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Solvent-free direct ortho C-acylation of phenolic systems by methanesulfonic acid as catalyst

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ABSTRACT

The use of methanesulfonic acid as a Brønsted acid for direct ortho-acylation of phenols and naphthols proves to be a convenient, more general and direct route to various hydroxyaryl ketones. The route is regioselective, leading to ortho C-acylated products in satisfactory to high yields in most cases. The solvent free reactions described below exhibited environmentally benign in terms of faster reaction, benign conditions and higher yield of the desired products. The influence of the temperature, the ratios of the reactants and the amounts of MSA were investigated. However, after a 10-18 minute reaction time at 60-100 °C, selectivity to over 98% ortho acylation products was obtained. This method represents an environmentally benign acylation route, because MSA is biodegradable acid which can easily be separated from the reaction mixture via decantation.

***Keywords**: Solvent Free, Methanesulfonic acid, Friedel–Crafts, ortho-Acylation, Regioselective*

1. Introduction

A methodological approach to conventional phenol chemistry based on the concepts and achievements of modern coordination chemistry allowed to find specific conditions for improving classical reactions and discovering new selective processes [1]. Orthohydroxyaryl ketones, as a variety of compounds with acyl group, are also important synthetic intermediates in the synthesis of biologically active compounds such as chalcones, flavanones, naphthoquinones and pesticides [2]. Substrates, reagents, and ligands could be organized around non transition metal cations in suitable complexes, which were able to control the reactions and to determine highly selective ortho-attack on phenol systems. Template reactions of phenol substrates with carbonyl compounds in the presence of suitable ligands lead to new general processes of ortho-formylation, ortho-acylation, ortho-alkylation and allylation [3-8].

The search for catalytic conditions has produced numerous investigative works, particularly in the use of Lewis's acids (LA) such as $FeCl_3$ [9,10], $ZnCl_2$ [11,12], $BiCl_3$ [13], or other metallic chlorides [14], or Bronsted acids, like super-acidic systems [15-19], a non-exhaustive listing of catalysts could include also LA-lithium or silver salt mixtures. Recently, there are some reports on catalytic Friedel Crafts acylation reactions using carboxylic acids as acylating agents in that zeolites [20-24], heteropoly acids and their salts [20,25], clay [26], Lewis acids [27], graphite/TsOH [28], hydrogen fluoride [29], Cooper (II) Oxide [30], *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) [31], poly phosphoric acid [32], fluorosulfonic acid [33] has been used as catalysts. Recently, it has been found that although phenolic substrates can be converted into acylated compounds by means of MSA/alumina and MSA/graphite as the catalyst under reflux conditions [34, 35], these methods have some limitations, such as; low yields, long reaction times, usage of solvents in the reaction process.

2. Experimental

Chemicals were purchased from the Merck Chemical Company in high purity. An IR spectrum was recorded as KBr pellet on a Perkin-Elmer 781 Spectrophotometer and an Impact 400 Nickolet FTIR Spectrophotometer. ^{1}H NMR spectra was recorded in $CDCl_3$ with (400 MHz) Spectrometer using of TMS as an internal reference. Melting points were obtained with a Yanagimoto micro melting point apparatus are uncorrected. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

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2.1. General procedure for acylation of phenol and naphthol derivatives

A 25 mL one-necked flask equipped with a reflux condenser is charged with a mixture of 0.2 gr (1.4 mmol) of 1-naphthol, 0.5 ml (8 mmol) of acetic acid and 0.05 gr (0.52 mmol) of methanesulfonic acid. The clear mixture is heated at reflux in an oil bath for 10 minutes, after the end of the reaction progress, the mixture is cooled to room temperature and dissolved in dichloromethane (10 ml) and H_2O (20 ml). After extraction of the organic phase (ethyl acetate 3×5 ml), the resulting is transferred to a 100-ml separatory funnel and washed with aqueous $NaHCO_3$ (2×20 ml), and water (3×50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to give a crude product. The yields refer to isolated pure products after column chromatography. The products were characterized by their spectroscopic and physical data that were consistent with previously reported data [37-39].

The selected spectral data:

2-acetyl-1-naphthol (1); recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 98-100°C; IR (KBr)/ υ (cm^{-1}) 3300-3600, 1625, 1570; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.6 (s, 3H), 7.5-8.3 (m, 6H), 13.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 26.1, 112.9, 117.6, 124.4, 124.6, 125.3, 126.9, 129.4, 137.6, 162.4, 202.04; MS (EI): m/z: 186, 171, 169, 127.

