

Zinc Mediated Friedel–Crafts Acylation in Solvent-Free Conditions under Microwave Irradiation

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Abstract: Zn powder is found to catalyze the Friedel–Crafts acylation of aromatic compounds with acyl halides efficiently under microwave irradiation in solvent-free conditions. Activated substrates undergo acylation predominantly at the para-position. The Zn powder can be re-used up to six times after simple washing with diethyl ether and dilute HCl.

Key words: Friedel–Crafts acylation, zinc powder, aromatic compounds, solvent-free conditions, microwave activation

Friedel–Crafts acylation of aromatic compounds is one of the most important synthesis of aryl ketones. In a typical Friedel–Crafts acylation reaction, an aromatic compound undergoes electrophilic substitution with an acylating agent in the presence of more than one equivalent of acid catalyst (e.g. anhydrous AlCl_3) due to its complexation by the ketone product. The catalyst used cannot be easily recovered and recycled. Therefore, a large amount of toxic waste is generated. In order to solve this problem, some catalytic Friedel–Crafts acylations have recently been developed. $\text{Ln}(\text{OTf})_3\text{--LiClO}_4$,¹ $\text{TiCl}(\text{OTf})_3\text{--TfOH}$,² $\text{ReBr}(\text{CO})_5$,³ $\text{LiClO}_4\text{--acylanhydride complex}$,⁴ FeCl_3 over KIO_5 and clay catalysts⁶ have been reported as catalysts for Friedel–Crafts acylations. In addition, the use of inorganic solid supported reagents⁷ or solid acids⁸ as catalysts, resulting in higher selectivity, easier work-up and environmentally safe reactions, has been reported. For instance, HZSM-5 zeolite has been reported to promote the liquid phase acylation of anisole with carboxylic acids.⁹ However, it presents limitations with regard to generality and efficiency. Recently, it was also shown that alumina promotes the acylation of reactive aromatics such as anisole and thiophene with carboxylic acid in the presence of trifluoroacetic anhydride.¹⁰

Zn powder, a non-toxic and inexpensive metal has been used for a number of organic reactions like ene-cyclization,¹¹ Diels–Alder reaction,¹² synthesis of benzhydrols,¹³ transesterification of β -ketoesters.¹⁴ Recently, Zn powder has been also involved in acylation and sulfonation of pyrrole.¹⁵

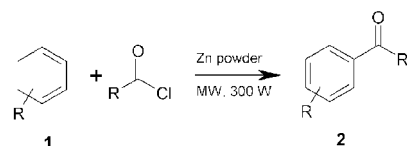
Microwave (MW) irradiation has been proved to be highly efficient for the rapid synthesis of a variety of compounds,¹⁶ some include Friedel–Crafts acylations.¹⁷ Chemical reactions are accelerated essentially because of selective absorption of microwave energy by polar molecules being inert to the microwave dielectric loss. Among them, heterogeneous reactions facilitated by supported reagents on various mineral oxides have received special attention in recent years.^{18–21} Relatively little attention is, however, paid to solvent-free reactions with neat reactants in the absence of a solid support.²²

During the course of our studies aimed at developing solvent-free procedures,²⁰ we found that Zn powder without any treatment, can promote the Friedel–Crafts acylation of aromatic compounds with acyl halides to afford the corresponding acylated products in high yields. Zn powder was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a temperature of 581 °C after 3 minutes of irradiation in a domestic oven ($P = 1000 \text{ W}$).²³

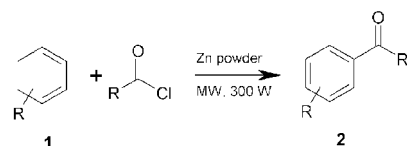
Another interesting behaviour of Zn powder lies in the fact that it can be re-used after simple washing with diethyl ether and dilute HCl, rendering thus process more economic. This constitutes a green and efficient alternative to the MW assisted method described by Dubac et al.^{17a–c} using metallic chlorides as catalysts, and essentially iron(III) chloride.

Zinc was shown to have a remarkable high activity for the acylation of aromatic compounds with acetyl chloride and benzoyl chloride to give the corresponding acylated compounds in high yields, without any of the environmental disadvantages of using toxic homogeneous reagents such as anhydrous AlCl_3 . Several substituted acetophenones and benzophenones have been prepared by this method (Table 1).

