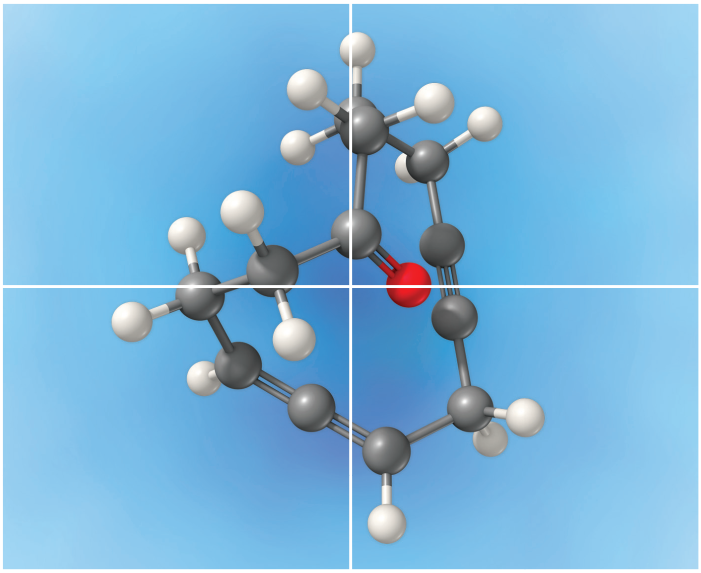
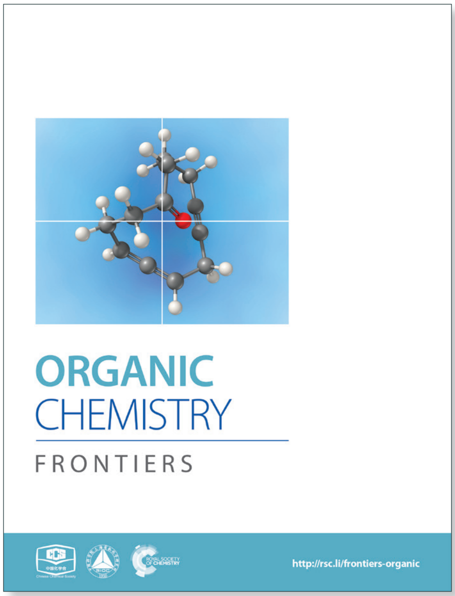
ORGANIC
CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Organic Chemistry Frontiers RSCPublishing

ARTICLE

Regioselective direct ortho C-acylation of phenol and naphthol derivatives catalyzed by modified $ZnCl_2$ on Al_2O_3 as a catalyst under solvent-free and microwave conditions

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Hossein Naemi,[a,]* Atefeh Amini[a] and Mohsen Moradian[b]

In this study, we attempt to present a new and practical method for the synthesis of some ortho *c*-acylated mono- and di-hydroxyaromatic moieties. A Friedel–Crafts reaction of phenolic substrates was carried out in the presence of zinc chloride supported on the alumina as a catalyst and carboxylic acids as acylated agents that lead to a regioselective ortho *c*-acylated compounds with respect to the phenolic hydroxyl group. The reaction proceeds smoothly under microwave irradiation with a wide range of starting materials. This reaction gives access to a variety of acylated compounds in high yield and in the absence of solvent by using of the more active and stable solid catalyst. Also, this reaction has occurred with highly regioselectivity at ortho position and can be compatible with other reported methods. The obtained hydroxyaryl ketones were characterized and confirmed by physical and spectroscopic data.

Introduction

Acylation reactions are largely employed in fine chemical industry to produce a variety of synthetic fragrances and pharmaceuticals [1]. Ortho-hydroxyacetophenone (o-HAP) is a key intermediate for producing 4-hydroxycoumarin and warfarin, which are both used as anticoagulant drugs [2], and it has been also employed for obtaining flavonones [3, 4]. Phenolic drugs containing acyl groups are attractive targets for prodrug design due to their extensive first pass metabolism [5] (Fig. 1).

