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Note

Microwave assisted rapid and efficient synthesis of aryl methyl ketones and β-keto esters using Meldrum's acid †

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Microwave mediated rapid and efficient synthesis of aryl methyl ketones and β-keto esters from acyl Meldrum's acid by hydrolysis and alcoholysis, respectively, has been reported.

Keywords: Microwave irradiation, Meldrum's acid, β-keto esters, aryl methyl ketones.

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Green Chemistry involves the design and redesign of chemical synthesis[1] and chemical products to prevent pollution and thereby solve the environmental problems. The use of chemical principles and methodologies for source-reduction is the most desirable form of pollution prevention. It incorporates pollution prevention practices in the manufacture of chemicals and promotes industrial ecology. It is a new way of handling chemicals and their manufacturing processes for minimizing negative environmental effects. Microwave (MW) chemistry is the current approach in Green Chemistry and used from kitchen to laboratory and has become a boon for synthetic organic chemists. The MW energy is utilized for rapid chemical transformations in the liquid or solution state as well as in the solid state[2] in absence of water or organic solvent. The MW mediated reactions[3] occur more rapidly, safely and in an environment friendly manner with higher yields as compared to conventional methods. Such reactions reduce the amount of side products and deliver the required products in high purity.

Ever since an example of Claisen condensation was discovered more than a century ago, β-keto esters have been among the most versatile intermediates in organic synthesis. β-Keto esters of the type $RCOCH_2COOR$ are widely used in the synthesis of heterocyclic compounds[4,5] such as 1,4- benzo-thiazines, 1,4-dihydropyridines, *etc*.

Many methods have been developed for the preparation of β-keto esters. Most of these methods involve the initial conversion of malonic acid derivatives into mono- or di-anion by the action of base such as metal alkoxides, organo-lithium compounds or tertiary amines, followed by acylation with carboxylic acid derivatives. In a general method, acyl Meldrum's acid derivatives were heated with an appropriate alcohol to give the desired β-keto esters [6].

Ketones and aldehydes are carbonyl compounds in which carbon is linked to oxygen by a double bond and the general methods of synthesis of carbonyl compounds[7] include, (i) oxidation of secondary alcohol, (ii) from alkyl cyanide using Grignard reagent, (iii) Friedel-Crafts acylation, (iv) hydro-boration of alkynes, (v) hydration of alkynes, (vi) ozonolysis of alkenes and (vii) from acetoacetic ester.

In the present work, microwave assisted hydrolysis and alcoholysis to obtain aryl methyl ketones **(Scheme I)** and β-keto esters **(Scheme II)**, respectively have been reported. In conclusion, an easy, convenient and efficient environment friendly methodology *i.e.* microwave irradiation technique has been developed for the synthesis of aryl methyl ketones and β-keto esters using Meldrum's acid.

Experimental Section

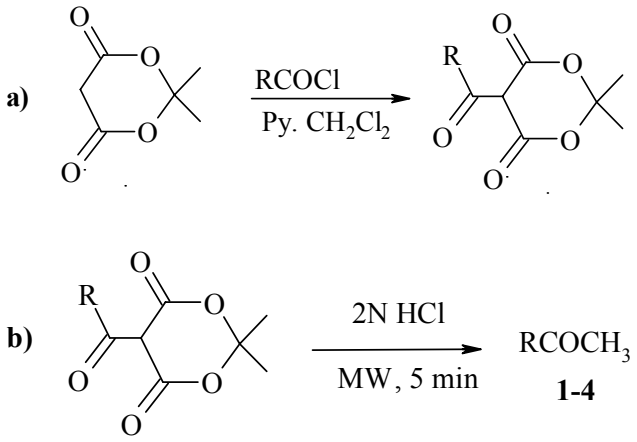
All chemicals used were of synthetic grade (S. D. Fine Chemicals Ltd, Mumbai). The acyl Meldrum's acids and acid chlorides were prepared in the laboratory[8,9]. The products were characterized by comparing the physical constants and IR spectral data of the prepared compounds with those of the authentic samples. The melting points were determined by open capillary method and are uncorrected. Kenstar (model OM9918C, 2350W) monomode microwave oven without modification was used to carry out reactions.

Preparation of acetyl Meldrum's acid[8]

To a solution of 1.44 g (0.01 mole) Meldrum's acid in 10 mL of dry dichloromethane, 1.58 g (0.02 mole) of pyridine was added dropwise with stirring under N_2

† This paper is dedicated to Prof. R.B. Mane, (Former Head) Department of Chemistry, Shivaji University, Kolhapur- 416 004.

atmosphere. The stirring was continued for 15 min. The reaction mixture was then cooled to 0ºC and 0.85 g (0.011 mole) acetyl chloride in 5 mL of dichloromethane was added dropwise with stirring. Stirring was continued for 1 hr at 0ºC and 6 hr at rt. The contents were then poured into 30 mL of water and extracted with dichloromethane. The organic extract was washed with water, dil. HCl, water, saturated $NaHCO_3$ solution and water in that order and dried over anhydrous calcium chloride. The removal of solvent gave the crude product, which was recrystallised from dichloromethane-pet.ether to give 1.7 g (91%) of acetyl Meldrum's acid, m.p. 85ºC. All other acyl Meldrum's acids were prepared using the above procedure **(Scheme Ia)**.



