Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 256 (2006) 242–246
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Facile, convenient and regioselective direct *ortho*-acylation of phenols and naphthols catalyzed by Lewis acids under free solvent and microwave conditions

Hossein Naeimi *, Leila Moradi

Chemistry Department, Faculty of Sciences, Kashan University, Kashan 87317, Islamic Republic of Iran

Received 15 February 2006; received in revised form 6 April 2006; accepted 6 April 2006
Available online 9 June 2006

Abstract

Direct *ortho*-acylation of phenol and naphthol derivatives with organic acids smoothly proceeded in the presence of various Lewis acids and microwave irradiation under atmospheric conditions. This method is a new, easy and clean reaction for preparation of *ortho*-hydroxyaryl ketones in excellent yields with high regioselectivity into substitution of acyl group in ortho situation. These reactions have some advantages in competition with other methods such as; short reaction times, high yield and regioselectivity of products, mild reaction conditions, ease the workup of reactions.

Keywords: Regioselective; Acylation; Phenols; Microwave; Free solvent; Lewis acid

1. Introduction

Acylation is one of the fundamental reactions in organic chemistry and can be carried out by wide variety of reagents [1]. Acyl groups play an important role in the chemistry of biomolecules [2], they are fragments of important natural products, such as peptides [2,3] or modified peptide bond isoesters [4] and also they serve as protecting groups [5].

ortho-Hydroxyaryl 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 [6].

Lewis acids have been used as catalysts for an enormous variety of organic reactions, including electrophilic additions to C–C multiple bonds [7–10], hydroborations [11], and acylation of aryl compounds [12–14].

Development of regioselective reactions of aromatic compounds is a fundamental but still important theme in organic synthesis. For example, 2-acylation reactions of phenol and naphthol derivatives provide useful synthetic methods for the preparation of 2-hydroxy phenyl or 2-hydroxy naphthyl ketone derivatives [15].

The acylation can be achieved by treating the free acid with a variety of condensing agents such as hydrogen fluoride [16], concentrated sulfuric acid [17], phosphorus pentoxide [18], poly phosphoric acid [19], fluorosulfonic acid [20] and methane sulfonic acid in alumina [21].

The aromatic acylation with carboxylic acids instead of acid anhydrides and acyl chlorides has attracted interest, because it is an environmentally benign reaction, resulting in formation of a Lewis acid–water complex as the only by-product [22].

On the other hand, microwave-assisted solvent-free synthesis [23] in organic reactions has been of growing interest as an efficient, economic and clean procedure [24].

In this research, we examined the *ortho*-acylation of hydroxyaryl compounds with organic acids, in the presence of Lewis acids and microwave irradiation under atmospheric pressure conditions. The acylation were performed without solvent, to efford the corresponding *ortho*-acylated hydroxyaryl compounds, in high yields.

2. Experimental

2.1. Materials

Chemicals were purchased from the Merck Chemical Company in high purity. All of the materials were of commercial

* Corresponding author. Tel.: +98 361 5555333; fax: +98 361 5552935.
E-mail address: naeimi@kashanu.ac.ir (Hossein. Naeimi).

1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.04.021

reagent grade. Phenol and naphthol compounds and organic acids were purified by standard procedures.

2.2. Apparatus

IR spectra were recorded as KBr pellet on a Perkin-Elmer 781 Spectrophotometer and an Impact 400 Nickolet FTIR Spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with (250 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.

2.3. General procedure

2.3.1. ortho-Acylation of phenol and naphthol derivatives by Lewis acid as catalyst

The procedures of the present *ortho*-acylation reactions are very simple. In a typical reaction of 1-naphthol, $SnCl_4$ (0.41 mmol), 1-naphthol (1 mmol) and acetic acid (1.2 mmol) were combined for 2 min under microwave irradiation (700 W) and atmospheric pressure condition. In all of the reactions, the reaction-mixture temperatures were reached to about 50 °C during microwave irradiation. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane (10 ml) and H_2O (about 20 ml). After extract the organic layer, it was washed with aqueous $NaHCO_3$ (20 ml), dried with $CaCl_2$, filtered and evaporated to give a crude product. Then crude products were chromatographed on silicagel using petroleum ether as the eluent. The products were confirmed by spectroscopic data and physical methods by being consistent with previously reported data [16,25–31].

2-Acetyl-1-naphthol (**a**) mp 98–100 °C (lit. [26] mp 98 °C); IR (KBr)/υ (cm^{-1}) 3300–3600, 1625, 1570; ^{1}H NMR/$CDCl_3$/δ ppm: 2.6 (s, 3 H), 7.5–8.3 (m, 6 H), 13.8 (s, 1 H).