1-(1-hydroxy-2-naphtyl)1-propanone (2); recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 84-85°C; IR (KBr)/ υ (cm^{-1}) 3330-3580, 1651, 1565; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 1.2 (t, 3H), 2.5 (q, 2H), 7.4-8.1 (m, 6H), 13.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 18.2, 25.5, 118.1, 119.1, 126.0, 127.6, 128.1, 128.7, 131.1, 135.4, 161.8, 205.1; MS (EI): m/z: 200, 183, 171, 143, 126.

1-(1-hydroxy-2-naphtyl)1-butanone (3); recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 94-96 °C; IR (KBr)/ υ (cm^{-1}) 3220-3580, 1641, 1564; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 1.1 (t, 3H), 2.1 (m, 2H), 2.4 (t, 2H), 7.6-8.4 (m, 6H), 13.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 14.5, 18.1, 51.1, 110.1, 115.0, 125.1, 126.7, 127.0, 128.5, 130.1, 133.6, 158.4, 195.0; MS (EI): m/z: 214, 171, 154, 127.

1-Acetyl-2-naphthol (4); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/ υ (cm^{-1}): 3200-3500, 1725, 1675; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.6 (s, 3H), 7.5-8 (m, 6H), 13.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 32.1, 114.5, 119.0, 123.8, 124.2, 127.9, 128.6, 129.6, 131.1, 136.7, 164.1, 202.0; MS (EI): m/z: 186, 169, 155, 143, 127.

2-Hydroxy-3-methyl acetophenone (5); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/ υ (cm^{-1}): 3200-3500, 1650, 1600; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.2 (s, 3H), 2.6 (s, 3H), 7.5-7.8 (m, 3H), 12.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 15.8, 28.8, 117.6, 118.2, 124.1, 128.3, 136.2, 160.7, 202.4; MS (EI): m/z: 150, 135, 119, 107, 91, 43.

2-Hydroxy-4-methyl acetophenone (6); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/ υ (cm^{-1}): 3200-3500, 1600, 1670; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 1.8 (s, 3H), 2 (s, 3H), 6.2-7 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 21.2, 27.4, 114.3, 118.9, 120.5, 129.4, 144.7, 162.4, 203.2; MS (EI): m/z: 150, 135, 133, 119, 91, 43.

2-Hydroxy-5-methylacetophenone (7); recrystallization from a *n*-hexane/CH_2Cl_2 (10:1 v/v) mixed solvents, mp 42-44°C; IR (KBr)/ υ (cm^{-1}): 3300- 3500, 1650, 1575; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.2 (s, 3H), 2.4 (s, 3H), 6.8-7.4 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 20.6, 27.3, 112.9, 118.2, 132.9, 134.4, 135.1, 160.3, 204.1; MS (EI): m/z: 150, 133, 119, 91, 43.

2-Hydroxy-3,5-dimethylacetophenone (8); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/ υ (cm^{-1}): 2900-3450, 1770-1650; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.4(s, 3H), 2.5 (s, 3H), 2.8 (s, 2H), 7.5 (d, 2H), 12.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 15.3, 20.1, 28.4, 121.1, 124.9, 129.4, 132.4, 134.9, 156.7, 204.3; MS (EI): m/z: 164, 147, 133, 121, 105, 43.

2-Hydroxy-5-bromoacetophenone (9); recrystallization from a *n*-hexane/CH_2Cl_2 (10:1 v/v) mixed solvents, mp 58-61°C; IR (KBr)/ υ (cm^{-1}): 3350- 3620, 1661, 1568; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 2.4 (s, 3H), 6.8-7.4 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 39.3, 116.0, 120.5, 131.0, 136.1, 137.1, 164.3, 198.0; MS (EI): m/z: 215, 200, 135, 120, 92.

1-(2-hydroxy-5-methylphenyl)-1-propanone: (12); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; (b.p. 123-124 °C); IR (Neat)/ υ (cm^{-1}): 3200, 1720, 1620; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 1.(t, 3 H), 2.0 (s, 3 H), 2.6 (m, 4 H), 6.5-7.2 (m, 3 H), 11.9 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 14.2, 18.9, 20.4, 45.3, 114.7, 118.1, 132.5, 134.0, 135.8, 160.8, 196.3; MS (EI): m/z: 178, 161, 135, 119, 91, 71.

