One-Pot Synthesis of Aromatic Hydroxyketones under Microwave Irradiation and Solvent-Free Conditions

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Abstract

An efficient one-pot synthesis of aromatic hydroxyketones with carboxylic acids as acylating agents without solvent under microwave irradiation was reported. The reaction time was only 1-5 min. Besides, this method has a feature of high yields, low cost, easy manipulation and less pollution.

Keywords: One-pot synthesis, Microwave irradiation, Aromatic hydroxyketones, Carboxylic acids, Solvent-free

1. Introduction

Aromatic hydroxyketones are valuble intermediates in the synthesis of pharmaceuticals (Szmant, H. 1989), perfumery (Naeimi, H. et.al 2006), acetophenone resins (Heitling, E. et.al 2004), etc. The classic synthesis commonly involves two steps, esterification of phenols and fries rearrangement which is an intermolecular Friedel-Crafts acylation of phenolic ester (Kozhevnikova, E. F. et.al 2004,Vogt, A. et.al 1995). The disadvantages associated with classic procedures include the use of toxic acid chlorides or acid anhydrates as acylating agents (Rupinder, K. L. et.al 2006, Ludwigshafen, J. M. et.al 1985) and aluminum trichloride as Lewis acids (Miller, E. et.al 1943) and an excess amount of reagents for separation of phenolic ester, which entains environment pollution and tedious workup. Recently, zeolite H-beta (Hoefnagel, A. J. 1993) and montmorillonite clay (Bolognini, M. et.al 2004) are reported to be used as catalysts for synthesis of aromatic hydroxyketones, but these catalysts both need special treatment before use such as calcination at a high temperature. Moreover, the whole reaction process normally requires long reflux times at oil bath. The drawbacks as above described have prompted considerable researches into the development of a new method which is low cost, easy manipulation and less pollution.

Microwave irradiation as a new technology has been widely used in various organic reactions, such as substitution (Mojtahedi, M. M. et.al 1999), addition (Mojtahedi, M. M. et.al 1999), dehydration (Bandgar, B. P. et.al 1999), rearrangement (Khadikar, B. M. et.al 1999) and redox (Palombi, L. et.al 1997). Solvent-free could avoid the use of auxiliary reagents that may be toxic or flammable, and also simplify the follow-up operation. The synthesis without solvent under microwave irradiation has been of growing interest as an efficient, economic and, clean procedure (Pasha, M. A. et.al 2007, Gopalakrishnan, M. et.al 2005). Carboxylic acids are common precursors of acid chlorides and anhydrides and their reactions produced water as the only by-product (Naeimi, H. et.al 2006). From an environment point of view, the aromatic acylation with carboxylic acids has also attracted interest.

In this paper, the mixture of phenols, carboxylic acids, phosphoric acid and phosphorus pentoxide (85% H_3PO_4/P_2O_5) were irradiated in a microwave oven, the target products were obtained by one-pot.

2. Experimental

2.1 General

All reactions were performed in a modified commercial domestic microwave oven (Midea PJ21C-BF) which was equipped with a reflux device. TLC was used to monitor the reaction process. TLC was GF254 thin- layer chromatography with petroleum ether/ethyl acetate (4:1v/v) used as eluent. Melting points were determined on a microscopy apparatus (SGW X-4). IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). All the liquid parent materials are fresh distilled. The products were characterized by comparison of their melting points and boiling points with the literature values.

2.2 General procedure for the preparation of o-/p- Hydroxyacetophenone

A mixture of phenol (9.4g), acetic acid (7.0mL), 85% H_3PO_4 (2mL) and P_2O_5 (0.9g) was irradiated at middle power (231W) in a 50mL one-necked, round-bottomed flask equipped with a reflux device which was placed into a 200mL beaker. The progress of the reaction was monitored by TLC. Upon completion, the products were poured into water (200mL). Extracted the acylation products from water with ether. The water layer was rejected. Distilled the ether layer to remove ether. The *p*-hydroxyacetophenone (*p*-HAP) 9.8g (72%yield) was obtained by filtration and purification. m.p.108-109 ^oC.(lit m.p.109 ^oC); The organic phase detached from the filtration was distilled. Collecting the distillation of 215-218 ^oC to obtain the *o*-hydroxyacetophenone (*o*-HAP) 2.4g (18%yield). (lit b.p.213 ^oC). The IR spectra of the products were accordant with the standard IR spectra respectively.