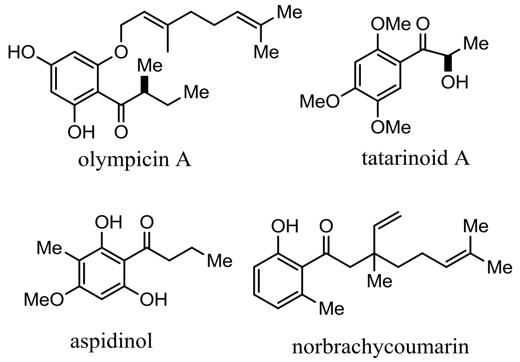


Fig. 1 Some natural products and drugs containing o-acylphenols

Three Major synthetic pathways can be followed in this transformation, 1) the well-known Friedel–Crafts acylation reaction [6, 7], 2) Copper-catalyzed ortho-acylation of phenols with aryl aldehydes [8] and 3) metal-catalyzed C–H activation of ketone moieties in the presence of [bis(trifluoroacetoxy)iodo]benzene as oxidant [9]. The Friedel–Crafts acylation of phenols has been generally carried out with Brønsted or Lewis acid catalysts[10, 11]. The Friedel–Crafts acylation can be achieved by reaction of acid chlorides with a variety of condensing agents such as hydrogen fluoride [12], concentrated sulfuric acid [13], phosphorus pentoxide [14], polyphosphoric acid [15] and methane sulfonic acid in alumina [16]. In the past few years the possibility of obtaining *o*- and *p*-hydroxyacetophenone derivatives using solid catalysts with respect to the more active, stable, easily separated and recycled catalysts has been studied. Strong Brønsted solid acids, such as ionic resins, nafion® and heteropolyacids exhibited moderate activity for the liquid-phase Fries rearrangement of phenols and form preferentially *p*-hydroxy acetophenone because are quickly deactivated by waste formation [17].

The development of cleaner technologies is a major challenge in green chemistry. Microwave enhanced chemistry represents a fundamental step forward in the capabilities of synthetic chemists. Today, the use of dedicated microwave instrumentations is becoming popular in many undergraduate laboratories, providing students with an in-depth view on the new advancements of the modern synthesis [18]. A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other mixtures [19]. Adsorption of surfactants at the solid–liquid interface is an important topic in numerous processes ranging from mineral beneficiation to detergency [20, 21]. Active alumina, due to its high surface area, mechanical strength and thermal stability has been found several

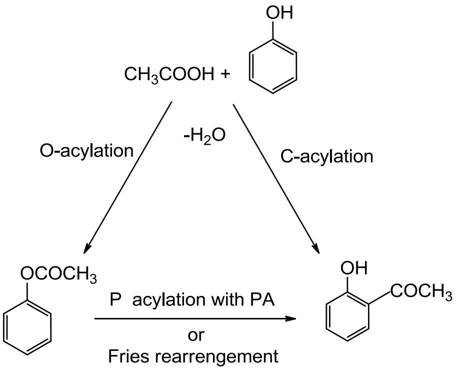
[a] *Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, 87317, I.R. Iran; Tel: +98-361-5912388; Fax; +98-361-5552397; Email: naeimi@kashanu.ac.ir*

[b] *Institute of Nanoscience and Nanotechnology, University of Kashan, Kashan, I.R. Iran*

Organic Chemistry Frontiers Accepted Manuscript

applications as an adsorbent and catalyst [22]. The application of zinc chloride supported on the alumina surface as catalyst were previously reported[23, 24]. In organic reactions, microwave-assisted solvent-free synthesis [25, 26] has been of growing interest as an efficient, economic and clean procedure [27].

In this research, we examined the ortho-acylation of phenol and naphthol compounds with organic acids as acylating agents catalyzed by alumina supported-Lewis acid as a new catalyst under microwave irradiation and atmospheric pressure conditions. They catalyze two main reaction pathways leading from phenol to *o*-hydroxyacetophenone, i.e. the direct *c*-acylation of phenol and the *o*-acylation of phenol forming the phenyl acetate intermediate, which is consecutively transformed via intermolecular phenol/phenyl acetate *c*-acylation (Scheme 1). All of the reactions were accomplished in the absence of solvent, to afford the corresponding ortho-acylated hydroxyaryl compounds in high yields.