Experimental conditions have been carefully monitored to regulate the use of Zn powder, irradiation time and power level of microwave oven to get the maximum yield. Higher proportions of Zn powder result in a quick rise of temperature thereby burning of the reaction mixture. The 1:1 ratio of Zn powder to substrate is the most acceptable ratio in terms of efficiency and safety; a power level of 300 Watts is the most suitable one.

Table 1 Microwave-Induced Synthesis of Acylated Ketones Using Zn Powder (Power = 300 W)R = CH₃ (entries 1–19); R = Ph (entries 20–36)

Entry	Substrate	Product	Reaction Temp. (°C)	Time (s)	Yield (%)	Mp/Bp (°C) Found/Reported
1	Benzene	Acetophenone	60–62	30	95	Liq/201–202 ^a
2	Toluene	4-Methylacetophenone	52–53	40	70	Liq/226 ^a
3	Chlorobenzene	4-Chloroacetophenone	65–68	30	99	Liq/232 ^a
4	Anisol	4-Methoxyacetophenone	80–82	7	99	Liq/152–154 ^a
5	Anthracene	9-Acetylanthracene ^c	45–47	60	83	74–75/75–76 ^b
6	Naphthalene	2-Acetonaphthanone ^c	53–55	25	69	54–56/56 ^b
7	Pyridine	4-Acetylpyridine ^c	42–44	15	65	Liq/212–214 ^b
8	Biphenyl	4-Acetylbiphenyl	52–54	25	72	119–121/120–121 ^b
9	Phenol	2-Hydroxyacetophenone	55–57	40	73	Liq/213 ^a
10	Quinol	2,5-Dihydroxyacetophenone ^c	47–48	60	70	198–200/202 ^b
11	Resorcinol	2,4-Dihydroxyacetophenone ^d	64–66	75	77	144–46/147 ^b
12	Catechol	3,4-Dihydroxyacetophenone ^c	44–46	55	71	115–17/117 ^b
13	3-Nitroaniline	5-Amino-3-nitroacetophenone ^c	52–54	20	68	149–52/152–153 ^b
14	2-Nitroaniline	4-Amino-3-nitroacetophenone ^c	70–72	15	74	152–55/153–157 ^b
15	<i>o</i> -Xylene	3,4-Dimethylacetophenone ^c	58–60	60	92	Liq/243 ^a
16	1,2-Dichlorobenzene	3,4-Dichloroacetophenone ^c	57–59	140	70	70–72/72–74 ^a
17	Nitrobenzene	3-Nitroacetophenone ^c	82–84	180	79	77–79/78–80 ^a
18	4-Cresol	2-Hydroxy-5-methylacetophenone ^c	55–57	240	70	43–44/45–48 ^a
19	Aniline	4-Aminoacetophenone	43–45	40	74	105–107 ¹
20	Benzene	Benzophenone	72–74	35	75	46–47/46–48 ^a
21	Toluene	4-Methylbenzophenone	71–73	20	99	57–58/56.5–57 ^a
22	Chlorobenzene	4-Chlorobenzophenone	98–100	30	85	75–76/75–77 ^a
23	Aniline	4-Aminobenzophenone	52–54	20	70	123–124/121–124 ^a
24	2-Nitroaniline	4-Amino-3-nitrobenzophenone	140–142	30	55	140–141/140–143 ^a
25	3-Nitroaniline	4-Amino-2-nitrobenzophenone	75–79	15	71	91–93/92–94 ^a
26	3-Toluidine	2-Amino-4-methylbenzophenone	70–72	10	70	64–66/65–66 ^a
27	Anisol	4-Methoxybenzophenone	120–121	10	71	60–62/60–63 ^a
28	Naphthalene	2-Benzoylnaphthalene	70–72	28	69	80–82/82 ^b
29	Biphenyl	4-Benzoylbiphenyl	100–102	30	68	99–100/99–101 ^a
30	Anthracene	9-Anthraphenone ^c	80–82	20	68	147–148/148 ^b
31	Phenol	4-Hydroxybenzophenone	55–57	18	74	133–35/132–35 ^a

