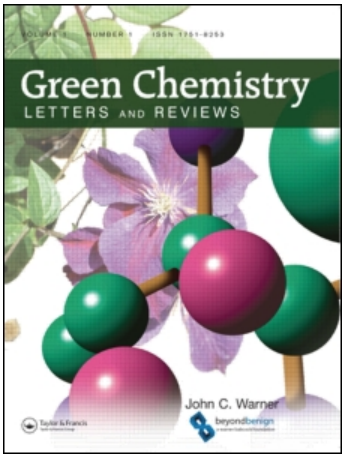

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Water mediated efficient one-pot synthesis of bis-(4-hydroxycoumarin)methanes

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RESEARCH ARTICLE

Water mediated efficient one-pot synthesis of bis-(4-hydroxycoumarin)methanes

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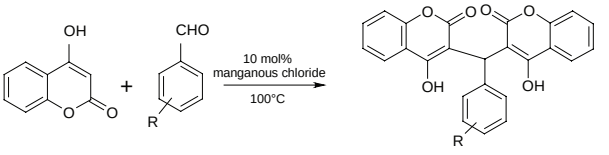
Manganous chloride ($MnCl_2 \cdot 4H_2O$) has been used as an efficient catalyst for an improved and rapid one-pot synthesis of bis-(4-hydroxycoumarin)methanes in excellent yields using water as a reaction medium. This aqueous mediated reaction of various aromatic and heteroaromatic aldehydes with 4-hydroxycoumarin using catalytic amounts of manganous chloride avoids the use of expensive, corrosive reagents, toxic solvents, and provides operational simplicity.



Keywords: bis-(4-hydroxycoumarin)methanes; manganous chloride; aqueous media

Introduction

Coumarin and its derivatives are widely used as additives to food, cosmetics, and optical brightening agents (*1,2*). Coumarin derivatives have recently revealed new biological activities with interesting potential in therapeutic application besides their traditional employment as anticoagulant (anti-vitamin K activity) and sustaining agents (photosensitizing action of flurocoumarin) (*3,4*). They have also been reported as antibiotics (novobiocin and analogs) (*5*) and antitumor drugs (geiparvarin) (*6*). For preparation of these compounds a variety of Lewis acid catalysts (*7–9*) and microwave reactions (*10,11*) were utilized. Recently molecular iodine has been used for the synthesis of the same compounds (*12*). Although various procedures are reported for the synthesis of bis-(4-hydroxycoumarin)methanes, disadvantages including low yields, prolonged reaction time, use of an excess of reagents or catalysts, and use of toxic-organic solvents necessitate the development of an alternative route for their simple and economic synthesis.

In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds (*13–17*), herein we wish to report a simple, economic, and efficient one-pot method for the synthesis of bis-(4-hydroxycoumarin)methanes in water using manganous chloride as the catalyst.

Results and discussion

Initially, we studied the catalytic efficiency of manganous chloride for the synthesis of 3,3′-(phenylmethylene) bis-(4-hydroxy-2H-chromen-2-one) **(3a)** using 4-hydroxrcoumarin and benzaldehyde in water using various concentrations of manganous chloride. The title compound **3a** was isolated with 99% yield using 10 mol% manganous chloride as catalyst (Table 1). Using the standardized reaction conditions, a range of bis-(4-hydroxycoumarin)methane derivatives were synthesized (Scheme 1). The same methodology was extended using heteroaromatic aldehydes and the results are summarized in Table 2.

The yields obtained for bis-(4-hydroxycoumarin)methane derivatives (**3a–3j**) were better to excellent and were in the range of the 93–99% (Table 2). The method was found to be equally effective for the condensation of 4-hydroxycoumarin with aromatic aldehydes bearing electron-withdrawing (**3a**, **3f**) as

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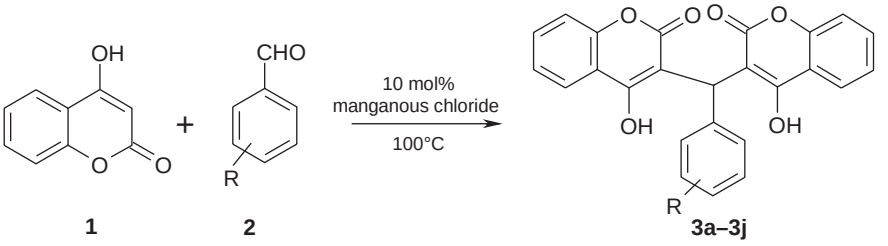
Table 1. Optimization of reaction conditions for synthesis of 3,3′-(phenylmethylene) bis-(4-hydroxy-2H-chromen-2-one) in water using 10 mol% manganous chloride catalyst.

Manganous chloride (mol%)	Reaction time (min)	Yield (%)
0	650	20
2.5	90	80
5	60	80
10	30	99
15	20	99
20	15	99



Scheme 1. Manganous chloride catalyzed synthesis of bis-(4-hydroxycoumarin)methane derivatives.

Table 2. Preparation of bis-(4-hydroxycoumarin)methane derivatives.

				Melting points	
Product	Aldehydes	Reaction time (min)	Yield (%)	Reported [10]	Found
3a	Benzaldehyde	30	99	228–230	229–232
3b	4-nitrorobenzaldehyde	20	99	232–234	233–234
3c	Crotonaldehyde	40	95	230–232	229–230
3d	4-chloro benzaldehyde	25	99	252–254	252–253
3e	2-hydroxybenzaldehyde	30	93	254–256	255–256
3f	4-methoxybenzaldehyde	30	97	242–244	242–243
3g	4-hydroxybenzaldehyde	35	95	222–224	224–226
3h	Furan-2-carbaldehyde	30	96	202	199–201
3i	Thiophene-2-carbaldehyde	25	95	210 (d)	212 (d)
3j	Indole-2-carbaldehyde	30	94	240–242	241–242

well as electron-donating (**3b**) substituents and heteroaromatic aldehydes (**3h**, **3i**, and **3j**). The present method was superior to the literature methods in terms of yield and use of easily available low priced catalyst in aqueous medium (*7–11*).

Experimental

Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m), and broad (br). Mass spectra were taken with Micromass – QUATTRO-II of WATER mass spectrometer.

General procedure for the synthesis of bis-(4-hydroxycoumarin)methanes

A mixture of 4-hydroxycoumarin **(1)** (20 mmol), aromatic and heteroaromatic aldehydes (10 mmol), and manganous chloride (2 mmol) in 25 ml of water was stirred under heating at 100°C for the appropriate time mentioned in Table 2. The completion of reaction was monitored by Thin Layer Chromatography System, solvent system – ethyl acetate:hexane (4:6). After completion of the reaction, the reaction mixture was cooled and poured over ice water

(50 ml). The solid crude product, which separated out, was filtered, washed with water and dried to give the desired compound.

All synthesized compounds were characterized with ^{1}H NMR and mass spectrometry. Also the melting points recorded were compared with the corresponding literature melting points and found to be matching. The representative analytical data for **3,3′-(phenylmethylene) bis-(4-hydroxy-2H-chromen-2-one) (3a)**.

White solid; mp 228–230°C; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 6.18$(s, 1H), 7.4–8.6 (m, 13H), 11.2 (brs, 2H); MS (EI, 70 eV): $m/z = 412$ $[M+H]^+$.

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