

## A comparative study : One pot synthesis of some prochiral ketones using conventional and microwave assisted methods

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**Abstract :** Polyphosphoric acid (PPA) has been used to synthesize a number of prochiral aryl ketones as well as  $\alpha,\beta$ -unsaturated diaryl ketones by conventional and microwave assisted methods in moderate to good yield. The microwave assisted method is advantageous due to increased yield and high purity of products within incredible short period of time.

**Keywords :** Acylation, chalcone, microwave, polyphosphoric acid, prochiral ketone.

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### Introduction

The various prochiral aryl ketones like monosubstituted and disubstituted propiophenone and benzophenone are used in the synthesis of agrochemicals, pharmaceuticals, and fine chemicals<sup>1</sup>. The propiophenone derivatives are important drug intermediates and used in the preparation of organic compounds such as alkoxides, imines, alcohols, acetals, cyonhydrins, etc. while some substituted benzophenones show interesting photochromic property in a variety of solvents at different pH values<sup>2</sup>. Now-a-days, benzophenone derivatives are widely used in sunscreen lotions for ultraviolet-A protection. Besides, they possess biological activity like antitumour and anti-convulsive<sup>3</sup> against RNA virus, hepatitis-C. In this context, we have synthesized various mono and disubstituted analogues of propiophenone and benzophenone by using polyphosphoric acid (PPA) as acylating agent. Polyphosphoric acid serves as a highly efficient and inexpensive catalyst for Friedal-Craft acylation of aromatic compounds using aromatic carboxylic acids<sup>4</sup>. It has been widely used in synthetic chemistry<sup>5-9</sup> for cyclization, dehydration, acylation, alkylation etc. We encouraged by a few recent reports of the use of PPA in conjugation with microwaves<sup>10,11</sup> to study the Friedal-Craft acylation using PPA-benzoic acid and PPA-propionic acid.

The synthesis of  $\alpha,\beta$ -unsaturated diaryl ketones viz. chalcones has been the subject of extensive study over many decade and a number of synthetic routes are reported e.g. Suzuki reaction<sup>12</sup>, Claisen-Schmidt condensation<sup>13</sup>, etc. We have explored the above protocol for

synthesis of various chalcones which is a solventless, one step and greener methodology.

### Results and discussion

Microwave-assisted organic synthesis is a technique which can be used for rapid synthesis of compounds having chemical diversity. It is a widely used and preferred tool for accelerating organic reactions in the absence of solvent resulting in shorter reaction time and higher product yield than those obtained by conventional heating<sup>14a-d</sup>. The reactions which are not possible under conventional conditions can sometimes be affected by the high energy of microwave irradiation (MWI). Thus the application of MWI leads to many advantageous uses like the use of non corrosive, inexpensive catalysts in addition to the economical and environmental impacts with concurrence of green chemistry issues.

In this context, we have adopted both microwave and classical heating methods for acylation using PPA. The acylation of anisole, toluene, chlorobenzene and various cresols **1(a-f)** with propionic acid-PPA gave **2(a-f)** in moderate to good yield. It was observed that among various cresols maximum yield was obtained with *m*-cresol **1(e)** to yield 4-hydroxy-2-methyl propiophenone **2(e)** at low temperature while *o*-cresol and *p*-cresol (**1d** and **1f**) gave 4-hydroxy-3-methyl propiophenone and 2-hydroxy-5-methyl propiophenone (**2d** and **2f**) in low yield. Also, the acylation of same substrates **1(a-f)** was carried out by using benzoic acid-PPA to give corresponding benzophenones **3(a-f)** in reasonable yield.