Table 1 Microwave-Induced Synthesis of Acylated Ketones Using Zn Powder (Power = 300 W) (continued)

Entry	Substrate	Product	Reaction Temp. (°C)	Time (s)	Yield (%)	Mp/Bp (°C) Found/Reported
32	Resorcinol	2,4-Dihydroxybenzophenone	50–52	55	70	143–146/144–146 ^b
33	Quinol	2,5-Dihydroxybenzophenone ^c	49–51	35	68	124–126/125 ^b
34	Catechol	3,4-Dihydroxybenzophenone ^c	46–48	60	68	132–134/134 ^b
35	<i>o</i> -Xylene	3,4-Dimethylbenzophenone ^c	57–59	180	70	43–46/45–47 ^a
36	1,2-Dichlorobenzene	3,4-Dichlorobenzophenone ^c	55–57	300	71	100–102/104.5 ^b

^a Aldrich Catalog Handbook of Fine Chemicals, 2000–2001.

^b Stevens, R. Dictionary of Organic Compounds, 4th Ed. Eyre & Spottiswoode Ltd. E. & F. N. Spon Ltd. 1971.

^c Purified by passing through column of silica gel and elution with 100% P.E. (60–80 °C).

^d Ratio of substrate to acyl halide is 1:3.

Recently, we have reported the acetylation²⁰ and benzoylation²¹ of –NH₂, –SH and –OH groups using acetyl chloride and benzoyl chloride over basic alumina as support. It is very interesting to note that, in the case of aniline and phenol, if Zn powder is added 15 seconds before acetyl chloride or benzoyl chloride acylation takes place predominantly with only 10% of acetylated aniline (acetanilide) and no phenyl acetate has been observed. But, if acetyl or benzoyl chloride is added previously to Zn powder, more than 30% of acetylated or benzoylated products have been formed in addition to acylated products. Thus Zn powder is suppressing the acetylation/benzoylation and catalyzing the acylation reaction. Further, substrates with activating groups (entries 4, 9, 19, 23 etc.) undergo acylation predominantly at the para-position. As the ortho-isomers are formed only in very small amounts, we report here only the major isomer, which has been isolated by column chromatography or crystallization.

Anhydrous zinc chloride²⁴ is well known for catalyzing the Friedel–Crafts acylation reaction. In order to check the possibility of in situ generation of zinc chloride from zinc powder and acylating agents, (acetyl chloride/benzoyl chloride) we carried out the acylation reaction in case of entries 4, 8, 27 and 29 using anhydrous zinc chloride instead of Zn powder. It has been found that under the same conditions of irradiation time and power output (cf. Table 1), only 12–18% of acylated products were formed, the complement being the starting materials. Thus the role of zinc chloride formed, would be minor and the major role is played by zinc powder, which can be reused up to 6 times by washing it with diethyl ether and HCl after each use. However, there is loss of activity after four uses.

Finally, in order to check the possibility of specific non-thermal effects of microwave irradiation, reactions were carried out using thermostated oil-baths (Δ) under similar

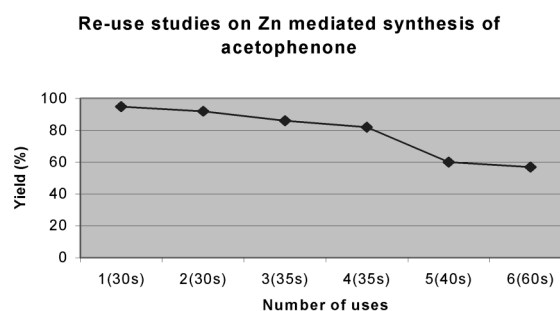


Figure 1 Re-use studies on the Zn mediated synthesis of acetophenone using 1 mmol of benzene and 1.2 mmol of acetyl chloride. The reaction was carried out in a microwave oven at 300 W. In parenthesis irradiation reaction time is given.

sets of conditions of time and temperature as for the microwave-assisted method (Table 2).