1-Acetyl-2-naphthol (**b**) IR (neat)/υ (cm^{-1}): 3200–3500, 1725, 1675; ^{1}H NMR/$CDCl_3$/δ ppm: 2.6 (s, 3 H), 7.5–8 (m, 6 H), 13.8 (s, 1 H).

2-Hydroxy-3-methyl acetophenone (**c**) Oil (lit. [28] bp 82–84 °C); IR (KBr)/υ (cm^{-1}): 3200–3500, 1650, 1600; ^{1}H NMR/$CDCl_3$/δ ppm: 2.2 (s, 3 H), 2.6 (s, 3 H), 7.5–7.8 (m, 3 H), 12.1 (s, 1 H).

2-Hydroxy-4-methyl acetophenone (**d**) Oil (lit. [31] bp 245 °C); IR (KBr)/υ (cm^{-1}): 3200–3500, 1600, 1670; ^{1}H NMR/$CDCl_3$/δ ppm: 1.8 (s, 3 H), 2(s, 3 H), 6.2–7.0 (m, 3 H), 11.8 (s, 1 H).

2-Hydroxy-5-methyl acetophenone (**e**) mp 42–44 °C (lit. [25] mp 43–44 °C); IR (KBr)/υ (cm^{-1}): 3300–3500, 1650, 1775; ^{1}H NMR/$CDCl_3$/δ ppm: 2.2 (s, 3 H), 2.4 (s, 3 H), 6.8–7.4 (m, 3 H), 11.8 (s, 1 H).

2-Hydroxy-3,5-dimethyl acetophenone (**f**) Oil, IR (KBr)/υ (cm^{-1}): 2900–3450, 1770–1650; ^{1}H NMR/$CDCl_3$/δ ppm: 2.4 (s, 3 H), 2.5 (s, 3 H), 2.8 (s, 2 H), 7.5 (d, 2 H), 12.6 (s, 1 H).

2,4-Dihydroxy acetophenone (**g**) mp 143–145 °C (lit. [25] 144–146 °C); IR (KBr)/υ (cm^{-1}): 3000–3500, 1620,1570; ^{1}H NMR/$CDCl_3$/δ ppm: 2.7 (s, 3 H), 6.4 (s, 1 H), 7.3–7.7 (m, 3 H), 12.8 (s, 1 H).

2,3-Dihydroxy acetophenone (**h**) mp 96–97 °C (lit. [31] mp 97–98 °C); IR (KBr)/υ (cm^{-1}): 3100–3600, 1620, 1490; ^{1}H NMR/$CDCl_3$/δ ppm: 2.8 (s, 3 H), 6 (s, 1 H), 6.8–7.6 (m, 3 H), 12.4 (s, 1 H).

2,5-Dihydroxy acetophenone (**i**) mp 197–199 °C (lit. [25] 198–200 °C) IR (KBr)/υ (cm^{-1}): 3100–3250, 1620, 1500–1580; ^{1}H NMR/DMSO/d_6/δ ppm: 2.4 (s, 3 H), 6.8–7.3 (m, 3 H), 8.7 (s, 1 H), 11.4(s, 1 H).

2-Hydroxy acetophenone (**j**) Oil, bp 215 °C (lit. [25] bp 213 °C); IR (KBr)/υ (cm^{-1}): 2600–3300, 1650, 1490; ^{1}H NMR/DMSO/ d_6/δ ppm: 2.5 (s, 3 H), 6.7 (s, 1 H), 6.8–7.6 (m, 4 H).

2.3.2. Acylation of p-cresol with various organic acids in the presence of $SnCl_4$ catalyst

A 0.1 ml (1.0 mmol) of *p*-cresol, 0.1 ml (1.0 mmol) of propanoic acid and 0.1 g (0.41 mmol) of $SnCl_4$, was treated together for 2 min under microwave irradiation, with 800 W powers. Extraction and identification of the products were carried out as same as procedure that was mentioned in previous section.

1-(2-Hydroxy-5-methylphenyl)-1-propanone (**k**) Oil, bp 121–123 °C (bp 123–124 °C) IR (KBr)/υ (cm^{-1}): 3200, 1720, 1620; ^{1}H NMR/$CDCl_3$/δ ppm: 1 (t, 3 H), 2(s, 3 H), 2.6 (q, 2 H), 6.5–7.2 (m, 3 H), 11.9(s, 1 H).

