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Synthesis of (2-chlorophenyl)(phenyl)methanones and 2-(2-chlorophenyl)-1-phenylethanones by Friedel–Crafts acylation of 2-chlorobenzoic acids and 2-(2-chlorophenyl)acetic acids using microwave heating

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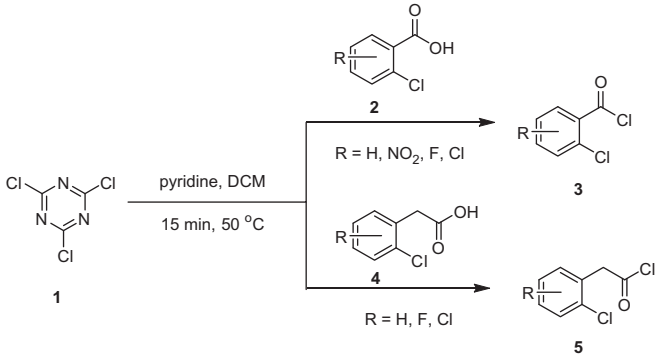
ABSTRACT

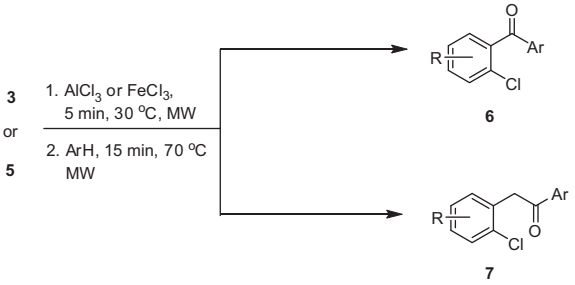
Several 2-(2-chlorophenyl)-1-phenylethanones and (2-chlorophenyl)(phenyl)methanones were prepared by the Friedel–Crafts acylation reaction of 2-(2-chlorophenyl) acetic acids and 2-chlorocarboxylic acids, respectively, in the presence of cyanuric chloride, pyridine, and $AlCl_3$ or $FeCl_3$ using microwave heating. The yields of the ketones were significantly higher than those obtained using conventional heating. In addition, similar reactions carried out with the less inexpensive and less toxic $FeCl_3$ gave titled ketones in comparable yields. Interestingly, the $FeCl_3$ catalyzed reactions gave pure ketones (no chromatographic purification required), whereas the $AlCl_3$ catalyzed reaction gave impure product that required chromatographic purification.

1. Introduction

During the course of our investigation of the synthesis of five-membered chalcogens[1], we needed to prepare a series of 2-chloro derivatives of benzo- and phenylacetophenones for use in ring closure reactions. We were intrigued by the procedure of Kangani and Day,[2] which involves the Friedel–Crafts acylation of an aromatic carboxylic acids or aliphatic carboxylic acids using cyanuric chloride, pyridine, and $AlCl_3$ at room temperature. High yields of ketones were produced quickly. However, when we attempted to extend this method to the synthesis of (2-chlorophenyl)(phenyl methanones and 2-(2-chlorophenyl)-1-phenylethanones low yields of these ketones were obtained. Presumably, the 2-chloro atom in these acids sterically hinders the Friedel–Crafts reaction. We thus decided to explore the use of microwave heating since such heating usually give products in higher yields and shorter reaction times than those subjected to conventional heating. The ketones so obtained should serve not only as valuable precursor to five-membered heterocycles, but also as important intermediates in the synthesis of pharmaceuticals, perfumes and chemicals such as insecticides and agrochemicals.[3–7] Initially the reactions were conducted in the microwave oven in one step at a constant



Scheme 1.



Scheme 2.

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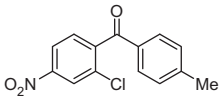
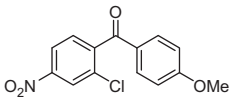
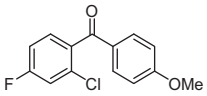
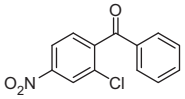
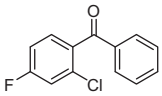
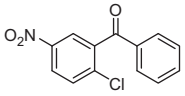
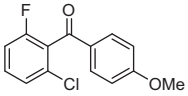
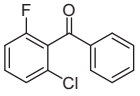
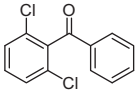
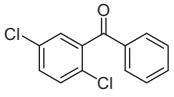
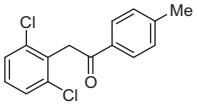
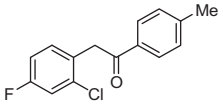
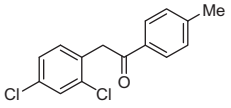
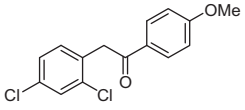
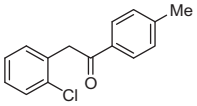
Table 1
Yields (%) of **6a–f** and **7a–e**

Entry	Compd #	Ketone[a]	Yield[b] (%), ($AlCl_3$)	Yield[b] (%), ($FeCl_3$)
1	**6a**		91	93
2	**6b**		71	58
3	**6c**		77	51
4	**6d**		75	65
5	**6e**		98	83
6	**6f**		55	96
7	**6g**		81	86
8	**6h**		95	98
9	**6i**		89	90
10	**6j**		87	89
11	**7a**		81	91
12	**7b**		98	87
13	**7c**		62	85
14	**7d**		98	73
15	**7e**		58	72

[a] All the products were characterized by ^1H NMR, ^{13}C NMR, IR and GC/MS spectroscopic studies and in comparison with known literature data.
[b] Isolated yields were reported.

temperature; however, this method failed to produce high yields of the product. Consequently, after a series of manipulations of methods we found that the most efficient and effective means to produce significant yields of ketones was to divide the reaction into three distinct steps that were each performed at different temperatures in the microwave oven.

