Hz, 2H), 7.52-7.63 (m, 4H), 7.78-7.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 115.2, 127.9, 128.3, 129.8, 132.1, 133.0, 138.1, 160.0, 194.2.

4-Hydroxy-2-methyl Acetophenone: IR (KBr): ν_{max} = 3200 (OH), 1650 (CO); ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 2.55 (s, 3H), 2.56 (s, 3H), 6.16 (s, 1H), 6.73 (m, 2H), 7.73 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ

(ppm): 21.7, 28.6, 112.3, 118.6, 128.2, 133.1, 141.1, 159.9, 198.6.

4-Hydroxy-3-methyl Acetophenone: IR (KBr): ν_{max} = 3150 (OH), 1650 (CO); ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 2.30 (s, 3H), 2.57 (s, 3H), 6.61 (s, OH, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 15.8, 26.0, 114.8, 124.8, 128.7, 129.1, 132.1, 160.2, 199.4.

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