1-(2-Hydroxy-5-methylphenyl)-1-butanone: (13); purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/ υ (cm^{-1}): 3300, 1730, 1620; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 0.9(t, 3 H), 1.6 (m, 4 H), 2.3 (s, 3 H), 2.6 (t, 2 H), 6.7-7 (m, 2 H), 7.2 (s,

Table 1. Investigation of MSA amount in the acylation reaction of *p*-cresol

Entry	Substrate (mmol)	MSA (mmol)	Temp. (°C)	Time (min)	Yield[a] (%)
1	1	0.1	80	10	72
2	1	0.2	80	10	86
3	1	0.3	80	10	91
4	1	0.4	80	10	95
5	1	0.4	90	10	95
6	1	0.4	70	10	76
7	1	0.4	65	10	60

[a]Isolated yield

Table 2. Catalytic acylation of phenol or naphthol derivatives with MSA using conventional heating conditions[a]

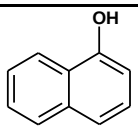
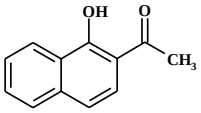
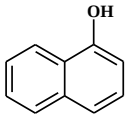
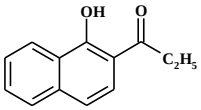
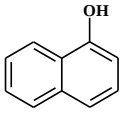
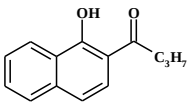
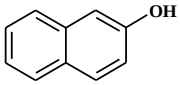
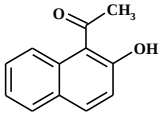
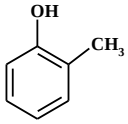
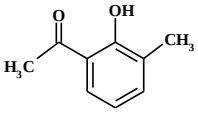
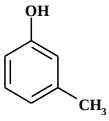
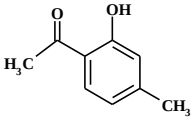
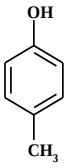
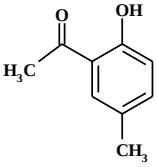
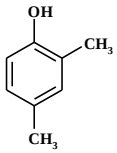
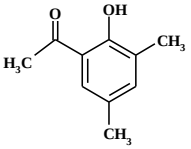
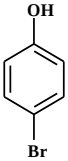
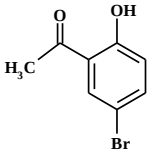
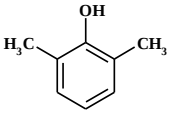
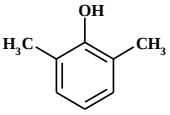
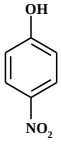
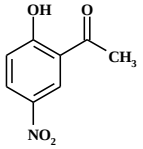
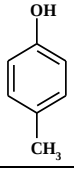
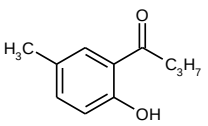
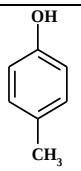
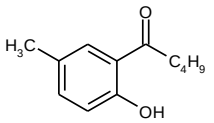
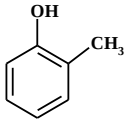
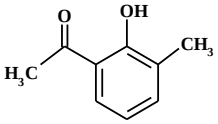
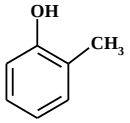
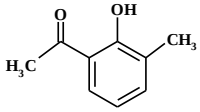
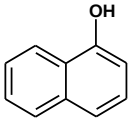
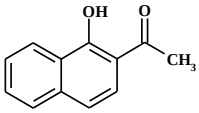
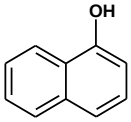
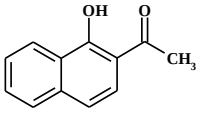
Entry	Substrate	Product	Temp. (°C)	Time (min)	Yield [b] (%)
1			60	10	95
2			60	12	97
3			60	12	95
4			90	10	40
5			70	12	45
6			80	7	80
7			80	10	95
8			60	15	90
9			95	12	85
10			100	30	-
11			100	30	5
12			80	10	95

Table 2. *(Continued)*

Entry	Substrate	Product	Temp. (°C)	Time (min)	Yield [b] (%)
13			85	10	90
14			AcOH/HZSM-5 Zeolite		55[c]
15			$AcOH/Al_2O_3$		73[d] o/p ratio 18/2
16			60	10	88[e]
17			60	10	83[f]

[a]For 1 mmol of substrate it used 5 mmol of aliphatic acid and 0.4 mmol of MSA
[b]isolated yield
[c, d]Ref [20]
[e]Reused catalyst in a first run under similar reaction conditions.
[f]Reused catalyst in a second run under similar reaction conditions.

