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Short communication

SHORT COMMUNICATION

Iodine-mediated one-pot synthesis of 3-cyanocoumarins and 3-cyano-4-methylcoumarins

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Abstract: 2-Hydroxybenzaldehydes **1a–e** on reaction with malononitrile (**2**) in the presence of iodine as catalyst give 3-cyanocoumarins **3a–e** in one step under thermal heating as well as under microwave irradiation. The latter conditions are much more efficient in terms of time (2–5 min) and yield as compared to the thermal conditions (2–2.5 h). Following a similar procedure, 3-cyano-4-methylcoumarins **3f–i** were also prepared by the reaction of 2-hydroxyacetophenones **1f–i** with **2**.

Keywords: 3-cyanocoumarin/3-cyano-4-methylcoumarin; malononitrile; iodine; microwave irradiation; one-pot reaction.

INTRODUCTION

3-Cyanocoumarins (2-oxo-2*H*-chromene-3-carbonitriles) constitute an important class of compounds because of their biological activities,[1] such as antimicrobial properties[2] and inhibition of α-chymotripsin.[3] These compounds have also been used as intermediates for the preparation of methine dyes,[4] cephalosporins,[5] modified pencillins,[6] oxygen-bridged tetrahydropyridones[7] and isoureases.[8]

3-Cyanocoumarins were earlier prepared by the reaction of 2-hydroxybenzaldehydes with malononitrile or with ethyl cyanoacetate under basic conditions using various bases, such as pyridine,[9] piperidine,[10] aqueous alkali,[11] Mg–Al hydrotalcite,[12] MgO[13] and ionic liquids.[14,15] In addition, these reactions have been performed under phase transfer catalysed conditions.[16] In recent reports, these compounds were obtained by the condensation of 2-hydroxybenzaldehydes with malononitrile using $ZrCl_4$/[bmim]BF_4[17] and $SiCl_4$ in ethanol.[18]

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However, these methods suffer from one or other limitations. The former reaction between 2-hydroxybenzaldehyde and malononitrile gives 2-imino-2*H*-chromene-3-carbonitrile as an intermediate that has to be hydrolysed under acidic conditions.[16] In the latter method, 3-carboxycoumarins are also formed along with 3-cyanocoumarins.[19]

In recent years, molecular iodine was used as a mild and efficient condensing agent in various organic reactions.[20–23] Thus, it was thought worthwhile to study the reaction of 2-hydroxybenzaldehydes and malononitrile using iodine as catalyst, which led to the synthesis of 3-cyanocoumarins in a single step.

RESULTS AND DISCUSSION

A solution of 2-hydroxybenzaldehyde (**1a**) and malononitrile (**2**) in dimethylformamide (DMF) was refluxed in the presence of a catalytic amount of iodine, and the reaction was found to proceed to completion in 2 h, as evidenced by thin layer chromatography (TLC), affording a colourless compound that was identified as 3-cyanocoumarin (**3a**) based on its IR, ^{1}H-NMR and ^{13}C-NMR spectral data.

As the reactions are known to be improved when they are performed under microwave irradiations,[24] the above reaction was repeated using microwave irradiation and it was found to be completed in 2 min and 3-cyanocoumarin was obtained in 90 % yield.

Using the above conditions, 3-cyano-4-methylcoumarins **3f**–**i** were also prepared by the reaction of 2-hydroxyacetophenones **1f**–**i** with **2** using iodine as catalyst under both thermal and microwave conditions.

The optimum conditions of the reaction were checked by varying the amount of iodine and 0.12 mmol of iodine was found to be sufficient for completion of the reaction. No reaction was found to take place in the absence of the catalyst. It appears that initial condensation between 2-hydroxybenzaldehyde and malononitrile was catalysed by iodine, which is known to act as a condensing agent due to its Lewis acidity.[25] Excessive amounts of iodine (20–40 mol %) were found excessive, as no further improvement of the reaction was found either in terms of the yield or the reaction time.

The methods reported earlier could not be used successfully for the preparation of 3-cyano-4-methylcoumarins involving reaction of 2-hydroxyacetophenones with malononitrile as it required stringent conditions and the yields were very poor. However, these compounds could be obtained in excellent yield (85––90 %) using the present method. The success of the method was established by the synthesis of various substituted 3-cyanocoumarins and 3-cyano-4-methylcoumarins **3a**–**i**. The identity of all the compounds was checked by their IR and ^{1}H--NMR spectral data, given in the Supplementary material to this paper, and comparison of the melting points with literature values, Table I.

EXPERIMENTAL

The melting points of **3a**–**i** were determined in open capillaries. The IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer using the KBr pellets technique. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance (400 MHz) instrument using TMS as an internal standard. The reactions were performed in a microwave oven (Samsung, model CE1031LFB, output energy 900 W, frequency 2450 MHz) with a temperature control arrangement maintaining the temperature of the oven at 100 °C using 50 % power for all the experiments.

