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Microwave-Assisted Ketone–Ketone Rearrangement: An Improved Synthesis of 3-(4-Alkoxyphenyl)-3-methylbutan-2-ones

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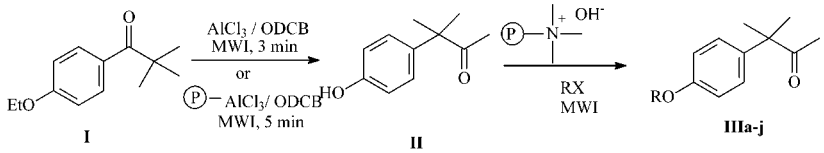
ABSTRACT



A novel procedure for the preparation of 3-(4-alkoxyphenyl)-3-methylbutan-2-one in excellent yield is described via polymer-supported $AlCl_3$-catalyzed rearrangement of 1-(4-ethoxyphenyl)-2,2-dimehtylpropan-1-one, followed by O-alkylation under microwave irradiation condition.

In our continuing study on the development of new cost-effective methodologies utilizing unconventional energy for the synthesis of new generation synthetic pyrethroids, for example, MTI-800,[1,2] we have achieved a simple methodology to synthesize the required intermediates, 3-(4-alkoxyphenyl)-3-methylbutan-2-ones (**III**), under microwave irradiation condition.

The synthesis of 3-(4-alkoxyphenyl)-3-methylbutan-2-ones (**III**) has been reported by various research groups but has involved complex procedures.[3−5] In our earlier communication,[1] the synthesis of 3-aryl-3-methylbutan-2-one by a simple rearrangement using the Lewis acid catalyst $AlCl_3$ was reported. Herein, the application of microwave and polymer-supported reagents for the rearrangement and subsequent alkylation along with a detailed study of this rearrangement with several other Lewis acids is described.

The reaction of 1-(4-ethoxyphenyl)-2,2-dimehtylpropan-1-one (**I**) with Lewis acids, BF_3·OEt_2, $TiCl_3$, $TiCl_4$, and $SnCl_4$ under both refluxing and microwave irradiation conditions favored only dealkylation of the aralkyl ether, whereas $ZnCl_2$, $FeSO_4$, and $LnCl_3$ did not promote any reaction. However, the reaction when performed with $AlCl_3$ in *o*-dichlorobenzene under microwave irradiation condition yielded the desired rearrangement product with concomitant dealkylation, in less than 3 min. (Table 1).

Table 1. Rearrangement of 1-(4-Ethoxyphenyl)-2,2-dimehtylpropan-1-one (**I**) with $AlCl_3$ in *o*-Dichlorobenzene under Various Reaction Conditions[11]

	Lewis acid	condition	time	yield (%)
1	$AlCl_3$	refluxing	1.5 h	78
2	$AlCl_3$	MWI	3 min	83
3	Ⓟ−$AlCl_3$	refluxing	2.0 h	71
4	Ⓟ−$AlCl_3$	MWI	5 min	75

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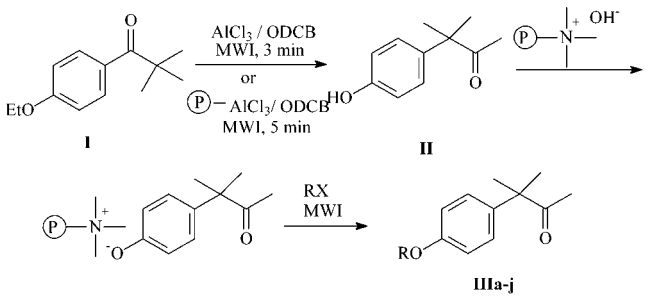
As polymer-supported reagents are gaining priority[6−9] for their easy handling, benign reaction condition, and simple workup procedures, an attempt has been made to use the polymer-supported $AlCl_3$ reagent for the rearrangement reaction. Polymer-supported $AlCl_3$ was prepared following the procedure reported in the literature.[10] This reagent, when used instead of naked $AlCl_3$, under microwave irradiation (MWI) conditions enabled the desired rearrangement reaction to proceed smoothly yielding the product in 5 min, thus circumventing direct handling of corrosive $AlCl_3$.