Scheme 1 Reaction network for the acylation of phenol with acetic acid

Results and Discussion

Analysis of the catalyst

The heterogeneous $ZnCl_2@Al_2O_3$ as a new and more active Lewis acid catalyst were investigated by powder X-ray diffraction (XRD) and FT-infrared spectroscopy (FT-IR) indicate successful bonding of zinc ions into the internal surface of solid alumina.

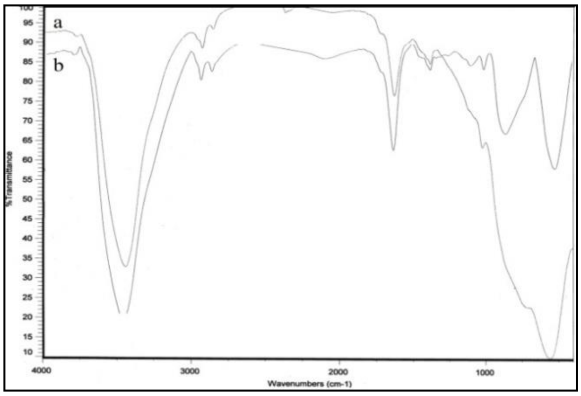


Fig. 2 FT-IR spectra of the Al_2O_3 (a) and $ZnCl_2@Al_2O_3$ (b)

A comparison between the IR spectra of catalyst with that of the initial alumina demonstrates the presence of zinc adsorbed on the surface of the solid alumina.

Fig. **2** shows the FT-IR spectra of alumina **a** and $ZnCl_2@Al_2O_3$ **b**, absorption bands near 3411 cm^{-1} represent O-H mode of the alumina. In the modified catalyst, the bands at 611 cm^{-1} and 735 cm^{-1} according to the Zn-O band are clearly represented [28].

The XRD pattern of alumina and $ZnCl_2@Al_2O_3$ demonstrates typically reflections between 2θ= 20 and 70°. The X-ray diffraction (XRD) pattern of modified alumina with zinc chloride is similar to those of untouched alumina (Fig. **2**), which shows the crystallinity of the catalyst is retained.

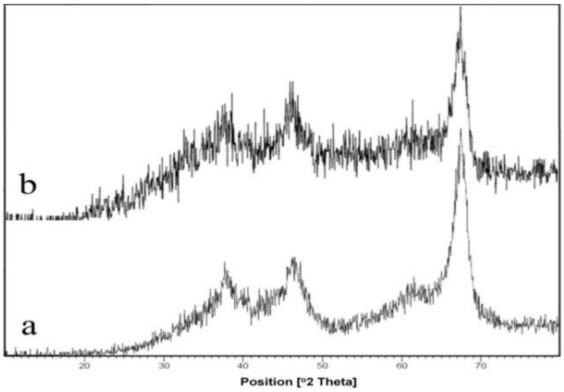
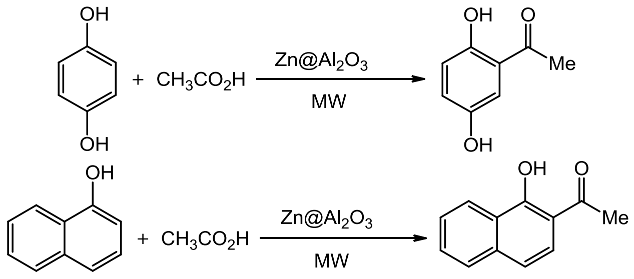


Fig. 3 XRD pattern of Al_2O_3 (a) and $ZnCl_2@Al_2O_3$

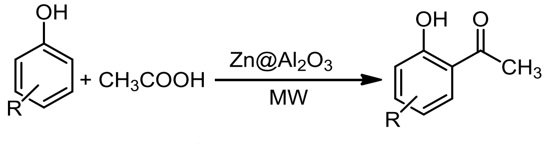
Catalytic studies

In the first time, we have studied the acylation reaction of hydroquinone (as a phenol moiety) with acetic acid in the presence of alumina supported zinc chloride ($ZnCl_2@Al_2O_3$) as new solid catalyst under microwave irradiation and solvent free conditions (Scheme 2). The results were shown that in the presence of $ZnCl_2@Al_2O_3$ the *ortho*-acylated products were obtained in high yields.



