SHORT PAPER

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Lithium perchlorate and lithium bromide catalysed solvent free one pot rapid synthesis of 3-carboxycoumarins under microwave irradiation

B.P. Bandgar*, L.S. Uppalla and V.S. Sadavarte

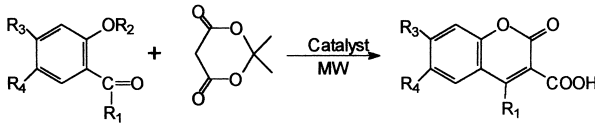
School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded-431 606, Maharashtra, India

Reaction of 2-hydroxy or 2-methoxy substituted benzaldehydes or acetophenones with Meldrum's acid in the presence of a catalytic amount of $LiClO_4$ or LiBr without solvent under microwave irradiation afforded 3-carboxycoumarins in excellent yields.

Keywords: lithium perchlorate, lithium bromide, 3-carboxycoumarins

Coumarins are very well known natural products displaying a broad range of biological activities.[1] Many synthetic coumarins have shown interesting properties such as anticoagulants[2] and triplet sensitisers.[3] This has stimulated the search for new and more convenient methods to accomplish their synthesis.[4] 3-Carboxycoumarins have been synthesised in two steps by condensing 2-hydroxy/methoxy benzaldehydes with Meldrum's acid in presence of DMF that plays the dual role of a base as well as a solvent to give the benzylidene derivative which was subsequently cyclised in the presence of sulfuric acid to afford 3-carboxy coumarins.[5] More recently a EPZG catalysed reaction for synthesis of 3-carboxy coumarins has been reported.[6] Also some other efficient methods have been reported recently for the facile synthesis of coumarins.[7]

In recent years lithium perchlorate and lithium perchlorate in diethyl ether (LPDE) have gained importance as versatile reagents for effecting organic transformations under neutral conditions.[8] Thus, development of method which allows the reaction under essentially neutral conditions should heighten the synthetic potential of the conversion. A related development that had a profound impact on these reactions is the use of microwave irradiation (MW) techniques for acceleration of organic reactions.[9]



1 **2** **3**

	R1	R2	R3	R4	R1	R3	R4
a	H	H	H	H	H	H	H
b	H	H	Cl	H	H	Cl	H
c	H	Me	H	OMe	H	H	OMe
d	CH_3	H	H	H	CH_3	H	H
e	CH_3	H	H	OH	CH_3	H	OH
f	CH_3	H	Cl	H	CH_3	Cl	H

Scheme 1

We now report herein use of combination of $LiClO_4$ [see Caution] or LiBr and microwave irradiation for rapid one pot synthesis of 3-carboxycoumarins from 2-OH or 2-OMe substituted benzaldehydes or acetophenones and Meldrum's acid. This reaction has been carried out under solvent-free condition (Scheme 1).

Table 1 Synthesis of 3-carboxycoumarins[a]

Entry	Aldehyde/ketone	Product	Catalyst	Time/s	Yield[b,c]/%	M.P./°C[Lit.]
1	**1a**	**3a**	$LiClO_4$	50	89	192
			LiBr	90	85	[191][5]
2	**1b**	**3b**	$LiClO_4$	60	85	121
			LiBr	90	84	[120][6]
3	**1c**	**3c**	$LiClO_4$	70	90	192
			LiBr	110	89	[192][5]
4	**1d**	**3d**	$LiClO_4$	75	85	154
			LiBr	120	75	[154][6]
5	**1e**	**3e**	$LiClO_4$	70	83	126
			LiBr	110	81	[126][6]
6	**1f**	**3f**	$LiClO_4$	70	79	153
			LiBr	120	75	[152][6]

[a]**See Caution**. [b]Yields of pure isolated products. [c]Products are characterised by spectral analysis.

* To receive any correspondence. E-mail: bandgar_bp@yahoo.com

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Various 2-hydroxy or 2-methoxy substituted benzaldehydes or acetophenones when treated with Meldrum's acid in the presence of a catalytic amount of $LiClO_4$, or LiBr under microwave irradiation afforded corresponding 3-carboxycoumarins in good to excellent yield . This Knoevenagel condensation yielded corresponding benzylidene derivatives as non-isolable intermediates. Subsequently these were cyclised spontaneously. The cyclisation was possible only when a 2-hydroxy or 2-methoxy group acts as a nucleophile to a nearby carbonyl function. Though the reaction involves loss of Me group and is thus not 100% atom efficient, this is the only route to such biologically important compounds. Attempts were made to synthesise 3-carboxycoumarins: (i) in the absence of MW; (ii) in the absence of $LiClO_4$ or LiBr; and (iii) in the absence of both MW and $LiClO_4$ or LiBr, but it was found that there was no reaction under these conditions even after stirring the reaction mixture for 3 h. The important feature of this protocol is the ease of work-up which involves dilution of the reaction mixture with aqueous methanol followed by filtration of the pure products which do not require further purification either by recrystallisation or column chromatography. Thus loss of excess of solvent for work-up or purification is avoided by this simple protocol.

In conclusion, we have described a rapid, one pot synthesis of 3-carboxycoumarins from 2-hydroxy or 2-methoxy benzaldehydes or acetophenones and Meldrum's acid with $LiClO_4$ or LiBr. The reaction has been carried out without solvent under microwave irradiation.

Experimental

All the chemicals were of analytical grade. Microwave oven Kelvinator T 37 (2450 MHz, 760 Watt) was used at its 100 % power. IR spectra were recorded on Bomem MB 104 IR spectrometer. ^1H NMR were recorded on 300 MHz (AC 300 F instrument) with TMS as an internal standerd.

Preparation of 3-carboxycoumarins: A mixture of 2-hydroxy or 2-methoxy benzaldehyde or acetophenone (5 mmol) and Meldrum's acid (5 mmol) in a beaker containing $LiClO_4$ or LiBr (1 mmol) was exposed to microwave irradiation for time specified (Table 1). After completion of the reaction (TLC), the reaction mixture was diluted with aqueous methanol and filtered to give the 3-carboxycoumarin as a crystalline product in excellent yield, in pure form (checked by TLC, physical constant and spectral analysis) that did not require further purification.

Caution: The catalytic amount (1 mmol) of lithium perchlorate was used under microwave irradiation without any problem. However, explosion may occur if more lithium perchlorate is used to scale-up of the process or an excess of lithium perchlorate is used. Appropriate precautions should therefore be taken.

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