IIIa CH_3 **IIIe** C_5H_{11} **IIIi** C_7H_{15}
IIIb C_2H_5 **IIIf** $CH(CH_3)_2$ **IIIj** C_8H_{17}
IIIc C_3H_7 **IIIg** $CH_2CH{=}CH_2$
IIId C_4H_9 **IIIh** $CH_2C(CH_3){=}CH_2$

3-(4-Alkoxyphenyl)-3-methylbutan-2-ones (**III**), alkyl derivatives of the 3-(4-hydroxyphenyl)-3-methylbutan-2-one (**II**), are important substrates for the elaboration of new generation synthetic pyrethroids. The phenolic compound **II**[12] in *o*-dichlorobenzene was passed through an anion-exchange resin column with hydroxide ions until the entire compound was adsorbed as phenoxide ion. Subsequent reaction of the phenoxide resin with the alkylating agents in THF under microwave irradiation condition yielded the alkylated products. The reactions were over within 5 min with reasonable yields[13] (Table 2).

Table 2. Alkylation of 3-(4-Hydroxyphenyl)-3-methylbutan-2-one

alkylating agent	product	time (min)	yield (%)
dimethyl sulfate	**IIIa**	3.5	90
diethyl sulfate	**IIIb**	3.0	85
1-bromopropane	**IIIc**	5.0	73
1-iodobutane	**IIId**	4.0	76
1-iodopentane	**IIIe**	4.0	79
isopropylbromide	**IIIf**	5.0	68
allylbromide	**IIIg**	5.0	72
methallyl chloride	**IIIh**	5.0	65
1-bromoheptane	**IIIi**	5.0	74
1-bromooctane	**IIIj**	5.0	62

Thus a simple procedure with benign reaction conditions for the preparation of 3-(4-alkoxyphenyl)-3-methylbutan-2-ones,[14] employing microwave irradiation condition and polymer-supported reagents, is reported.

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(11) **Preparation of 3-(4-Hydroxyphenyl)-3-methylbutan-2-one (II) under MWI.** To a suspension of anhydrous $AlCl_3$ (5.32 g, 40 mmol) in *o*-dichlorobenzene (20 mL) was added 1-(4-ethoxyphenyl)-2,2-dimethylpropan-1-one (**I**, 4.03 g, 20 mmol), and the mixture was irradiated in a modified domestic microwave oven (IFB-Megatron; wattage 1100 W; power max 750 W; voltage 230 Hz; frequency 2450 MHz) with refluxing unit for 3 min. The temperature of the reaction within the microwave experiments was 180 °C. The reaction mixture was poured into ice-cold water and extracted with *o*-dichlorobenzene (3 × 15 mL). The organic layer was washed with NaOH solution (5 N, 3 × 15 mL), and the aqueous solution was neutralized with cold HCl (2 N, 25 mL). The separated phenolic compound was then re-extracted with ethyl acetate (3 × 15 mL), and the organic layer was washed with water (2 × 15 mL) and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (ethyl acetate/hexane 5:95) of the crude product yielded 3-(4-hydroxyphenyl)-3-methylbutan-2-one (**II**) (2.69 g, 83%). **Preparation of 3-(4-Hydroxyphenyl)-3-methylbutan-2-one under MWI using Polymer-Supported $AlCl_3$ Resin.** To a suspension of polymer-supported $AlCl_3$ (12 g of resin, 5.01% of Al as $AlCl_3$ per gram of the resin; 4.4 mmol) in *o*-dichlorobenzene (20 mL) was added 1-(4-ethoxyphenyl)-2,2-dimethylpropan-1-one (400 mg, 2.0 mmol), and the mixture was irradiated in a modified domestic microwave oven with refluxing unit for 5 min. The reaction mixture was filtered and repeatedly washed with *o*-dichlorobenzene (10 mL). The filtrate was poured into ice-cold water and extracted with *o*-dichlorobenzene (3 × 15 mL). The organic layer was washed with NaOH solution (5 N, 3 × 15 mL), and the aqueous solution was neutralized with cold HCl (2 N, 25 mL). The separated phenolic compound was then re-extracted with ethyl acetate (3 × 15 mL,) and the organic layer was washed with water (2 × 15 mL) and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (ethyl acetate/hexane 5:95) of the crude product yielded 3-(4-hydroxyphenyl)-3-methylbutan-2-one (**II**) (0.288 g, 75%).

(12) **3-(4-Hydroxyphenyl)-3methylbutan-2-one:** bp 202−204 °C/5 mm LRMS (EI M^+ *m/z*) 178; ^{1}H NMR 7.21 (d, 2H, J = 7.6 Hz), 6.95 (d, 2H, J = 7.6 Hz), 6.60 (bs, 1H, D_2O exchangeable) 1.95 (s, 3H), 1.48 (s, 6H); ^{13}C NMR 213.2, 155.0, 135.6, 127.2, 115.7, 51.9, 25.5, 25.2.