Scheme 2 Acylation of hydroquinone and 2-naphthol

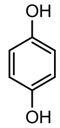
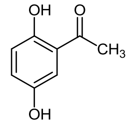
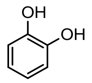
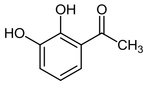
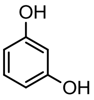
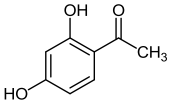
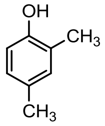
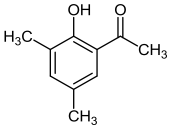
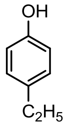
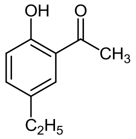
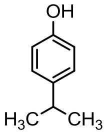
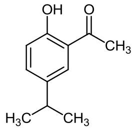
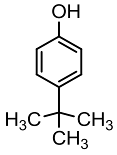
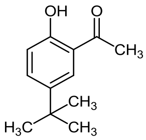
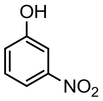
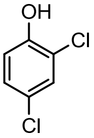
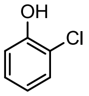
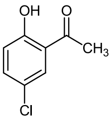
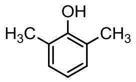
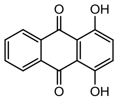
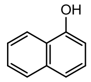
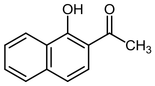
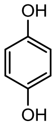
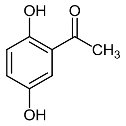
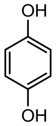
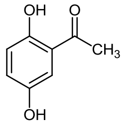
In continuation of this work, we have used $ZnCl_2@Al_2O_3$ for *ortho*-acylation of various phenol and naphthol derivatives with acetic acid, under microwave conditions (Scheme 3). The corresponding results were indicated in Table 1. As shown in Table 1, the reaction is regioselective in which *c*-acylation is occurred. In all of cases, particularly those with available *para* positions, the reaction was obtained the *o*-acylated product in high yields and the *para* products nearly were not observed.



Scheme 3 Acylation reaction of various phenols

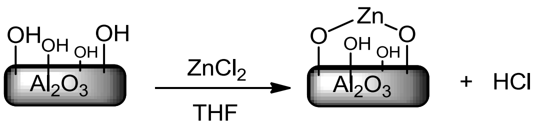
Organic Chemistry Frontiers Accepted Manuscript

Table 1 Catalytic ortho *c*-Acylation of some phenolic moieties with acetic acid[a]

Entry	Substrate	Product	Power (W)	Time (min)	Yield (%)
1			450	1.3	98
2			450	1.5	97
3			450	1.8	98
4			600	2	95
5			450	2	83
6			450	2.2	85
7			450	2	80
8		-	900	3.0	0
9		-	900	5.0	0
10		-	900	5.0	0
11			900	5.0	20
12		-	900	3.0	0
13		-	900	4.0	0
14			900	1.6	98
15[c]			900	10	0
16[d]			900	8	62

[a] Reaction conditions: phenol or naphthol derivatives 0.95 mmol, HOAc 1.2 mmol, [Zn] 0.73 mmol as $ZnCl_2@Al_2O_3$. [b] Isolated yield based on the phenol and naphthol substrates. [c] In the presence of excess clean Al_2O_3 as catalyst. [d] In the presence of $ZnCl_2$ (1 mmol) as catalyst.

The hydroxyl groups on the surface of activated alumina were reacted with zinc chloride and formed a new composite modified alumina that the zinc ions bonded to oxygen of the surface (Scheme 4). In this case, the zinc ions supported on the surface and can be applied as catalyst.



