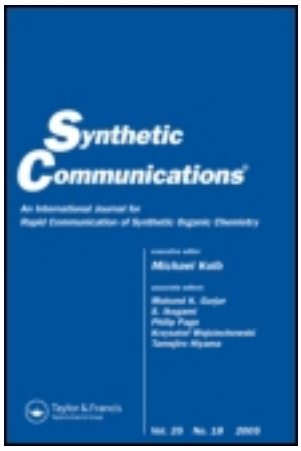

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PREPARATION OF 1-INDANONES WITH CONVENTIONAL HEATING VERSUS MICROWAVES

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ABSTRACT

The acylation reactions of *p*-methylphenol with crotonic and 2-octenoic acids was carried out with the employment of conventional heating and irradiation by microwaves. The use of microwaves led to a significant reduction in the time of reaction from several hours to 2 min and 30–60% yield

Key Words: Acylation; Indanones; Microwaves

INTRODUCTION

1-Indanone and its analogs have been demonstrated to be versatile and useful intermediates in the preparation of different products, some of

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which have applications as pharmaceuticals, especially as analgesics[1] and antihypertensives,[2] as well as tobacco flavoring agents.[3]

The synthesis of indanones is usually carried out by reaction of Friedel-Crafts or Fries rearrangement using acyl chlorides or α,β-unsaturated carboxylic acids.[4] This methodologies have some limitations, for example, low yields,[5] use of toxic reagent and long reaction times.[6]

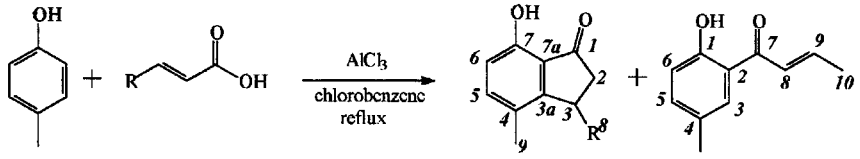
The objective of this work was to investigate the preparation of 1-indanones by reaction of *p*-methylphenol with α,β-unsaturated carboxylic acids using conventional heating and irradiation with microwaves. The interest in this last methodology is that it accelerates a variety of synthetic transformations and has potential to improve reactions from an environmental point of view.[7]

RESULTS AND DISCUSSION

Although different methodologies to promote acylation of aromatic compounds are known,[8,9] we used initially the conventional procedures,[10] that is the direct Friedel-Crafts reaction between *p*-methylphenol and α,β-unsaturated carboxylic acids in presence of an appropriate Lewis acid in a suitable solvent or the Fries rearrangement of the corresponding *O*-acylated intermediate (Sch. 1). This procedure was used to prepare 1-indanones **1** and **3** in 40 and 60% yield (Table 1).

Interestingly, the *o*-acylphenol **2** was obtained only when the acylating agent was crotonyl chloride. Although it is known that **2** can be obtained from the reaction of the phenol and crotonic acid in tetrachloroethane,[10] similar results were observed when chlorobenzene was used as solvent (Entries 1 and 2 in Table 1).

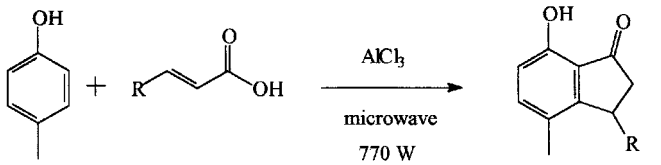
The tests of this reaction system with longer reaction times (Entry 3 in Table 1) led predominantly to the cyclization product **1**, indicating that compound **2** can be the intermediate in the formation of indanone **1**.[11] It was observed that, when 2-octenoic acid was used, a better yield of the novel 1-indanone **3** was obtained (Entries 4 and 5 in Table 1).



Scheme 1. Products formed using conventional heating.