(13) **3-(4-Alkoxyphenyl)-3-methylbutan-2-ones (IIIa−j). General Procedure. Preparation of Phenoxide Resin.** IRA-400 (50 g, OH^-) was packed in a column, and compound **II** (5 g) in *o*-dichlorobenzene was repeatedly passed through the column until compound **II** was completely adsorbed as phenoxide ion. The phenoxide resin thus prepared (2 g resin/200 mg of **II**, 1.14 mmol) was reacted with various alkylating agents (1.5 mmol) in THF in a modified domestic microwave oven with refluxing unit. After the completion of reaction (TLC), the reaction mixture was filtered and the solvent was removed. The residue on column chromatography yielded the respective 3-(4-alkoxyphenyl)-3methylbutan-2-ones **IIIa−j** (Table 2).

(14) **Spectral Details. IIIa:** ^{1}H NMR 7.32 (d, 2H, J = 7.4 Hz), 6.75 (d, 2H, J = 7.4 Hz), 3.95 (s, 3H), 2.15 (s, 3H), 1.35 (s, 6H); LRMS (EI M^+ *m/z*) 192. **IIIb:** ^{1}H NMR 7.28 (d, 2H, J = 7.6 Hz), 6.74 (d, 2H, J = 7.6 Hz), 3.95 (q, 2H, J = 7.0 Hz), 2.14 (s, 3H), 1.40 (t, 3H, J = 7.0 Hz), 1.35 (s, 6H); LRMS (EI M^+ *m/z*) 206. **IIIc:** ^{1}H NMR 7.30 (d, 2H, J = 7.4 Hz), 6.79 (d, 2H, J = 7.5 Hz), 3.80 (t, 2H, J = 6.5 Hz), 2.11 (s, 3H), 1.65 (m, 2H), 1.35 (s, 6H), 1.12 (t,3H, J = 6.4 Hz); LRMS (EI M^+ *m/z*) 220. **IIId:** ^{1}H NMR 7.32 (d, 2H, J = 7.4 Hz), 6.80 (d, 2H, J = 7.4 Hz), 4.01 (t, 2H, J = 6.3 Hz), 2.05 (s, 3H), 1.52−1.67 (m, 4H), 1.35 (s, 6H), 1.13 (t, 3H, J = 6.3 Hz); LRMS (EI M^+ *m/z*) 234. **IIIe:** ^{1}H NMR 7.41 (d, 2H, J = 7.3 Hz), 6.91 (d, 2H, J = 7.2 Hz), 4.05 (t, 2H, J = 6.5 Hz), 2.09 (s, 3H), 1.50−1.68 (m, 6H), 1.33 (s, 6H), 1.03 (t, 3H, J = 6.5 Hz); LRMS (EI M^+ *m/z*) 248. **IIIf:** ^{1}H NMR 7.30 (d, 2H, J = 7.4 Hz), 6.79 (d, 2H, J = 7.5 Hz), 3.96 (m, 1H), 2.19 (s, 3H), 1.35 (s, 6H), 1.22 (d, 6H, J = 6.0 Hz); LRMS (EI M^+ *m/z*) 220. **IIIg:** ^{1}H NMR 7.36 (d, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 7.6 Hz), 5.62−5.71 (m, 3H), 4.65 (d, 2H, J = 8.5 Hz), 2.19 (s, 3H), 1.35 (s, 6H); LRMS (EI M^+ *m/z*) 218. **IIIh:** ^{1}H NMR 7.34 (d, 2H, J = 7.6 Hz), 6.80 (d, 2H, J = 7.6 Hz), 5.60−5.65 (s, 2H), 4.58 (s, 2H), 2.01 (s, 3H), 2.21 (s, 3H), 1.35 (s, 6H); LRMS (EI M^+ *m/z*) 232. **IIIi:** ^{1}H NMR 7.41 (d, 2H, J = 7.3 Hz), 6.91 (d,2H, J = 7.2 Hz), 4.05 (t, 2H, J = 6.5 Hz), 2.09 (s, 3H), 1.54−1.72 (m, 10H), 1.33 (s, 6H), 0.98 (t, 3H, J = 6.5 Hz); LRMS (EI M^+ *m/z*) 276. **IIIj:** ^{1}H NMR 7.41 (d, 2H, J = 7.3 Hz), 6.91 (d, 2H, J = 7.2 Hz), 4.05 (t, 2H, J = 6.5 Hz), 2.09 (s, 3H), 1.48−1.70 (m, 12H), 1.39 (s, 6H), 1.06 (t, 3H, J = 6.5 Hz); LRMS (EI M^+ *m/z*) 290.