

Microwave Assisted Direct Ortho-Acylation of Phenol and Naphthol Derivatives by $BF_3 \cdot (C_2H_5)_2O$

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The solventless acylation of phenol and naphthol derivatives with various organic acids and $BF_3 \cdot (C_2H_5)_2O$, under microwave conditions, was studied. High yields of the *o*-acylated products were achieved in a very short time.

Friedel–Crafts acylations are very important reactions carried out industrially. Intermediates for pharmaceutical, perfumes, flavors, fragrances, dyes, plastics, antioxidants, stabilizers, fungicides, etc., are prepared using these reactions.[1]

This type reaction employs acid chloride or anhydride in the presence of catalysts, like aluminum chloride or tin(IV) chloride. Acylation can also be achieved by treating the free acid with a variety of condensing agents. These include liquid hydrogen fluoride,[2] concentrated sulfuric acid,[3] phosphorus pentoxide,[4] polyphosphoric acid,[5] fluorosulfonic acid,[6] and alumina in methane-sulfonic acid.[7]

Aromatic acylation with carboxylic acids instead of acid anhydrides and acyl chlorides has attracted interest, because it is an environmentally benign reaction, resulting in the formation of a Lewis acid–water complex as the only a by-product.[8] The direct acylation of phenol derivatives, using $AlCl_3$ or $TiCl_4$ as a promoter, also provides useful synthetic method for the preparation of *o*-hydroxyaryl ketone derivatives.[9–12]

Recently, while exploring the scope and utility[13] of the solid-phase conditions in organic synthesis, it was observed that the no solvent conditions are also effective for the synthesis of alkyl and acylarenes.

A solvent-free or solid-state reaction may be carried out using the reactants alone, or by incorporating them in clays, zeolites, silica, alumina, or matrices. A thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction. Solvent-free reactions obviously reduce the pollution, and decrease the handling costs due to simplification of the experimental procedure, work-up technique and saving in labor. These would be especially important during industrial production.[14]

Microwave-assisted solvent-free synthesis[15] in organic reactions has been of growing interest as an efficient, economic, and clean procedure.[16]

Boron triflouride (BF_3) is an inorganic fluorinated gas; it is highly toxic, colorless, nonflammable, and used as a catalyst in many chemical reactions, including polymerization,[17–19] alkylation,[20,21] and acylation.[22]

In this research, we examined the acylation of phenol and naphthol derivatives with aliphatic acids and $BF_3 \cdot (C_2H_5)_2O$ under microwave conditions to enhance the reaction rate.

Results and Discussion

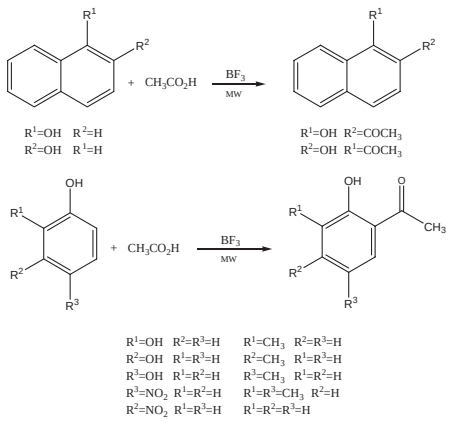
For the first time, we attempted to carry out acylation reactions of phenol and naphthol derivatives with acetic acid in the presence of $BF_3 \cdot (C_2H_5)_2O$ under a solvent-free condition and microwave irradiation (Scheme 1). The results are indicated in Table 1. As shown in this Table, using of BF_3 gave regioselectively ortho acylated products in very high yields, and within short reaction times.

The yields of the reaction products can be compared with the yields of acylated phenol or naphthol derivatives in previously reported acylation methods in which a Lewis acid is employed as a catalyst.

In this reaction, acylation occurred as highly regioselective toward ortho hydroxy alkyl aryl ketones. By using of 2,6-dimethylphenol as a substrate in the reaction, no product was obtained, and the unreacted starting materials were completely recovered (entry 13).

In these reactions, the reaction rates were increased with the presence of an electron-donating substituent, and decreased with the existence of an electron-withdrowing substituent on phenolic compounds (entries 10, 12, and 14 compared with the other entries).

The presence of –OH stretching broad bonds in the 3100–3500 cm^{-1} region and C=O stretching strong bonds in the 1620–1670 cm^{-1} IR region, and the existence of a broad sin-



Scheme 1.