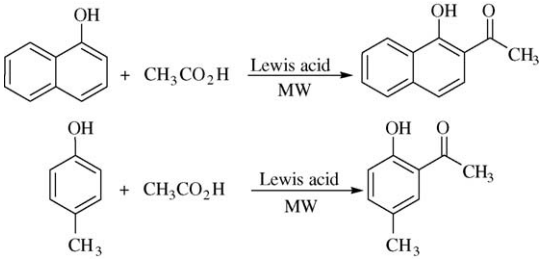
1-(2-Hydroxy-5-methylphenyl)-1-butanone (**l**) Oil, IR (KBr)/υ (cm^{-1}): 3300, 1730, 1620; ^{1}H NMR/$CDCl_3$/δ ppm: 1.2 (t, 3 H), 1.7 (q, 2 H), 2.3 (s, 3 H), 6.7–7 (m, 3 H), 7.2 (s, 1 H), 11.9 (s, 1 H).

1-(2-Hydroxy-5-methylphenyl)-1-pentanone (**m**) Oil, IR (KBr)/υ (cm^{-1}): 3250, 1730, 1630; ^{1}H NMR/$CDCl_3$/δ ppm: 0.7 (t, 3 H), 1.4 (m, 4 H), 2 (s, 3 H), 2.6 (t, 2 H), 6.4–7(m, 3 H), 7.2(s, 1 H).

3. Results and discussion

In the first time, we have studied the acylation reaction of *p*-cresol (as a phenol derivative) and 1-naphthol (as a naphthol derivative) with acetic acid in the presence of several Lewis acids such as; $FeCl_3$, $ZnCl_2$, $BiCl_3$, $SnCl_4$, $AlCl_3$, $BF_3(C_2H_5)_2O$, $ZrCl_4$, $SbCl_3$ and Al_2O_3 (Scheme 1).

The results show that in the presence of medium and weak Lewis acids, $SnCl_4$, $BF_3(C_2H_5)_2O$, $ZnCl_2$ and $FeCl_3$, *ortho*-acylated products were obtained in high yields whereas by using the $ZrCl_4$, Al_2O_3 and $SbCl_3$ as catalyst, no acylated product was obtained (Tables 1a and 1b).



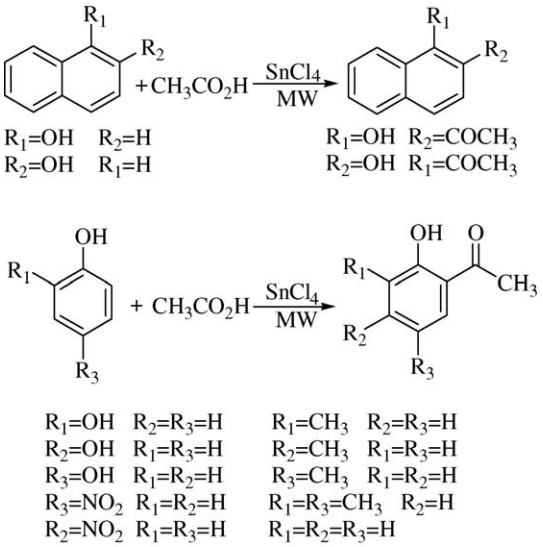
Scheme 1.

Table 1a
Acylation of 0.69 mmol 1-naphthol with various Lewis acids by 1.2 mmol of HOAc

Entry	Lewis acid	mmols of Lewis acid	Power (W)	Time (min)	Yield (%)
1	$SnCl_4$	0.41	700	2	90
2	$BF_3(C_2H_5)_2O$	0.41	600	2	95
3	$ZnCl_2$	0.73	800	2	70
4	$FeCl_3$	0.62	500	2	60
5	$AlCl_3$	0.37	700	4	0
6	$BiCl_3$	0.32	200	0.66	10
7	$ZrCl_4$	0.43	800	3	0
8	$SbCl_3$	0.44	900	3	0
9	Al_2O_3	0.49	900	3	0

Table 1b
Acylation of 0.95 mmol *p*-cresol with various Lewis acids by 1.2 mmol of HOAc

Entry	Lewis acid	mmol of Lewis acid	Power (W)	Time (min)	Yield (%)
1	$SnCl_4$	0.41	800	3	95
2	$BF_3(C_2H_5)_2O$	0.21	800	1.7	98
3	$ZnCl_2$	0.73	400	2	95
4	$FeCl_3$	0.31	400	2	95
5	$AlCl_3$	0.37	800	2	0
6	$BiCl_3$	0.63	300	2	90
7	$ZrCl_4$	0.43	800	3	0
8	$SbCl_3$	0.44	800	3	0
9	Al_2O_3	0.49	900	3	0



Scheme 2.