3. Results and Discussion

Carboxylic acids are less reactive than acid chlorides or acid anhydrates, in the present case, however, the high charge density of the aromatic ring in phenols makes carboxylic acids the best candidate for the electrophilic reaction. Microwave irradiation promoted this electrophilic acylation, because the water as its only by-product was easily removed under microwave irradiation.

3.1 The catalytic medium for the preparation of aromatic hydroxyketones

In our study, the mixture of phosphoric acid and phosphorus pentoxide (85% H_3PO_4/P_2O_5) was choosen as a catalytic medium which was mild, cheap and, easy to be got. More importantly, phosphoric acid and phosphorus pentoxide both were easily washed away by water. The weight ratio of 85% H_3PO_4 to P_2O_5 was 4:1. P_2O_5 mainly played a role of dehydrating agent, since the use of P_2O_5 alone always failed to promote acylation. Phosphoric acid was crucial to the catalytic effectiveness. As a liquid catalyst, it not only promoted acylation but also supplied convenience for the mixing of solids reactants. This catalytic medium has an efficiency under microwave irradiation. Large amount of the catalyst might make reactants darked and parched like the phenomenon reported in previous literature in short times and low power (Kozhevnikova, E. F. et.al 2004), we guessed it may result from the polymerization of olefine ketone which is easily produced under excessive catalyst. The optimal molar ratio of H_3PO_4 to aromatic substrate is 0.3:1.

With carboxylic acids as acylating agents, this “protonic-acid catalytic method” is a preferred one because of its simplicity. There is no large amount of metal salts formed after reaction like Lewis acids. Furthermore, the usage amount of catalyst was largely reduced. This not only saved the production cost, but also decreased the pollution to environment.

3.2 Effect of power and reaction time on yield of products

The power and reaction time both have an obvious effect on yield of products. Taking phenol to react with acetic acid for example, as is shown in table 1, the yield was higher at 231W than that at 119 W, however, when the power was 385 W or upwards, lots of side products formed due to the oxidation of phenols and other side reactions. Microwave irradiation can produce lots of heat in short time, so the temperature is not easy to control if the reaction time is too long. The optional microwave irradiation power was 231W and the reaction time was 2min.

3.3 Acylation of various phenols with acetic acid

Various phenols were treated with acetic acid along with a catalytic amount of catalyst under microwave irradiation and solvent-free conditions. As shown in table 2, most phenols afforded their corresponding aromatic hydroxyketones in excellent yields by one-pot and the reaction time was only 1-3min which was greatly reduced compared with long reflux times by conventional heating. The phenols with electron-donating groups such as $–OCH_3$ were more reactive than those with electron-withdrawing groups such as –Cl, that mainly because the electron-donating groups could increase the electron density of aromatic ring which caused the reaction easier. When a $–NO_2$ on the aromatic ring (entry9), the reaction did not afford the corresponding hydroxyketone. Most phenols could obtain their *ortho*-acylated products in high yields. Due to the poor regioselectivity of phenol (entry1)

and catethol (entry2), the acylation result was a mixture of *ortho*-acylated and *para*-acylated products. However, the regioselectivity of phenol and catethol was enhanced and the *para*-isomer was obtained in high yields under this reaction conditions. In addition, the naphthols and heteroaromatic compound substituted with hydroxyl group also can react in excellent yields.

3.4 Acylation of phenol with various carboxylic acids

In continuation, the acylation of phenol with propionic acid, butanoic acid, valeric acid, succinic acid and benzoic acid in the presence of catalyst without solvent under microwave irradiation was tried, respectively. These reactions also produced *para*-acylated compounds in high yields and in short times except succinic acid. Succinic acid was a binary acid, because of the high charge density of phenol, the diphenyl succinate was easily formed under this reaction conditions. The obtained results of other carboxylic acids were shown in table 3. Thereinto, *p*-hydroxypropiophenone (entry1) is a key intermediate for preparation of ritodrine which is an agonist for β_2 acceptor of adrenalin. Compared with the previous method (Rupinder, K. L. et.al 2006, Ludwigshafen, J. M. et.al 1985, Miller, E. et.al 1943), this new method only took 2 min to finish the reaction with yield of 79%. In an environmentally benign, it is more favourable for large-scale chemical industry production. In addition, microwave irradiation has greatly promoted the smooth progress of the reaction between phenol and solid carboxylic acids such as benzoic acid (entry4) without solvent. Easy sublimation of benzoic acid at 100℃ made the yield lower than that of aliphatic carboxylic acids in table 3.