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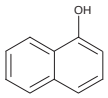
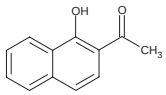
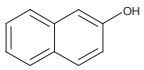
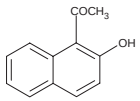
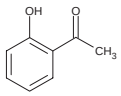
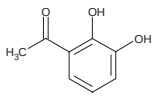
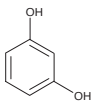
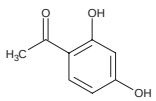
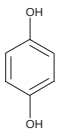
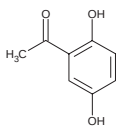
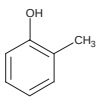
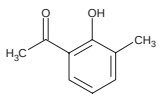
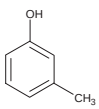
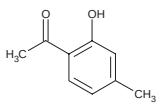
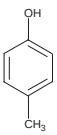
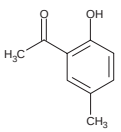
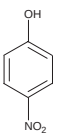
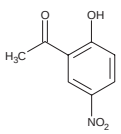
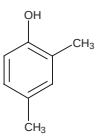
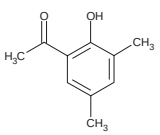
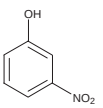
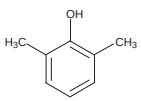
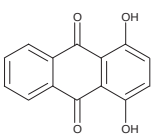
Table 1. Acetylation of 1 mmol Phenol and Naphthol[a)] Derivatives with 1.2 mmol HOAc under $BF_3 \cdot (C_2H_5)_2O$ in MW Conditions

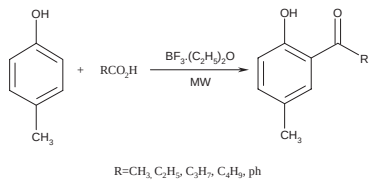
Entry	Substrate	mmol of BF_3	Power/W	Time/min	Product	Yield/%
1		0.41	600	2		95
2		0.41	300	1.7		40
3		0.83	400	3		90
4		0.83	300	1.3		85
5		0.41	200	2		98
6		0.83	300	2		98
7		0.83	600	2		50
8		0.41	600	3		98
9		0.21	800	1.7		98
10		0.83	700	2		10
11		0.83	700	2		98
12		0.83	900	2	—	0
13		0.83	900	2	—	0
14		0.83	900	2	—	0

a) mmols of naphthols are 0.70.

Table 2. Acylation of 1 mmol of *p*-Cresol with Organic Acids by 0.83 mmol of BF_3

Entry	Acid	mmol of acid	Time/min	Power/W	Yield[b)]/%
1[a)]	CH_3CO_2H	1.2	1.83	800	98
2	$C_2H_5CO_2H$	1.3	2.5	600	98
3	$C_3H_7CO_2H$	1.08	2	700	95
4	$C_4H_9CO_2H$	0.95	2	600	98
5	$PhCO_2H$	1.6	2	600	95

a) By 0.21 mmol of BF_3. b) Isolated yields.



Scheme 2.

glet peak with δ 11.8–13.8 ppm in the ^{1}H NMR data from all of the products, is completely consistent with the ortho-acylated phenols and naphthols.

In order to develop the use of BF_3 in the acylation reaction, we used various organic acids in the acylation reaction of *p*-cresol in the presence of $BF_3 \cdot (C_2H_5)_2O$ under microwave irradiation and solvent-free conditions (Scheme 2).

The results are given in Table 2. It was considered that the yields of the reaction products were excellent for acylation reactions with all of the various organic acids.

In conclusion, this new method for the acylation of phenol and naphthol derivatives has some advantages, such as: simplicity of the reaction, very high yields of the products, a short reaction time, and simplicity of the work-up. In these reactions, ortho aryl alkyl ketones were regioselectively yielded as the products under efficient, mild, and solvent-free conditions.

Experimental

Chemicals were purchased from the Merck Chemical Company in high purity. BF_3 was used in the reactions as $BF_3 \cdot (C_2H_5)_2O$, boron trifluoride etherate (50%). IR spectra were recorded from a KBr pellet on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nickolet FT IR Spectrophotometer. ^{1}H NMR were recorded in $CDCl_3$ with (60 MHz) spectrometer using of TMS as an internal reference. Melting points were obtained with a Yanagimoto micro melting-point apparatus, and are uncorrected. Purity determinations of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

General Procedure for the Acylation Reaction. In the general procedure, a mixture of 1 mmol of phenolic or 0.7 mmol of naphtholic compound, $BF_3 \cdot (C_2H_5)_2O$, and 1.2 mmol acetic acid, reacted together under microwave irradiation, without any solvent for a short time. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane (10 mL) and H_2O (about 20 mL). After extraction of the organic phase, it was washed with aqueous $NaHCO_3$ (20 mL), dried with $CaCl_2$, filtered and evaporated to give a crude product. The crude products were then purified by chromatography on silica gel using petroleum ether as the eluent. The products were confirmed by spectroscopic data and physical methods by being consistent with the reported data.[7,23–28]

2-Acetyl-1-naphthol: mp 98–100 °C (lit.[18] mp 98 °C); IR (KBr) ν (cm^{-1}): 3300–3600, 1625, 1570; ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H), 7.5–8.3 (m, 6H), 13.8 (s, 1H).