In continuation of this work, we have used $SnCl_4$, as the best reagents for *ortho*-acylation of various phenol and naphthol derivatives with acetic acid, under microwave conditions (Scheme 2). The corresponding results were indicated in Table 2.

As shown in Table 2, the reaction is regioselective and chemoselective in which C-acylation is occurred. In all of cases, particularly those with available para positions, we have obtained only the *ortho*-C-acylated product and no *para*-acylated product, was obtained.

Table 2
Acylation of 1 mmol phenol or naphthol derivatives with 1.2 mmol HOAc and 0.41 mmol of $SnCl_4$

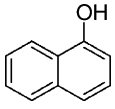
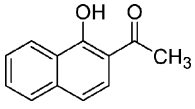
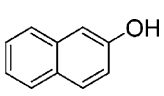
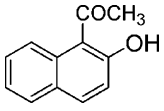
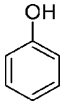
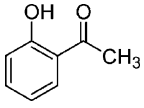
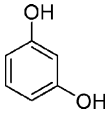
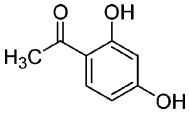
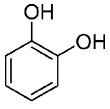
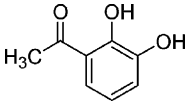
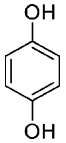
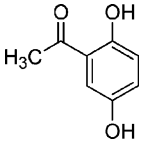
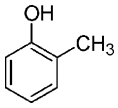
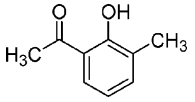
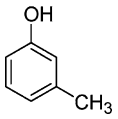
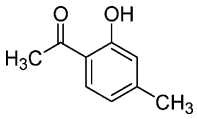
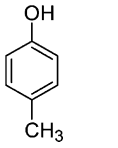
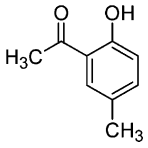
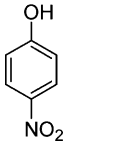
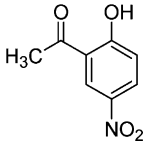
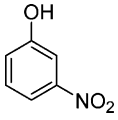
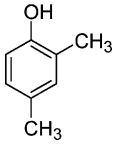
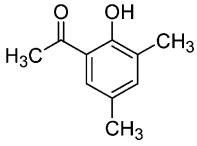
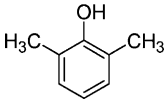
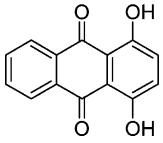
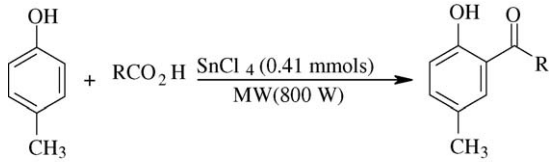
Entry	Substrate	Product	Power (W)	Time (min)	Yield (%)[a]
1			700	2	90
2			700	2	20
3			700	2	90
4			600	2	95
5			600	2	95
6			600	2	95

Table 2 (*Continued*)

Entry	Substrate	Product	Power (W)	Time (min)	Yield (%)[a]
7			800	3	40
8			700	2	90
9			800	3	95
10			800	2	20
11		–	800	3	0
12			800	3	95
13		–	800	3	0
14		–	800	3	0

[a] Isolated yield based on the phenol and naphthol substrates.

This sequence are consisted with attention to entry 13 in Table 2 in that 2,6-dimethyl phenol did not produce *para*-acylated product in the reaction conditions. Also, when substituents on substrate were electron withdrawing, no acylated product was obtained (entries 11 and 14). In other cases, *ortho*-acylated compounds were chemo-selectively achieved in high yields.



R=CH_3, C_2H_5, C_3H_7, C_4H_9, Ph

Scheme 3.

For development of using the $SnCl_4$ in acylation reactions with other organic acids, we have used this Lewis acid in acylation of *p*-cresol, by propanoic, butanoic, pentanoic and benzoic acid under free solvent and microwave conditions (Scheme 3). The obtained results are summarized in Table 3. As shown in this Table, in the reaction of *p*-cresol with all of the organic acids

Table 3
ortho-Acylation of 1 mmol *p*-cresol with 1 mmol of various organic acids, in the presence of $SnCl_4$

Entry	Acid	Time (min)	Yield (%)
1	CH_3CO_2H	3	95
2	$C_2H_5CO_2H$	2	90
3	$C_3H_7CO_2H$	2	95
4	$C_4H_9CO_2H$	2	95
5	$PhCO_2H$	4	95

were also produced *ortho*-acylated compounds in high yields and short reaction times.