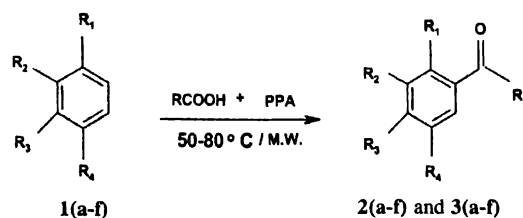
It is instructive to compare the results obtained by PPA catalysed intramolecular acylation reactions with those of other well known methods. The versatility and general utility of PPA arise from the fact that it is a mild reagent even though a strong dehydrating agent. Generally, it neither undergoes a violent reaction with hydroxyl compounds nor brings about phosphorylation of aromatic compounds. For these reasons its use frequently leads to fewer side reactions and higher yield of desired products than the use of other agents like  $\text{H}_2\text{SO}_4$ , HF or  $\text{AlCl}_3$ . Also, often methoxy group undergoes cleavage with  $\text{AlCl}_3$  which can be avoided by using PPA. Thus, it is obvious that the PPA method is frequently superior and seldom markedly inferior to the other methods.

Along with the conventional method, the microwave assisted PPA reactions were also carried out with the same reactants to give corresponding products **2(a-f)** and **3(a-f)** (Scheme 1). In this study, we found an opportunity to compare the results obtained for the compounds synthesized by conventional methods to those obtained employing microwave irradiation (Table 1). In present work, it was observed that, the MW reactions proceed efficiently in good yield within few minutes. Interestingly, the same

reactions required 2–4 h when conducted under conventional heating which confirms that the rate of reaction increases tremendously under microwave conditions. In view of these results, during MWI, we recorded the temperature of the mixture immediately while taking out the reaction vessel from the microwave oven which is in the range of 100–110 °C to yield the product 70–90%. But when the same reaction is carried out at 100–110 °C for the same time period by conventional heating method, the yield is only 5–10%. Therefore, it is evident that merely thermal effect of the microwave irradiation is not the only factor, "non thermal microwave effect" plays a significant role for the improvement of these reactions. Also, it is to be noted that highly pure products were obtained during MWI and in most cases no further purification was needed. On the contrary, in conventional methods vigorous purification of the final products was essential.

It was observed that, monosubstituted aromatic ring with activating groups such as alkoxy, alkyl, or halogen **2(a-c)** were easily acylated at *p*-position and microwave assisted methodology was superior to give good yield with high purity of compounds. In disubstituted aromatic compounds in which both the substituent groups are activating like -OR and -CH<sub>3</sub> **2(d-f)**, the acylation takes place at *p*-position to -OH group instead of CH<sub>3</sub>. As a consequence, *m*-cresol gave 4-hydroxy-2-methyl propiophenone (**2e**) as a major product with good yield. The same effect of substituted groups was observed in synthesis of **3(a-f)**.

We explored the same protocol for the synthesis of



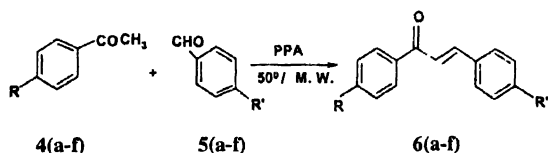
Scheme 1

Table 1. PPA assisted reactions for preparation of compounds **2(a-f)** and **3(a-f)**

Sr. no.	Compd.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R	Conventional		Microwave		M.p./ b.p. (°C)	Lit. <sup>15</sup> (°C)
							Period (h)	Yield (%)	Period (min)	Yield (%)		
1.	<b>2a</b>	H	H	OCH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	3	65	2	80	272 <sup>a</sup>	275 <sup>a</sup>
2.	<b>2b</b>	H	H	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	2	50	1.5	80	240 <sup>a</sup>	238 <sup>a</sup>
3.	<b>2c</b>	H	H	Cl	H	C <sub>2</sub> H <sub>5</sub>	1.5	50	1.5	70	134 <sup>a</sup>	132 <sup>a</sup>
4.	<b>2d</b>	H	CH <sub>3</sub>	OH	H	C <sub>2</sub> H <sub>5</sub>	2	40	2	60	84	86
5.	<b>2e</b>	CH <sub>3</sub>	H	OH	H	C <sub>2</sub> H <sub>5</sub>	2	60	2.5	75	117	117
6.	<b>2f</b>	OH	H	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	2.5	25	2.5	50	124 <sup>a</sup>	124 <sup>a</sup>
7.	<b>3a</b>	H	H	OCH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	3	60	3.5	70	60	60
8.	<b>3b</b>	H	H	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	3.5	45	3	70	56	59
9.	<b>3c</b>	H	H	Cl	H	C <sub>6</sub> H <sub>5</sub>	4	55	3.5	65	75	77
10.	<b>3d</b>	H	CH <sub>3</sub>	OH	H	C <sub>6</sub> H <sub>5</sub>	3	20	4	50	174	174
11.	<b>3e</b>	CH <sub>3</sub>	H	OH	H	C <sub>6</sub> H <sub>5</sub>	3.5	50	4	60	130	129
12.	<b>3f</b>	OH	H	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	3.5	20	4	50	85	87