1-Acetyl-2-naphthol: IR (neat) ν (cm^{-1}): 3200–3500, 1725, 1675; ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H), 7.5–8.0 (m, 6H), 13.8 (s, 1H).

1-(2-Hydroxy-3-methylphenyl)-1-ethanone: oil, (lit.[21] bp 82–84 °C) IR (KBr) ν (cm^{-1}): 3200–3500, 1650, 1600; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H), 2.6 (s, 3H), 7.5–7.8 (m, 3H), 12.1 (s, 1H).

1-(2-Hydroxy-4-methylphenyl)-1-ethanone: oil, (lit.[26] bp 82–84 °C) IR (KBr) ν (cm^{-1}): 3200–3500, 1600, 1670; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3H), 2.0 (s, 3H), 6.2–7.0 (m, 3H), 11.8 (s, 1H).

1-(2-Hydroxy-5-methylphenyl)-1-ethanone: mp 42–44 °C (lit.[17] mp 43–44 °C) IR (KBr) ν (cm^{-1}): 3300–3500, 1650, 1775; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H), 2.4 (s, 3H), 6.8–7.4 (m, 3H), 11.8 (s, 1H).

1-(2-Hydroxy-3,5-dimethylphenyl)-1-ethanone: oil, IR (KBr) ν (cm^{-1}): 2900–3450, 1770–1650; ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.5 (s, 3H), 2.8 (s, 2H), 7.5 (d, 2H), 12.6 (s, 1H).

1-(2,4-Dihydroxyphenyl)-1-ethanone: mp 143–145 °C (lit.[17] mp 144–146 °C) IR (KBr) ν (cm^{-1}): 3000–3500, 1620, 1570; ^{1}H NMR ($CDCl_3$) δ 2.7 (s, 3H), 6.4 (s, 1H), 7.3–7.7 (m, 3H), 12.8 (s, 1H).

1-(2,3-Dihydroxyphenyl)-1-ethanone: oil, IR (KBr) ν (cm^{-1}): 3100–3600, 1620, 1490; ^{1}H NMR ($CDCl_3$) δ 2.8 (s, 3H), 6.0 (s, 1H), 6.8–7.6 (m, 3H), 12.4 (s, 1H).

1-(2,5-Dihydroxyphenyl)-1-ethanone: mp 197–199 °C (lit.[17] mp 198–200 °C) IR (KBr) ν (cm^{-1}): 3100–3250, 1620, 1500–1580; ^{1}H NMR (DMSO-d_6) δ 2.4 (s, 3H), 6.8–7.3 (m, 3H), 8.7 (s, 1H), 11.4 (s, 1H).

1-(2-Hydroxyphenyl)-1-ethanone: oil, (lit.[23] bp 213 °C) IR (KBr) ν (cm^{-1}): 2600–3300, 1650, 1490; ^{1}H NMR (DMSO-d_6) δ 2.5 (s, 3H), 6.7 (s, 1H), 6.8–7.6 (m, 4H).

1-(2-Hydroxy-5-methylphenyl)-1-propanone: oil, IR (KBr) ν (cm^{-1}): 3200, 1720, 1620; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3H), 2.0 (s, 3H), 2.6 (q, 2H), 6.5–7.2 (m, 3H), 11.9 (s, 1H).

1-(2-Hydroxy-5-methylphenyl)-1-butanone: oil, IR (KBr) ν (cm^{-1}): 3300, 1730, 1620; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 1.7 (q, 2H), 2.3 (s, 3H), 6.7–7.0 (m, 3H), 7.2 (s, 1H), 11.9 (s, 1H).

1-(2-Hydroxy-5-methylphenyl)-1-pentanone: oil, IR (KBr) ν (cm^{-1}): 3250, 1730, 1630; ^{1}H NMR ($CDCl_3$) δ 0.7 (t, 3H). 1.4 (m, 4H), 2.0 (s, 3H), 2.6 (t, 2H), 6.4–7.0 (m, 3H), 7.2 (s, 1H).

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