Scheme 4 Preparation of the solid heterogeneous $ZnCl_2@Al_2O_3$ as a catalyst

Generally, in this method, due to the low activity of the catalyst, the phenol rings with electron withdrawing groups such as halogens and nitro groups hardly reacted and the desired products have low yields (Table 1, entries 8-11). If both *ortho* position of the phenol ring occupied with some other substituent, the reaction does not occur (Table 1, entry 12). This sequence is consisted with attention to entry 9 in Table **1** in that 2,6-dimethyl phenol did not produce *para*-acylated product in the reaction conditions. In other cases, *ortho*-acylated compounds were chemo-selectively achieved in high yields (Table 1, entries 1-7 and 14). In Table 1, entry 11, the reaction of 4-chlorophenol with acetic acid in the presence of the $ZnCl_2@Al_2O_3$ as solid catalyst only produce 20 % of the desired product and the initial substituted phenol was remain untouched at end of the reaction.

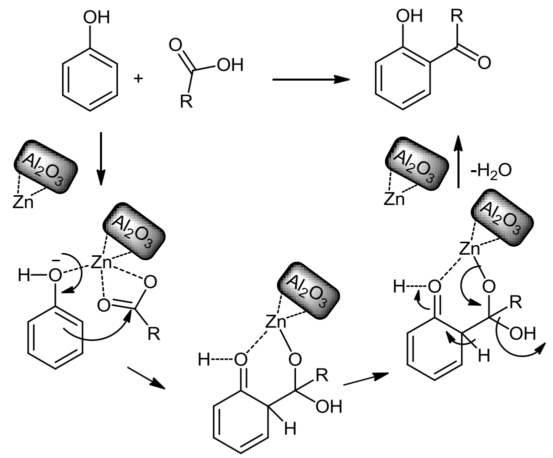
For further investigation about catalytic activity of modified alumina, the desired reaction was performed in the presence of clean Al_2O_3 as catalyst and any product was observed. Also, in the presence of $ZnCl_2$ as a neat catalyst, the desired product was formed only with 68 % yield (Table 1, entries 15 and 16).

A simplified and possible mechanism for this useful protocol was provided in the Scheme **5**. Regioselectivity is fundamental for this methodology and achieved from the key step of zinc chelation to the both phenol and carboxylic acid substrates. After chelation, the acid substrate localized at nearest position of the phenol substrate. Thereupon, the active phenol ring attacks and then joint to the carbonyl group of carboxylic acid from the *ortho* position (Scheme 5).

For extended application of this solid catalyst in acylation reactions, in continuation, we also examined acylation of hydroquinone with other organic acids, such as propanoic, butanoic, and pentanoic acid under free solvent and microwave conditions. The obtained results are summarized in Table 2. As shown in this Table, in this reaction, the solid catalyst can

Organic Chemistry Frontiers Accepted Manuscript

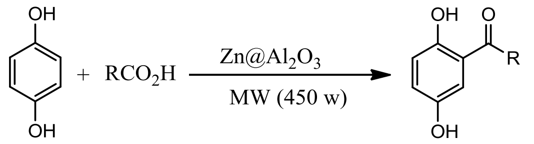
catalyze the reaction in the presence of some organic acids and produced *ortho*-acylated compounds in high yields and short reaction times.



Scheme 5 A possible mechanism of the acylation reaction in the presence of modified alumina as catalyst

The presence of OH stretching broad bands in the 3100–3500 cm^{-1}, C=O stretching strong bands in 1735–1750 cm^{-1} IR region, and existence of the broad singlet peak with δ (9.4–11.9) ppm in the ^{1}H NMR data in all of the products, are completely consistent with the *ortho*-acylated phenols and naphthols.