<sup>a</sup>Represents boiling point.

$\alpha,\beta$ -unsaturated diaryl ketones viz. chalcones. Chalcones were prepared by the condensation of substituted acetophenone and benzaldehyde in PPA (Scheme 2). Generally, the reaction takes place in presence of dilute alkali<sup>16</sup>. But we have carried out the same reaction using PPA. To the best of our knowledge, we report for the first time the application of PPA for the preparation of chalcones. The preparation of chalcones in dil. alkali require rectified spirit as a solvent and products are often contaminated with various undefined side products. While in our reaction using PPA, the reaction is solvent free with simple work up and the products are obtained in high purity. We have attempted to accelerate the aforementioned reaction with microwave irradiation by PPA. By comparing our novel results with those previously obtained by conventional method (Table 2), the best results were obtained under greener, solventless methodology of MWI within shorter the reaction time with high purity of the product. Using aryl methyl ketones with electron withdrawing group (e.g. 4-NO<sub>2</sub>), the chalcone was obtained in poor yield.



Scheme 2

Table 2. PPA assisted reactions for preparation of chalcones

Entry	Compd	R	R'	Conventional		Microwave		M.p. (°C)	Lit.
				Period (h)	Yield (%)	Period (min)	Yield (%)		
1	6a	OCH <sub>3</sub>	Cl	6	70	3	80	132	134 <sup>17a</sup>
2	6b	Cl	OCH <sub>3</sub>	6	60	4	75	122	122 <sup>17b</sup>
3	6c	CH <sub>3</sub>	Cl	4	65	3	80	140	146 <sup>17b</sup>
4	6d	OCH <sub>3</sub>	H	7	50	4	70	100	106 <sup>17c</sup>
5	6e	CH <sub>3</sub>	H	5	60	4	80	70	77 <sup>17c</sup>
6	6f	H	Cl	4	70	3	70	115	112 <sup>17d</sup>

## Experimental

The IR spectra were recorded in nujal as a KBr pellet or as a liquid film on Perkin-Elmer, FT-IR spectrophotometer. The NMR spectra were recorded in CDCl<sub>3</sub> with TMS as internal reference standard on Varian Gemini 200 NMR spectrometer. Melting points and boiling points were determined by electrothermal method and are uncorrected. The purity of the compounds were routinely

checked by TLC using silica gel. For the microwave assisted process, reactions were carried out in a domestic microwave oven model BPL-Sanyo-BMO-700T.

### Synthesis of 2(a-f) and 3(a-f) by conventional method :

An equimolar mixture of propionic acid (or benzoic acid) and anisole 1(a) was heated with PPA (2.5 ml *o*-phosphoric acid + 5.6 g P<sub>2</sub>O<sub>5</sub>) for 2–4 h at 50–60 °C. After cooling the reaction mixture was treated with crushed ice and extracted with ether. The ether layer was washed with water and sodium bicarbonate and dried over anhydrous sodium sulphate. Removal of ether gave crude product which was purified by crystallization using suitable solvent to give pure acylated products 2(a) and 3(a). By using the same procedure, remaining prochiral ketones were prepared.