Significant lower yields were obtained under conventional heating than using MW-assisted method under identical conditions of time and temperature. Even by extending reaction times, yields remain lower under thermal conditions when compared to MW activation. This observation demonstrates clearly that the effect of MW irradiation is not purely thermal. This behaviour is consistent with mechanistic considerations of the reaction.²⁵ As they are connected to polarity medium, specific MW effects are expected if the transition state (TS) is more polar than the ground state (GS) of the reaction. Due to dipole-dipole electrostatic interactions being more developed in the TS, the stabilisation of the TS is superior to the GS, leading thus to a decrease in the activation energy. In this case one should consider the rate-determining step in the SEAr mechanism (cf Scheme 1). In the TS, the polarity of the system is enhanced as looser ion pairs are involved (with

Table 2 Comparison of Results under Both MW and Thermal Conditions (Power = 300 W)

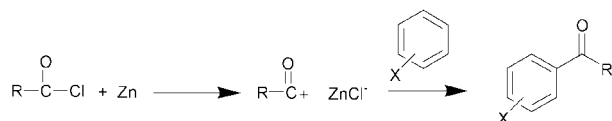
Entry	Method	T (°C) ^a	Time	Yield (%) ^b
1	MW	60–62	30 s	95
	Δ	62	30 s	20
	Δ	62	8 min	79
2	MW	52–53	40 s	70
	Δ	53	40 s	8
	Δ	53	8 min	55
17	MW	82–84	3 min	79
	Δ	84	3 min	10
	Δ	84	20 min	62
20	MW	72–74	35 s	75
	Δ	74	35 s	5
	Δ	74	12 min	60
21	MW	71–73	20 s	99
	Δ	76	20 s	28
	Δ	76	6 min	80

^a Reaction temperature was measured by immersing A glass thermometer into the reaction mixture immediately after exposure to MW irradiation.

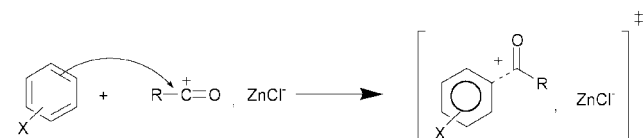
^b Yields of isolated products.

a very soft cation due to charge delocalization in the aromatic ring) when compared to the GS.

In conclusion, we have described a novel and highly efficient microwave-induced solvent-free protocol for Friedel–Crafts acylation of aromatic compounds using non-toxic and inexpensive Zn powder. The advantages of this environmentally benign and safe protocol include a simple reaction set-up not requiring specialized equipment, high product yields, short reaction times, and the



Rate determining step

**Scheme 1**

elimination of solvents or solid support. Moreover, the activated aromatic substrates give the para-isomer as the major product.

Mps were determined on a Buchi melting point apparatus and are uncorrected. ¹H NMR spectra were obtained on a JNM-PMX 60 NMR spectrometer (60MHz) in CDCl₃ using TMS as internal standard. The IR spectra were recorded using KBr disc on Hitachi 270-30 spectrophotometer. The reactions were monitored by TLC. For the microwave irradiation experiments described below a conventional (unmodified) household microwave oven equipped with a turntable was used (BPL BMO 800, 800 W and operating at 2450 MHz).

Preparation of Acetophenone, Entry 1; Typical Procedure

To a mixture of benzene (0.078 g, 1 mmol) and Zn powder (0.065 g, 1 mmol) in a 50 mL borosil beaker, AcCl (0.078 g, 1 mmol) was added. The reaction mixture was mixed properly with the help of a glass rod (10 s) and then irradiated in a microwave oven for 30 s at 300 W (monitored by TLC). The reaction mixture was cooled and extracted with Et₂O (3 × 10 mL). After drying the ether extracts over anhydrous Na₂SO₄, the acetophenone was obtained by removal of the solvent under reduced pressure. Finally, the product was purified by column chromatography (silica gel) using P.E. as eluent (0.114 g, 95%).

The reaction was also performed with benzene (0.390 g, 5 mmol), Zn powder (0.325 g, 5 mmol) and AcCl (0.390 g, 5 mmol) in a 50 mL borosil beaker following the same procedure. After an irradiation time of 30 s, acetophenone (0.56 g, 94%) was obtained by passing through column of silica gel and elution with P.E.

The structure of the products was confirmed by ¹H NMR, IR and comparison with authentic samples obtained commercially or prepared by reported methods.

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