Table 2 Ortho-Acylation of hydroquinone with various aliphatic carboxylic acids[a]



Entry	R	product	Time (min)	Yield (%)[b]
1	C_2H_5	**g**	1.8	100
2	C_3H_7	**h**	3.0	95
3	C_4H_9	**i**	3.3	100

[a] Reaction conditions: hydroquinone 0.95 mmol, various organic acids 1.3 mmol in the presence of 0.73 mmol [Zn] as $ZnCl_2@Al_2O_3$. [b] Isolated yields Footnote text.

Experimental Section

Materials

Chemicals were purchased from the Merck and Fluka Chemical Companies in high purity. All of the materials were of commercial reagent grade. The phenols and naphthols were purified by standard procedures and purity determined by thin layer chromatography (TLC) and gas chromatography (GC).

Apparatus

IR spectra were recorded as KBr pellet on a Perkin-Elmer 781 Spectrophotometer and an Impact 400 Nickolet FTIR Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with (400 MHz) Spectrometer using of TMS as an internal reference. Microwave irradiations were carried out in microwave oven specially designed for organic synthesis (Milestone LAVIS 1000 Basic Microwave) from Milestone Company. Meting 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.

Preparation of supported zinc chloride at alumina

A suspension of activated Al_2O_3 at 300 °C during 5 h (3.0 g) and $ZnCl_2$ (1.0 g) in 40 ml of THF was refluxed at 80 °C for 15 h. After cooling the resulting masses to room temperature, the solids were filtered, washed successively with acetone and absolute ethanol and was dried under vacuum. The amount of the zinc ion on the surface of solid modified catalyst was obtained from atomic absorption spectroscopy (1.45 mmol/g Al_2O_3). The solid modified catalyst also characterized by FT-IR and XRD spectrophotometers.

Typical procedure for the synthesis of phenol and naphthol derivatives by alumina supported-Lewis acid

The procedures for the *ortho*-acylation reaction are very simple. In a typical reaction, hydroquinone (0.95 mmol), $ZnCl_2@Al_2O_3$ (0.50 g) and acetic acid (1.2 mmol) were combined for 80 sec under microwave irradiation (450 W) and under atmospheric pressure condition. The reaction-mixture temperatures were reached to about 40 °C during microwave irradiation. After cooling to room temperature, the reaction mixture was dissolved in ethyl acetate (15 ml) and H_2O (about 30 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 [29-31].

2,5-Dihydroxy acetophenone (***a***) mp 194–196 °C (lit.[31] mp 198–200 °C); IR (KBr)/υ (cm^{-1}): 3100–3500, 1620, 1500–1580, 1200, 1290; ^{1}H NMR/DMSO/d^6/δ ppm: 2.4 (s, 3 H), 6.5–6.9 (m, 3 H), 8.6 (s, 1 H), 9.4(s, 1 H).

2,6-Dihydroxy acetophenone (***b***) mp 158–162 °C (lit.[30] mp 156–158 °C); IR (KBr)/υ (cm^{-1}): 3100–3500, 1630, 1515, 1586, 1297; ^{1}H NMR/$CDCl_3$/δ ppm: 2.6 (s, 3 H), 6.4 (d, 2H, J=5.8 Hz), 7.2 (m, 1 H), 11.8 (s, 2 H).

2,4-Dihydroxy acetophenone (***c***) mp 142–145 °C (lit. [31] mp 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-Hydroxy-3,5-dimethyl acetophenone (***d***) Oil, b.p. 230 °C (lit.[29] b.p. 227 °C); IR (KBr)/υ (cm^{-1}): 3100–3450, 1770, 1650, 1190, 1250; ^{1}H NMR/$CDCl_3$/δ ppm: 1.9 (s, 3 H), 2.4 (s, 3 H), 2.8 (s, 3 H), 6.8 (s, 1 H), 7.3 (s, 1 H), 12.6 (s, 1 H).

2,3-Dihydroxy acetophenone (***e***) mp 96–97 °C (lit. [29] mp 97–98 °C); IR (KBr)/υ (cm^{-1}): 3100–3600, 1724, 1450; ^{1}H NMR/$CDCl_3$/δ ppm: 2.6 (s, 3 H), 6.8 (t, 1H, J=5.2 Hz), 7.1 (d, 1H, J=5.3 Hz), 7.6 (d, 1H, J=5.4 Hz), 5.8 (s, 1 H), 12.4 (s, 1 H).