4. Conclusions

In this paper, we reported an efficient one-pot synthesis of aromatic hydroxyketones with carboxylic acids as acylating agents without solvent under microwave irradiation. In competition with the previous method, it not only simplies the procedure but also diminishes the waste problem of the aforementioned known reactions with metal chlorides. Besides, the reaction time was greatly reduced, from many hours to 1-5 min.

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Kozhevnikova, E. F., Raficc, E., & Kozhevnikov, I. V. (2004). Fries rearrangement of arylesters catalysed by heteropoly acid catalyst regeneration and reuse. *Applied Catalysis A: General*, 260, 25.

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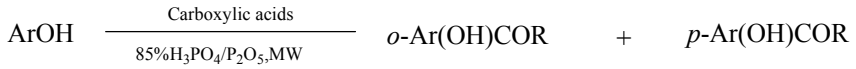

R=-CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -Ph

Scheme 1. Friedel-Crafts acylation between phenols and carboxylic acids

Table 1. Effect of the power and reaction time on yield of aromatic ketones

Power (W)	Time (min)	Yield (%)	Power (W)	Time (min)	Yield (%)
119	5	79	385	1	75
231	1	72	385	2	83
231	3	90	539	1	70
231	5	87	700	30s	68

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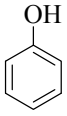
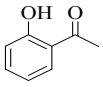
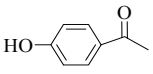
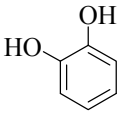
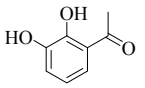
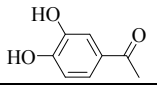
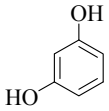
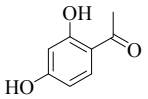
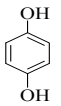
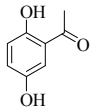
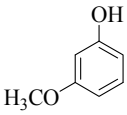
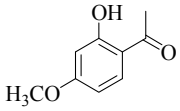
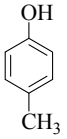
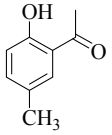
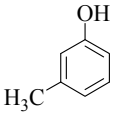
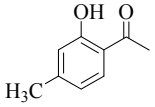
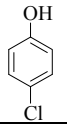
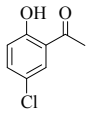
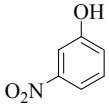
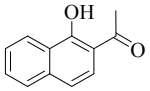
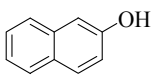
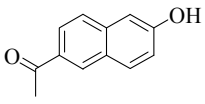
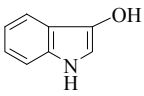
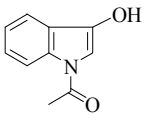
Table 2. Acylation of phenols with acetic acid to aromatic hydroxyketones

Entry	Substrate	Product	Time (min)	Power (W)	Yield (%)	M.p/b.p(℃) Found/Reported[c,d]
1			2	231	90	Liq/213[a]
						108-109/109
2			2	231	89	96-97/97-98
						118-119/119-121
3			2	231	87	143-145/144-146
4			2	231	89	203-205/204-206
5			1	231	95	48-49/47-50
6			3	231	87	43-44/42-44
7			2	231	90	Lip/245[a]
8			2	385	72	52-54/54-56
9		——[b]	4	385	0	——[b]
10			3	119	72	98-100/98
11			3	119	70	169-170/171
12			2	119	75	139-140/140-142

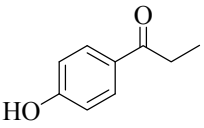
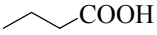
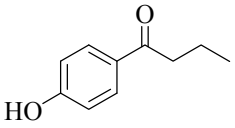
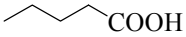
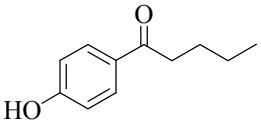
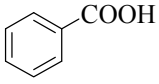
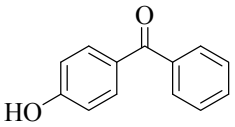
[a] boiling points were determined.

[b] "_____" represents no corresponding hydroxyketone obtained.

[c] Adrich catalog handbook of fine chemicals, 1996-1997.

[d] melting or boiling points from Chemical Abstracts

Table 3. Acylation of phenol with various carboxylic acids to aromatic hydroxyketones

Entry	Substrate	Product	Time (min)	Power (W)	Yield (%)	M.p/b.p(℃) Found/Reported
1			2	231	79	89-90/91[8]
2			3	231	81	146-147/148[a]
3			3	231	83	59-60/60-62[a]
4			5	385	60	130-132/132-135[a]

[a] Adrich catalog handbook of fine chemicals, 1996-1997.