**Microwave assisted method :** A mixture of propionic acid (or benzoic acid) and anisole stirred with PPA and exposed to MWI for 30 s (Table 1). The reaction mixture was stirred well, cooled, and using usual work up, the corresponding products were obtained in pure form without any necessity of further purification in most of the cases.

**Synthesis of 6(a-f) :** Chalcones were prepared by condensation of substituted acetophenone and benzaldehyde in presence of PPA by conventional as well as microwave assisted methods. As a trial case, to a well stirred solution of an equimolar amount of *p*-methoxy acetophenone and *p*-chloro benzaldehyde (10 mmol each) PPA was added and stirring was continued. The progress of the reaction was monitored by TLC. The routine work up (as described earlier) of the mixture yielded desired  $\alpha,\beta$ -unsaturated diarylketone viz. chalcone 6(a). By using the same procedure chalcones 6(b-f) were prepared. The synthesized compounds were purified and characterized by physical and spectral data.

All compounds gave satisfactory spectral data. Selected spectral data has been reported here :

(2a) Colourless liquid, b.p. 272 °C (lit.<sup>15</sup> 274 °C); IR (neat)  $\nu$  cm<sup>-1</sup> : 1680 (C=O), 1602, 1508; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 1.18 (3H, *t*, *J* 7 Hz, -CH<sub>2</sub>-CH<sub>3</sub>), 2.92 (2H, *q*, *J* 6.8 Hz, CH<sub>2</sub>-CH<sub>3</sub>), 3.82 (3H, *s*, Ar-OMe), 6.93 (2H, *d*, *o*- to Ph-OMe), 7.91 (2H, *d*, *o*- to Ph-C=O) (Found : C, 73.10; H, 7.30. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> : C, 73.17; H, 7.31%).

(2b) Colourless liquid, b.p. 240 °C (lit.<sup>15</sup> 238 °C); IR (neat)  $\nu$  cm<sup>-1</sup> : 1685 (C=O), 1608, 1573; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 1.21 (3H, t, CH<sub>2</sub>-CH<sub>3</sub>), 2.37 (3H, s, Ar-CH<sub>3</sub>), 2.95 (2H, q, CH<sub>2</sub>-CH<sub>3</sub>), 7.23 (2H, d, Ar-H, *m*- to C=O), 7.81 (2H, d, Ar-H, *o*- to C=O); MS : *m/z* 148 (M<sup>+</sup>), 133, 119 (B), 103, 91, 65 (Found : C, 81.0; H, 8.09. Calcd. for C<sub>10</sub>H<sub>12</sub>O · C, 81.08; H, 8.10%).

(2c) Colourless liquid, b.p. 134 °C (lit.<sup>15</sup> 132 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1685 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 1.21 (3H, t, CH<sub>2</sub>-CH<sub>3</sub>), 2.95 (2H, q, CH<sub>2</sub>-CH<sub>3</sub>), 7.44 (2H, d, Ar-H, *m*- to C=O), 7.81 (2H, d, Ar-H, *o*- to C=O) (Found : C, 64.07; H, 5.3; Cl, 21.0. Calcd. for C<sub>9</sub>H<sub>9</sub>OCl : C, 64.08; H, 5.34%).

(2e) White needles (EtOH), m.p. 116 °C (lit.<sup>15</sup> 117 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 3450 (-OH), 1685 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 1.18 (3H, t, CH<sub>2</sub>-CH<sub>3</sub>), 1.25 (s, Ar-OH), 2.52 (3H, s, Ar-CH<sub>3</sub>), 2.90 (2H, q, CH<sub>2</sub>-CH<sub>3</sub>), 6.69 (1H, d, *p*- to Ar-CH<sub>3</sub>), 6.71 (1H, s, *o*- to Ar-CH<sub>3</sub>), 7.67 (1H, d, *o*- to C=O) (Found : C, 73.10; H, 7.10. Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> : C, 73.17; H, 7.31%).