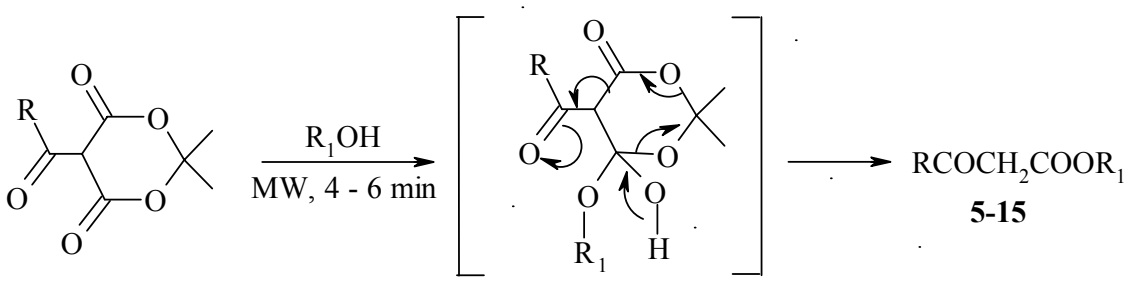
Scheme I

General procedure for microwave assisted synthesis of aryl methyl ketones 1-4.

A mixture of acyl Meldrum's acid (0.01 mole) and 5 mL of 2N HCl was irradiated for 5 min at power level 40. The reaction was monitored by silica gel TLC. (benzene:ethyl acetate; 80:20). After the completion of reaction, the reaction mixture was extracted with ether. The ether extract was washed successively with saturated sodium bicarbonate solution and water and then dried over anhydrous sodium sulphate. Removal of ether afforded aryl methyl ketones **1-4 (Table I**, **Scheme I)**. In addition to comparative TLC, characterization by IR spectroscopy showed absorption at 1745-1680 (C=O) and 1615-1605 cm^{-1} (C=C).

General procedure for microwave assisted synthesis of β-keto esters 5-15.

A mixture of acyl Meldrum's acid (0.01 mole) and excess of alcohol (methanol, ethanol, *t*-butyl alcohol or benzyl alcohol) (5 mL) was taken in an Erlenmeyer flask fitted with a funnel as loose top upon which a round bottom flask containing ice was placed to serve the purpose of condenser. The mixture was irradiated



Scheme II

Table I − Aryl methyl Ketones

Compd	R	b.p.(°C) (Lit.[11] b.p.)	Yield (%) MW [Conventional] [10]	Time (min) MW [Conventional, hr] [10]
1	C_6H_5	202 (202)	90 [70]	5 [4]
2	*o*-$NO_2C_6H_4$	159 (158-59)	90 [60]	5 [4]
3	*m*-NO_2 C_6H_4	202 (202)	80 [70]	5 [4]
4	C_6H_5-CH=CH	260 (260)	85 [60]	5 [4]

Table II — β-Keto esters

Compd	R	R_1	b.p. / m.p.*(°C) (Lit [11] m.p./b.p.)	Yield (%) MW [Conventional] [6]	Time (min) MW [Conventional, hr] [6]
5	CH_3	CH_3	170 (170)	98 [70]	4 [2.5]
6	CH_3	CH_3CH_2	181 (182)	92 [75]	4 [2.5]
7	CH_3CH_2	CH_3	193 (195-98)	90 (75]	4 [2.5]
8	CH_3CH_2	CH_3CH_2	199 (199-01)	96 [75]	5 [2.5]
9	$C_6H_5CH_2$	CH_3CH_2	265-70 (265-70)	90 [70]	5 [2.5]
10	CH_3	$C_6H_5\ CH_2$	273 (275-80)	94 [83]	4 [2.5]
11	CH_3	$(CH_3)_2CHCH_2$	200 (200-05)	96 [72]	5 [2.5]
12	4-$NO_2C_6H_4$	CH_3	106 (106)	91 [70]	5 [2.5]
13	4-$NO_2C_6H_4$	CH_3CH_2	71*(72)	90 [80]	5 [2.5]
14	C_6H_5	CH_3	106(106)	89[70]	5 [2.5]
15	$C_6H_5CH_2$	CH_3	309(310-15)	88[75]	5 [2.5]

for 5-6 min at power level 30. The progress of reaction was monitored by silica gel TLC (pet.ether:ethyl acetate, 80:20). After completion of reaction, the unreacted excess of alcohol was distilled off followed by distillation of esters under reduced pressure or extraction of reaction mixture with ether as above, to give the products **5-15 (Table II**, **Scheme II)**. In addition to comparative TLC, the characteristic IR absorption bands were observed for β-keto esters at 1750-1735 (C=O) and 1300-1100 cm^{-1} (C-O).

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