In the first step, the 2-chloro derivatives of benzoic acid (**2**) and phenylacetic acid (**4**) were acylated to the corresponding acid chlorides **3** and **5** in the presence of cyanuric chloride (**1**), pyridine and DCM using microwave radiation for 15 min at 50 °C (Scheme 1).

After the reaction mixture was completed (as determined by GC/MS), the mixture cooled to 30 °C, and $AlCl_3$ or $FeCl_3$ (2 M equiv) was added directly to the reaction mixture, which was then irradiated in the microwave for 5 min at 30 °C at 250 psi (powermax on). It should be noted that when $AlCl_3$ or $FeCl_3$ was added to the acid chloride and spun conventionally with the use of a vortex mixer, it took 20–25 min for the $AlCl_3$ to completely dissolve. Hence, the use of microwave heating significantly decreased the time needed for the reaction to take place. Finally, after the formation of the alumina complex, benzene, toluene, or anisole was added and the resulting mixture was irradiated in the microwave at 70 °C for 15 min to give desired ketones **6** and **7**, respectively. These last two steps are shown in Scheme 2.

As shown in Table 1, using $AlCl_3$ as catalyst, the benzophenones (entries 1–10) were formed in yields ranging between 98% and 55%, whereas the acetophenones (entries 11–15) were formed in yields ranging between 98% and 58%. The structures of the ketones are listed in Table 1, and were supported by GC/MS, ^{1}H NMR, ^{13}C NMR and IR spectroscopy. Some of the reactions listed in the table were run using $FeCl_3$ a more environmentally friendly catalyst than $AlCl_3$. As shown, the $FeCl_3$ catalyzed reactions gave pure ketones in similar yields (93–51%); however, dissimilar to $FeCl_3$ catalyzed reactions, in $AlCl_3$ catalyzed reactions crude mixtures containing an unknown impurity was obtained, which then had to be purified by column chromatography. The products were identified on the basis of ^{1}H NMR, ^{13}C NMR, and GC/MS.

In conclusion we have developed a one-pot, 3-step microwave-assisted reaction for the preparation of novel, titled ketones in good to excellent yields. A typical example for the preparation of **6a** is given.[8] The experimental details and physical properties of the various ketones are listed in the Supplementary data.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.052.

Reference and notes

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8. *Preparation of (2-chloro-4-nitrophenyl)(p-tolyl)methanone* (**6a**). *Method A (using $AlCl_3$)*: 2-Chloro-4-nitrobenzoic acid (201 mg, 1.0 mmol) and cyanuric chloride (368 mg, 2 mmol) in 2 mL CH_2Cl_2 were treated with pyridine (79 mg, 1.0 mmol) and irradiated in the microwave for 15 min at 50 °C. Then, the resulting mixture was treated with $AlCl_3$ (400 mg, 3.01 mmol) and irradiated in the microwave for 5 min at 30 °C. Finally, 3 mL of toluene was added to the solution and irradiated in the microwave for 15 min at 70 °C. Then the reaction mixture was poured onto the ice and filter from Celite. The filtrate was washed with water followed by brine solution. The separated organic layer was dried on Na_2SO_4 and concentrated under reduced pressure to give crude product, which is purified by column chromatography (98:2 heptane/ethyl acetate) to give the pure white color product **6a** (269.5 mg, 91% yield). *Method B (using $FeCl_3$)*: 2-Chloro-4-nitrobenzoic acid (201 mg, 1.0 mmol) and cyanuric chloride (368 mg, 2 mmol) in 2 mL CH_2Cl_2 were treated with pyridine (79 mg, 1.0 mmol) and irradiated in the microwave for 15 min at 50 °C. Then, the resulting mixture was treated with $FeCl_3$ (324 mg, 2.0 mmol) and irradiated in the microwave for 5 min at 30 °C. Finally, 3 mL of toluene was added to the solution and irradiated in the microwave for 15 min at 70 °C. Then the reaction mixture was filtered from Celite. The filtrate was washed with sodium thiosulphate followed by brine solution. The separated organic layer was dried on Na_2SO_4 and concentrated under reduced pressure to give pure product **6a** (269.5 mg, 93% yield). Mp 110–112 °C (lit. [1] 111.2 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.26 (d, J = 7.45 Hz, 2H), 7.54 (d, J = 7.45 Hz, 1H), 7.61 (d, J = 6.85 Hz, 2H), 8.26 (dd, J = 6.85, 2.7 Hz, 1H), 8.30 (d, J = 7.4 Hz, 1H); ^{13}C NMR (500 Hz, $CDCl_3$): δ 21.4 (CH_3), 122.0 (CH), 125.1 (CH), 129.6 (CH), 129.7 (CH), 130.15 (CH), 132.2 (C), 144.6 (C), 146.2 (C), 148.9 (C), 193.5 (CO); IR (cm^{-1}): 638.3, 740.8, 801.5, 836.3, 863.0, 1000.7, 1025.9, 1052.5, 1005.1, 1133.9, 1158.3, 1180.7, 1272.5, 1294.3, 1315.8, 1349.1, 1403.2, 1449.5, 1461.2, 1528.8, 1573.3, 1595.7, 1607.9, 1673.9, 3087.5; GC/MS: 275 [M^+]; HRMS: calcd for $C_{14}H_{10}ClNO_3$: 275.0349. Found: 275.0467.