Table 1. Preparation of 1-Indanones Using the Conventional Route

Entry	Substrate	Time (h)	Product/Yield (%)	
1	Crotonic acid	5	**1**/(2)	2/(10)
2	Crotonic acid	19	**1**/(3)	2/(39)
3	Crotonic acid	24	**1**/(40)	2/(4)
4	2-Octenoic acid	9	**3**/(35)	Not observed
5	2-Octenoic acid	19	**3**/(60)	Not observed



R = methyl **(1)**
R = pentyl **(3)**

Scheme 2. Production of 1-indanone with microwave.

Table 2. Preparation of 1-Indanones Using Microwaves

Entry	Substrate	Time (min)	Product/Yield (%)
1	Crotonic acid	2	**1**/45
2	2-Octenoic acid	2	**3**/33

Looking for new routes to prepare derived 1-indanones, the use of microwave radiation was investigated as the source of the necessary reaction activation energy.[12] In this reaction sequence (Sch. 2) the same compounds were used (*p*-methylphenol, the two α,β-unsaturated carboxylic acids and $AlCl_3$ in a ratio 1/1/2), but the reactions were carried out without solvent. It was observed that the reactions were completed in a short time, as detected by thin layer chromatography, forming the indanones **1** and **3** as the only isolated products in 45% and 33% yields, respectively (Table 2).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ in a Varian Unity-300 (300 MHz ^1H and 75 MHz for ^{13}C) and a Bruker DPX 200

(200 MHz ^{1}H and 50 MHz for ^{13}C) spectrometers, using TMS as an internal standard. Infrared spectra were recorded with a Nicolet Protégé 460 E.S.P. All melting points are uncorrected and measured in a Fisher-Johns apparatus. TLC analyses were carried out on precoated silica gel aluminium plates 60 F_{254} (Merck). Column chromatography was performed using Merck silica gel 60 (230–400 mesh). Microwave irradiations were carried out in a commercial Panasonic model NNS59BH microwave oven.

General Procedure

Reaction with conventional heating: To a stirred suspension of anhydrous $AlCl_3$ (1.10 g, 8.5 mmol) in chlorobenzene (2 mL) at 30°C was slowly added a solution of *p*-methylphenol (0.45 mg, 4.2 mmol) and the α,β-unsaturated carboxylic acid (4.2 mmol) in chlorobenzene (3 mL) over a period of 20 min. During the addition, hydrogen chloride evolved vigorously from the reaction mixture. The mixture was gradually heated in oil bath and kept under reflux for the desired time (Table 1). Thereafter the mixture was chilled and poured over water (1 mL) containing crushed ice (7 g) and concentrated hydrochloric acid (17.5 mmol). The organic layer was separated, washed with saturated bicarbonate solution and water and dried over anhydrous magnesium sulfate. After filtration, the solvents were removed under vacuum to afford an oil. The reaction products were isolated by flash chromatography[13] using ethyl acetate–hexane (1 : 10) as eluent.

Reaction with microwave heating: In a porcelain crucible was added *p*-methylphenol (0.12 g, 1.1 mmol) and the desired α,β-unsaturated carboxylic acid (1.1 mmol) followed by $AlCl_3$ (0.60 g, 4.5 mmol). The mixture was heated in a microwave oven (770 W) for 2 min, evolution of HCl during the reaction was observed. After this time the temperature was allowed to reach room temperature and 30 mL of distilled water were added to the reaction mixture. Then, the mixture was extracted three times with ethyl ether (15 mL) and, after drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The reaction products were isolated by flash chromatography[13] using ethyl acetate–hexane (1 : 10) as eluent.