2-Acetyl-1-naphthol (***f***) mp 96–98 °C (lit.[29] mp 98 °C); IR (KBr)/υ (cm^{-1}) 3100–3500, 1632, 1573, 1599; ^{1}H NMR/$CDCl_3$/δ ppm: 2.7 (s, 3 H), 6.85 (d, 1H, J=6.4 Hz), 7.3 (m, 2 H), 7.62 (t, 2H, J=5.5 Hz), 6.49 (d, 1H, J=5.6 Hz), 14.2 (s, 1 H).

D. Acylation of hydroquinone with various organic acids in the presence of $ZnCl_2@Al_2O_3$ *catalyst;* 0.1 gr (0.95 mmol) of hydroquinone, 0.1 ml (1.3 mmol) of propanoic acid and $ZnCl_2@Al_2O_3$ catalyst (prepared by the method described in

Organic Chemistry Frontiers Accepted Manuscript

This journal is © The Royal Society of Chemistry 2012

part 2.3.1), was treated together for 110 s under microwave irradiation, with 450W powers. Extraction and identification of the products were carried out as same as procedure that was mentioned in previous section.

1-(2,5-Dihydroxy phenyl)-1-propanone (***g***) mp 96-99 °C (lit.[31] mp 95-99 °C) IR (KBr)/υ (cm^{-1}): 3100-3500, 1735, 1440, 1520, 1180; ^{1}H NMR/CDCl$_3$/δ ppm: 1.1 (t, 3 H, J=6.1 Hz), 2.5(m, 2 H), 6.5 (s, 1 H), 6.7 (d, 1 H, J=5.8 Hz), 6.9 (d, 1 H, J=5.8 Hz), 8.6 (s, 1 H), 9.4(s, 1 H).

1-(2,5-Dihydroxy phenyl)-1-butanone (***h***) bp 346.5 °C; IR (KBr)/υ (cm^{-1}): 3250-3500, 1750, 1600, 1650, 1180; ^{1}H NMR/CDCl$_3$/δ ppm: 1.1 (t, 3 H, J=5.5 Hz), 1.8 (m, 2 H), 2.5 (m, 2 H), 6.8 (d, 1 H, J=7.1 Hz), 6.9 (d, 1H, J=7.1 Hz), 7.1 (s, 1H), 5.5 (s, 1H), 11.9 (s, 1 H).

1-(2,5-Dihydroxy phenyl)-1-pentanone (***i***) bp 357.5 °C; IR (KBr)/υ (cm^{-1}): 3160-3400, 1740, 1510, 1190; ^{1}H NMR/CDCl$_3$/δ ppm: 0.9 (m, 3 H), 1.4 (m, 2 H), 1.6 (m, 2 H), 2.5 (t, 2 H, J=6.0 Hz), 6.5(s, 1 H), 6.7 (d, 1 H, J=5.5 Hz), 6.8 (d, 1 H, J=5.3 Hz), 8.6 (s, 1 H), 9.4(s, 1 H).

Conclusions

This new solid catalyst can be used for acylation of mono- and di-hydroxybenzene moieties, to form ortho-hydroxyaryl ketones in high yields. This reaction using the solid acid has advantages such as; reduced pollution, low cost, easy process and workup with high efficiency. The reactions have also occurred in solvent-free conditions under microwave irradiation with respect to the development of cleaner technologies in green chemistry. Also we reported the way for preparation of new compounds with different chemical characteristics that increase the range of underlying causes of this product and achieve optimal conditions for the preparation of this material.

Acknowledgments

The authors are grateful to University of Kashan for supporting this work by Grant No. 159148/15.

Notes and references

1 H. K. Kouwenhoven and H. Van Bekkum, *Handbook of Heterogeneous catalysis*, VCH, Weinheim, Germany, 1997.

2 K. K. and N. Böker, *1,2-, 1,4-, 2,9- and 9,10-anthraquinones and higher fused polycyclic quinone derivatives*, Thieme Verlag, Stuttagart, 2006.