TABLE I. Physical data of 3-cyanocoumarins and 3-cyano-4-methylcoumarins; method A: thermal conditions; method B: microwave conditions

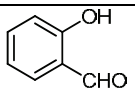
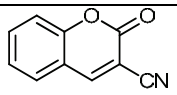
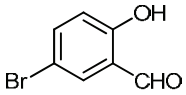
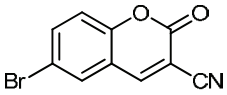
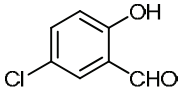
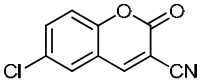
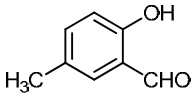
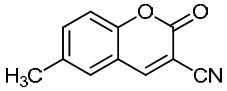
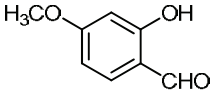
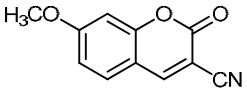
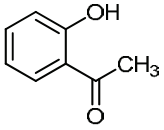
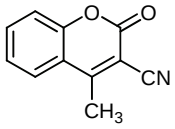
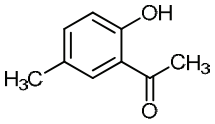
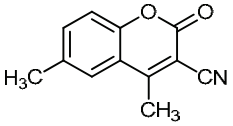
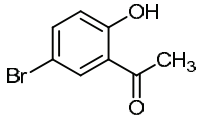
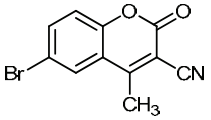
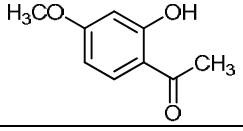
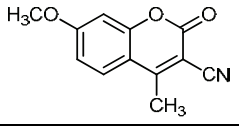
Compound	Structure	Compound	Structure
1a		**3a**	
1b		**3b**	
1c		**3c**	
1d		**3d**	
1e		**3e**	
1f		**3f**	
1g		**3g**	
1h		**3h**	
1i		**3i**	

TABLE I. Continued

Compound	R	R_1	R_2	Method A		Method B		M.p. / °C
				Time, h	Yield, %	Time, min	Yield, %	
3a	H	H	H	2	85	2	90	179–181[10]
3b	H	H	Br	2	92	2.5	95	195–196[26]
3c	H	H	Cl	2	86	2.5	92	190–192[27]
3d	H	H	CH_3	2	80	3	85	204–206[28]
3e	H	OCH_3	H	2	82	3	86	223–226[29]
3f	CH_3	H	H	2.5	86	4	92	190–192[30]
3g	CH_3	H	CH_3	2.5	90	5	95	200–201[26]
3h	CH_3	H	Br	2.5	90	4	95	178–180[26]
3i	CH_3	OCH_3	H	2.5	85	5	87	220–222[29]

*General procedure for the synthesis of 3-cyano-/3-cyano-4-methyl-coumarins **3a–i***

Method A (thermal conditions). A mixture of 2-hydroxybenzaldehydes/2-hydroxyacetophenones **1a–i** (4.71 mmol), malononitrile (**2**, 0.32 g, 4.71 mmol), iodine (0.03 g, 0.12 mmol) and dimethylformamide (10 mL) in a round bottom flask (50 ml) was heated in an oil bath at 140–145 °C for 2–2.5 h. Completion of the reaction was monitored by thin layer chromatography (silica gel plates using the solvent benzene: acetone, 1:1). The reaction mixture was cooled and ice-cold sodium thiosulphate solution (10 %, 30 mL) was added to remove any iodine present in the reaction mixture. The solid that separated out was filtered, washed with water and recrystallised from aqueous ethanol to give **3a–i**.

Method B (microwave conditions): A mixture of 2-hydroxybenzaldehydes/2-hydroxyacetophenones **1a–i** (4.71 mmol), malononitrile (**2**, 0.32 g, 4.71 mmol), iodine (0.03 g, 0.12 mmol) and dimethylformamide (5 mL) taken in a loosely stoppered round bottom flask was subjected to microwave irradiation for 2–5 min. Completion of the reaction was controlled by thin layer chromatography and the work-up was as described above to give **3a–i**.

CONCLUSION

In conclusion, the presented method appears to be extremely simple and highly efficient giving 3-cyano- and 3-cyano-4-methyl-coumarins in a single step.

SUPPLEMENTARY MATERIAL

Spectral data for the synthesised coumarins are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

ЈЕДНОСТАВНА СИНТЕЗА 3-ЦИЈАНОКУМАРИНА И 3-ЦИЈАНО-4-МЕТИЛКУМАРИНА У ПРИСУСТВУ ЈОДА

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2-Хидроксибензалдехиди **1a–e** у реакцији са малондинитрилом (**2**), у присуству јода као катализатора, под условима термалног загревања или микроталасног озрачивања, као производ дају 3-цијанокумарине **3a–e**. Реакције под микроталасима трају знатно краће време (2–5 min) у поређењу са термичким загревањем (2–2,5 h). При-

меном сличних реакционих услова, 3-цијано-4-метилкумарини **3f**–**i** су добијени полазећи од 2-хидроксиацетофенона **1f**–**i** и **2**.

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