1 H), 11.9 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 20.3, 22.8, 26.4, 44.1, 113.8, 118.1, 132.4, 134.0, 135.8, 160.1, 191.5; MS (EI): m/z: 192, 177, 175, 149, 91, 57.

3. Results and Discussion

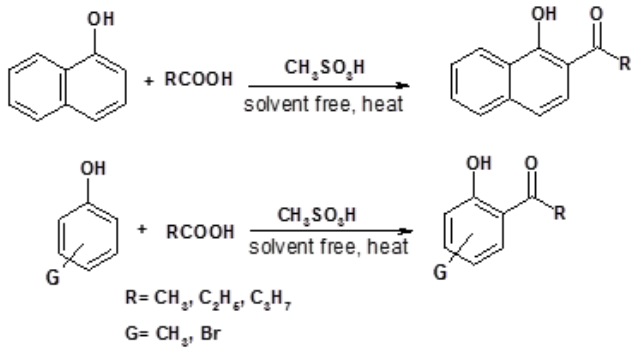
MSA is a strong acid (pK_a=−1.9), which is almost completely ionized at 0.1 M in an aqueous solution, and has a low tendency to oxidize organic compounds. Moreover, it is, far less corrosive and toxic than the usual mineral acids. Under normal conditions aqueous solutions evolve no dangerous volatiles, making it safe to handle. Finally, it is readily biodegradable within 28 days, only forming CO_2 and sulfate, making it an environmentally benign material [36]. Furthermore, it has the advantage, as will be shown, that it can be separated readily from the reaction mixture and reused.

Table 3. *Ortho*-Acylation of 1 mmol *p*-cresol with 5 mmol of various organic acids catalyzed by MSA[a]

Entry	Acid	Temp (°C)	Time (min)	Yield[b] (%)
1	CH_3CO_2H	80	10	95
2	$C_2H_5CO_2H$	85	15	84
3	$C_3H_7CO_2H$	80	10	95
4	$C_4H_9CO_2H$	85	10	90

[a]The reaction occurred in 0.4 mmol MSA under heating conditions
[b]Isolated yield

In this research, we have developed the direct ortho-acylation of phenols and naphthols with methanesulfonic acid (MSA) as the catalyst under conventional heating process (Scheme 1). Firstly, the amount of methanesulfonic acid as catalyst in the acylation reaction of *p*-cresol and the temperature of the reaction were studied. The results of the reaction were shown in the Table **1**. As can be seen in this Table, the optimum mole ratio of substrate/MSA was obtained 1/0.4. We were performed the reaction via heating and solvent free condition for some derivatives of phenol systems that the results are shown in Table **2**. In all of cases, the acylation of these phenolic compounds were performed with aliphatic acids without solvent by using MSA to afford the corresponding ortho-acylated hydroxyaryl compounds, in high yields and short reaction times. As it can be seen from Table **2**, our reported conditions are generally



Scheme 1

applicable to phenols and naphthols derivatives. The reaction is regioselective in that ortho-acylated products are obtained in the most cases, except, with entry 10 (Table 2) in which two ortho positions are occupied with methyl groups and no acylated product was obtained. This sequence proved the high regioselectivity of these reactions into direct ortho acylation. This regioselectivity can be related to chelating the phenolic OH with methanesulfonic acid accomplished with carboxilic acid for the formation of acylium ion. In entry 11, electron-withdrawing substituents reduce the reactivity of substrates and thus, in the long reaction time and high temperature it was afforded in very low yield. For development of using the MSA in acylation reactions with other organic acids, the reaction of *p*-cresol with acetic, propanoic, butanoic and pentanoic acid under free solvent conditions were examined (Table **3**). In this reaction, all the products were formed in high yields and short reaction times under thermal conditions. The IR spectrum of all the acylated products shows broad medium bands in the 3200–3450 cm^{-1} ranges, which attributed to intramolecular hydrogen bonding between phenolic hydrogen and neighboring carbonyl group to confirm the ortho acylated of substrates. Another evidence for this claiming is the general ^1H NMR spectrum that shown a broad band signal at 12.0-12.7 δ as a singlet for phenolic (O-H) groups.

4. Conclusion

This new method for acylation of phenols and naphthols is a mild, efficient, easy and clean reaction for preparation of ortho hydroxyaryl ketones in excellent yields with high regioselectivity into substitution of acyl group in ortho situation. The reactions have occurred without solvent on the various phenol and naphthol derivatives with different organic acids in the presence of of methanesulfonic acid as a Brønsted acid for direct ortho-acylation of phenols and naphthols proves to be a convenient, more general and direct route to various hydroxyaryl ketones.

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