7-Hydroxy-3,4-dimethyl-2,3-dihydro-1H-inden-1-one (1):[10] Yellow oil, conventional route (2–40%), microwaves (45%); EM (M^+=176–77%), (161–100%), (133–31%), (77–38%); IR (neat, cm^{-1}) 3379 (OH), 1674 (C=C), 1204 (C-O); ^{13}C NMR (50 MHz, $CDCl_3$, Pendant) δ 17.3 (C-8), 21.0 (C-9), 32.9 (C-3), 45.7 (C-2), 114.0 (C-6), 121.6 (C-7a), 127.1 (C-4), 139.3 (C-5), 155.7 (C-3a), 157.6 (C-7), 210.0 (C-1);

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (d, $^3J_{H\text{-}H} = 7.1$ Hz, H-8), 2.30 (s, H-9), 2.31 (dd, $^2J_{H2A\text{–}H2B} = 19.1$ Hz, $^3J_{H2B\text{-}H3} = 1.6$ Hz, H-2b), 2.96 (dd, $^2J_{H2A\text{-}H2B} = 19.1$ Hz, $^3J_{H2A\text{-}H3} = 7.1$ Hz, H-2a), 3.46 (m, H-3), 6.68 (d, $^3J_{H\text{-}H} = 8.2$ Hz, H-6), 7.25 (d, $^3J_{H\text{-}H} = 8.2$ Hz, H-5), 9.03 (s, OH).

1-(2-Hydroxy-5-methyl)phenyl-2-buten-1-one (2):[14] Yellow oil, conventional route (4–40%) EM ($M^+ = 176$–20%), (161–100%), (135–30%), (105–10%), (77–30%); IR (neat, cm^{-1}) 1651 (C=O), 1588 (C-C=O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0 (C-10), 20.8 (C-11), 118.4 (C-6), 119.4 (C-2), 125.8 (C-5), 129.8 (C-3), 137.4 (C-8), 138.1 (C-4), 145.8 (C-9), 161.6 (C-1), 194.1 (C-7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (d, $^3J_{H\text{-}H} = 6.6$ Hz, H-10), 2.32 (s, H-11), 6.90 (d, $^3J_{H\text{-}H} = 8.6$ Hz, H-6), 7.06 (d, $^3J_{H\text{-}H} = 15.0$ Hz, H-8), 7.19 (dq, $^3J_{H8\text{-}H9} = 15.0$ Hz, $^3J_{H9\text{-}H10} = 6.6$ Hz, H-9), 7.29 (d, $^3J_{H\text{-}H} =$ 8.6 Hz, H-5), 7.58 (s, H-3), 12.54 (s, OH).

7-Hydroxy-4-methyl-3-pentyl-2,3-dihydro-1H-inden-1-one (3): Yellow solid, m.p. = 65–66°C, conventional route (35–60%), microwaves (33%); EM ($M^+ = 232$–77%), (175–12%), (161–100%), (133–17%), (77–21%); IR (KBr, cm^{-1}) 3366 (OH), 1680 (C=C); ^{13}C NMR (50 MHz, $CDCl_3$, Pendant) δ 14.2 (C-12), 17.4 (C-13), 22.7 (C-11), 27.1 (C-9), 32.0 (C-10), 34.6 (C-8), 38.3 (C-3), 43.1 (C-2), 113.9 (C-6), 122.1 (C-7a), 126.0 (C-4), 139.3 (C-5), 155.7 (C-3a), 156.7 (C-7), 210.2 (C-1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (m, H-12), 1.29 (m, H-8, H-9, H-10 and H-11), 2.29 (s, H-13), 2.43 (d, $^2J_{H2A\text{-}H2B} = 19.1$ Hz, H-2b), 2.83 (dd, $^2J_{H2A\text{-}H2B} = 19.2$ Hz, $^3J_{H2A\text{-}H3} =$ 7.4 Hz, H-2a), 3.38 (m, H-3), 6.69 (d, $^3J_{H\text{-}H} = 8.2$ Hz, H-6), 7.26 (d, $^3J_{H\text{-}H} =$ 8.2 Hz, H-5), 9.03 (s, OH). $C_{15}H_{20}O_2$ (232.32): Anal. Calcd. C 77.50%, H 8.70%. Found C 77.69%, H 8.71%.

CONCLUSION

We have developed a facile and effective procedure for the synthesis 1-indanone from *p*-methylphenol and α,β-unsaturated carboxylic acids using microwave radiation. Further studies involving the bioactivity of these products and the optimization and amplification of this reaction are in progress.

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