3 M. J. Climent, A. Corma, S. Iborra and J. Primo, *J. Catal.*, 1995, **151**, 60-66.

4 M. T. Drexler and M. D. Amiridis, *J. Catal.*, 2003, **214**, 136-145.

5 C. Santos, M. L. Mateus, A. P. dos Santos, R. Moreira, E. de Oliveira and P. Gomes, *Bioorgan. Med. Chem*, 2005, **15**, 1595-1598.

6 Z. Rappoport, *The chemistry of phenols*, Wiley-Interscience, 2003.

7 J. H. P. Tyman, *Synthetic and natural phenols*, Elsevier Science, 1996.

8 J. Hu, E. A. Adogla, Y. Ju, D. Fan and Q. Wang, *Chem. Commun.*, 2012, **48**, 11256-11258.

9 F. Mo, L. J. Trzepkowski and G. Dong, *Angew. Chem. Int. Ed. Engl.*, 2012, **124**, 13252-13256.

10 I. Neves, F. Jayat, P. Magnoux, G. Perot, F. Ribeiro, M. Gubelmann and M. Guisnet, *J. Mol. Catal. A*, 1994, **93**, 169-179.

11 G. Y. Popova, A. A. Davydov and T. V. Andrushkevich, *React. Kinet. Catal. Lett.*, 1990, **41**, 33-38.

12 L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, 1940, **62**, 1640-1645.

13 R. D. Haworth, *J. Chem. Soc.*, 1932, **0**, 2717-2720.

14 J. W. Cook, *J. Chem. Soc.*, 1933, **0**, 1592-1597.

15 J. Koo, *J. Org. Chem.*, 1963, **28**, 1134-1135.

16 H. Sharghi and B. Kaboudin, *J. Chem. Res.(S)*, 1998, 628-629.

17 M. J. Climent, A. Corma, S. Iborra and A. Velty, *J. Catal.*, 2004, **221**, 474-482.

18 R. S. Varma and V. V. Namboodiri, *Pure Appl. Chem*, 2001, **73**, 1309-1313.

19 G. Nagendrappa, *Resonance*, 2002, **7**, 59-68.

20 W. Wang and J. C. T. Kwak, *Colloid. Surface A* 1999, **156**, 95-110.

21 L. Huang, C. Maltesh and P. Somasundaran, *J. Colloid Interf. Sci.*, 1996, **177**, 222-228.

22 M. Trueba and S. P. Trasatti, *Eur. J. Inorg. Chem.*, 2005, **2005**, 3393-3403.

23 N. Bukhanko, A. Samikannu, W. Larsson, A. Shchukarev, A.-R. Leino, K. Kordás, J. Wärnå and J.-P. Mikkola, *ACS Sustainable Chem. Eng.*, 2013, **1**, 883-893.

24 Z. Fu, Y. Yu, D. Yin, Y. Xu, H. Liu, H. Liao, Q. Xu, F. Tan and J. Wang, *J. Mol. Catal. A-Chem.*, 2005, **232**, 69-75.

25 D. Habibi, M. Nasrollahzadeh and A. T. Kamali, *Green Chem.*, 2011, **13** 3499-3504.

26 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 2000, **1998**, 1213-1234.

27 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279-282.

28 K. B. Kumar and P. Raji, *Rec. Res. Sci. Tech.*, 2011, **3**, 48-52.

29 R. W. Stoughton, *J. Am. Chem. Soc.*, 1935, **57**, 202-204.

30 J. J. Gorman, B. L. Ferguson and T. B. Nguyen, *Rapid Commun Mass Sp.*, 1996, **10**, 529-536.

31 S. Paul, P. Nanda, R. Gupta and A. Loupy, *Synthesis*, 2003, **2003**, 2877-2881.

Organic Chemistry Frontiers Accepted Manuscript

This journal is © The Royal Society of Chemistry 2012