(3a) White solid, m.p. 60 °C (lit.<sup>15</sup> 60 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1675 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 3.91 (3H, s, Ar-OMe), 6.99 (2H, d, *o*- to Ar-OMe), 7.54 (5H, m, Ar-H), 7.76 (2H, d, *m*- to Ar-OMe) (Found : C, 79.0; H, 5.60. Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> : C, 79.24; H, 5.66%).

(3b) White solid, m.p. 56 °C (lit.<sup>15</sup> 59 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1670 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 2.47 (3H, s, Ar-CH<sub>3</sub>), 6.90 (2H, d, *o*- to Ar-CH<sub>3</sub>), 7.60 (5H, m, Ar-H), 7.72 (2H, d, *m*- to Ar-CH<sub>3</sub>) (Found : C, 85.70; H, 6.10. Calcd. for C<sub>14</sub>H<sub>12</sub>O : C, 85.71; H, 6.12%).

(3c) White solid, m.p. 75 °C (lit.<sup>15</sup> 75 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1660 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 7.43–7.73 (9H, m, Ar-H); MS : *m/z* 216 (M<sup>+</sup>), 181, 139, 113, 105, 77 (Found : C, 72.0; H, 4.10; Cl, 16.30. Calcd. for C<sub>13</sub>H<sub>9</sub>OCl : C, 72.05; H, 4.16; Cl, 16.40%).

(3e) White solid, m.p. 130 °C (lit.<sup>15</sup> 129 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 3460 (-OH), 1670 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 1.58 (s, Ar-OH), 2.45 (3H, s, Ar-CH<sub>3</sub>), 6.72–7.5 (8H, m, Ar-H) (Found : C, 75.10; H, 5.50. Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> : C, 75.25; H, 5.66%).

(6a) Yellow solid, m.p. 132 °C (lit.<sup>17a</sup> 134 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1663 (C=O), 1606 (conj. C=C), 1216, 757; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 3.89 (3H, s, -OMe), 6.98 (2H, d, *J* 8 Hz, Ar-H *o*- to OMe), 7.30 (2H, d, *J* 16 Hz, olefinic protons), 7.70 (2H, d, *J* 16 Hz, olefinic

protons), 7.39 (2H, d, *J* 2 Hz, Ar-H *m*- to OMe and *o*- to Cl), 7.56 (2H, d, Ar-H *m*- to OMe and *o*- to Cl), 7.8 (2H, d, *J* 16 Hz, Ar-H *m*- to Cl) (Found : C, 70.50; H, 4.70; Cl, 12.85. Calcd. for C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>Cl : C, 70.58; H, 4.77; Cl, 12.86%).

(6b) Yellow solid, m.p. 122 °C (lit.<sup>17b</sup> 122 °C); IR (KBr)  $\nu$  cm<sup>-1</sup> : 1663 (C=O), 1605 (conj. C=C), 1216, 757; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  ppm : 3.86 (3H, s, -OMe), 6.94 and 7.96 (2H, d, *J* 8 Hz, Ar-H *o*- to and *m*- to OMe), 7.40 (2H, d, *J* 16 Hz, olefinic proton), 7.78 (2H, d, *J* 16 Hz, olefinic proton), 7.41 (2H, d, Ar-H *o*- to and *m*- to Cl), 7.61 (2H, d, Ar-H *o*- to and *m*- to Cl) (Found : C, 70.50; H, 4.70; Cl, 12.85. Calcd. for C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>Cl : C, 70.58; H, 4.77; Cl, 12.86%).

In conclusion, we have developed a greener methodology for the synthesis of monosubstituted and disubstituted prochiral aryl ketones as well as  $\alpha,\beta$ -unsaturated diaryl ketones using conventional and microwave methods. The microwave irradiation is environment-friendly methodology with several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the yield owing to specific non thermal microwave effect.

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