The presence of OH stretching broad bands in the 3100–3500 cm^{-1}, C=O stretching strong bands in 1620–1670 cm^{-1} IR region, and existence of the broad singlet peak with δ (11.8–13.8) ppm in the ^1H NMR data in all of the products, are completely consistent with the *ortho*-acylated phenols and naphthols.

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 obtained compounds are very important because they are intermediates in the synthesis of many other organic compounds. The reactions have also occurred without solvent on the various phenol and naphthol derivatives with different organic acids in the presence of a lot of mild Lewis acids under microwave irradiation and atmospheric condition.

These reactions have some advantages in competition with other methods such as; short reaction times, high yields and regioselectivity of products, simplicity of the reaction, mild reaction conditions, ease the workup of reactions.

Acknowledgements

We are grateful to the University of Kashan Research Council for the partial support of this work and indebted to Mr. Mahdi Naghibi Fard for his valuable helps.

References

[1] M.A. Ogliaruso, J.F. Wolfe, in: S. Patai (Ed.), In the Chemistry of Acid Derivatives: Supplement B, Part 1, Interscience, Chichester, 1979, pp. 267–490.
[2] R.J. Simmonds, Chemistry of Biomolecules: An Introduction, The Royal Society of Chemistry, Cambridge, 1992.
[3] M. Bodanszky, Peptide Chemistry, Springer, Berlin, 1993.
[4] J. Magrath, R.H. Abeles, J. Med. Chem. 35 (1992) 4279–4283.
[5] T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons Inc., New York, 1991.
[6] D.J. Crouse, S.L. Hulbut, J. Org. Chem. 46 (1981) 370.
[7] J.H. Clark, A. Rénson, K. Wilson, Catal. Lett. 61 (1999) 51.
[8] G. Capozzi, G. Romeo, F. Marcuzzi, J. Chem. Soc.: Chem. Commun. (1982) 959.
[9] D.S. Bose, V. Lakshminarayana, Synthesis (1999) 66.
[10] J.S. Panek, P.F. Cirillo, J. Org. Chem. 58 (1993) 999.
[11] D.A. Evans, A.R. Muci, R. Stuermer, J. Org. Chem. 58 (1993) 5307.
[12] M. Misono, N. Nojiri, Appl. Catal. 64 (1990) 1.
[13] O. Mitsui, K. Yohei, Patent DE 3441072 (1985).
[14] M. Guisnet, G. Perot, in: R.A. Sheldon, H. van Bekkum (Eds.), The Fries Rearrangement in Fine Chemicals Through Heterogeneous Catalysis, Wiley-VCH, Weinheim, 2001, pp. 211–216.
[15] R. Martin, Org. Prep. Proced. Int. 24 (1992) 369.
[16] L.F. Fieser, E.B. Hershberg, J. Am. Chem. Soc. 62 (1940) 49.
[17] R.D. Haword, J. Chem. Soc. (1932) 1125.
[18] J.W. Cook, J. Chem. Soc. (1932) 1472.
[19] J. Koo, J. Org. Chem. 28 (1963) 1134.
[20] W. Baker, G.E. Coates, F. Glockling, J. Chem. Soc. (1951) 1376.
[21] H. Sharghi, B. Kaboudin, J. Chem. Res. S (1998) 628.
[22] I.V. Kozehevinco, Appl. Catal. A: Gen. 256 (2003) 3–18.
[23] (a) A. Loupy, J. Peti, F. Hameline, Synthesis (1998) 1213;
(b) R.S. Varma, Green Chem. 1 (1999) 43.
[24] (a) R. Gedye, F. Smith, K.C. Westaway, H. Ali, L. Baldisera, L. Labergl, J. Rousell, Tetrahedron Lett. 27 (1986) 279;
(b) R.J. Giguere, R.J. Bray, S.M. Duncan, G. Majetich, Tetrahedron Lett. 27 (1986) 4945.
[25] S. Paul, P. Nanda, R. Gupta, A. Loupy, Synthesis (2003) 2877.
[26] R.W. Stoughton, J. Am. Chem. Soc. 57 (1935) 202.
[27] D.J. Crouse, L.S. Hurlbut, D.M.S. Wheeler, J. Org. Chem. 46 (1981) 374.
[28] A. Bensary, N.T. Zavery, Synthesis (2003) 267.
[29] M. Julia, F. Chastrette, Bull. Chem. Soc. Fr. (1962) 2255.
[30] S. Kobayashi, M. Moriwaki, I. Hachiya, Synlett (1995) 1153.
[31] R. Stevence, Dictionary of Organic Compounds, 5th ed., Eyre & Spottiswoode Ltd. E. & F. N. Spon Ltd., 1982.