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CHEMISTRY RESEARCH ARTICLE

Environment friendly selective bromination of substituted coumarins

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Abstract: Coumarin, the simplest member of the benzo-2-pyrones, is naturally present in various plants and microorganisms and is widely employed as a fluorophore due to its high quantum yield, superior photostability, biological inertness, low toxicity, and aqueous compatibility. These properties make coumarins and their derivatives valuable in analytical and biological applications as chemosensors. Brominated coumarins, in particular, are crucial intermediates in the synthesis of formyl and aryl derivatives, as well as precursors for furocoumarins and dihydro-furocoumarins, which are used as photosensitizers and chemotherapeutic agents for skin disease treatment. Additionally, halogenated coumarins exhibit insecticidal and fungicidal activities, broadening their pharmaceutical and agricultural relevance.

In this study, a green bromination method for activated coumarins using potassium bromide (KBr) and hydrogen peroxide (H_2O_2) under environmentally benign conditions is presented. This sustainable approach eliminates the need for corrosive reagents, providing a safer and more environmentally friendly alternative to traditional bromination protocols while maintaining high selectivity and product purity.

Keywords: Coumarin; Chemosensors; Bromination; Eco-friendly

1. Introduction

Coumarin, the simplest member of the oxygen heterocyclic class known as benzo-2-pyrones, is naturally occurring in various plants and microorganisms [1]. Coumarin and its derivatives are widely utilized as fluorophores due to their favourable optical properties, including high quantum yield, superior photostability, biological inertness, non-toxicity, and compatibility with aqueous media [2]. These attributes make them valuable chemosensors in analytical and biological applications.

Brominated coumarins have significant synthetic and pharmaceutical applications. They are used as key intermediates in the synthesis of formyl and aryl derivatives and serve as precursors for furocoumarins and dihydro-furocoumarins, which are widely employed as photosensitizers and chemotherapeutic agents for the treatment of skin diseases [3, 4]. Additionally, halogenated coumarins exhibit insecticidal and fungicidal properties, further expanding their utility [5, 6].

Several methods have been reported for the regioselective bromination of coumarins, including $CuBr_2/Al_2O_3$ in bromobenzene under reflux conditions [7], Br_2 in glacial acetic acid [8], Br_2/Al_2O_3

under microwave irradiation [9], N-bromosuccinimide (NBS) in chloroform [10], $Et_4N^+Br^-$ with hypervalent iodine reagents [11], and NBS in tetrabutylammonium bromide under molten salt conditions [12]. Despite these available methods, only the dioxan dibromide method offers a more systematic approach for brominated coumarin synthesis [13]. However, the synthesis of dioxan dibromide requires elemental bromine, which is highly corrosive and poses significant environmental risks due to potential leakage.

In the present study, bromination of activated coumarins is achieved using potassium bromide (KBr) and hydrogen peroxide (H_2O_2) as the oxidant under environmentally benign conditions. This approach offers a greener, safer alternative to conventional methods, addressing the need for more sustainable synthetic protocols.

2. Results & discussion

Bromination of various types of Coumarin derivatives were performed at room temperature (25 °C) by using an easy and environment friendly procedure. All the reactions are carried out in aqueous acetic acid medium (6:1 v/v mixture of AcOH and H_2O). The method is an application of oxidative bromination which is based on in-situ generation of Br_2 on oxidation of KBr with H_2O_2. Though HBr-H_2O_2 combination is widely used to prepare bromo derivatives, experimental hazards could not be ruled out as HBr is extremely harmful for eyes and respiratory system.

In this method the active chemical reaction is shown below (Equation 1) with the electrochemical potential values which indicates the favourableness of the formation of bromine in the reaction condition. Acetic acid is used in the reaction as the proton source as well as a co-solvent for the organic compounds.

Equation 1:

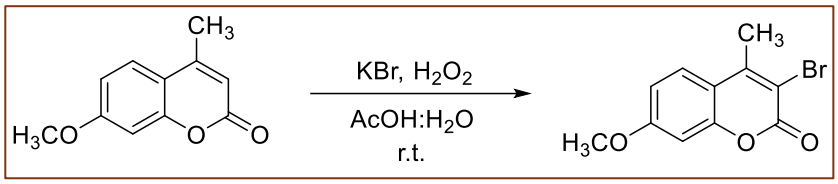
$$H_2O_2 + 2H^+ + 2e^- \longrightarrow 2H_2O\,, \qquad E^0 = 1.776\ V$$
$$2Br^-(aq) - 2e^- \longrightarrow Br_2(aq)\,, \qquad E^0 = 1.0873\ V$$

$$H_2O_2 + 2H^+ + 2Br^-(aq) \longrightarrow Br_2(aq) + 2H_2O,\ E^0 = 0.6887\ V$$

To determine the optimum reaction condition different concentration of KBr and H_2O_2 is used (**Table 1**). when the initial concentration of H_2O_2 and KBr were low (conditions used for bromination of coumarin in our experiments, Scheme 1), it was shown that poor amount of bromo-coumarin product was obtained. With the very high concentration of H_2O_2 and KBr the yield is very bad with much noumber of side products. As H_2O_2 has strong oxidising property, the excess addition of H_2O_2 into the reaction mixture during the reaction can decompose the lactone moiety of coumarin ring using; multiple bromination in extreme condition is also a probability. Thus, the optimum

condition is the use of ultimately 3 equivalent (w. r. t. substrate) brominating reagent i.e. KBr and 30% H_2O_2 (1:2 equivalent ratio).

Results of the bromination of variety of coumarin by KBr-H_2O_2 show that stepwise addition of H_2O_2 (three portions) produced higher amount of brominated products than when H_2O_2 was added in a single addition. Therefore, reaction of coumarin ring with 2 equiv. H_2O_2 with respect to KBr gave α-brominated products in a higher amount of isolated yield, where the further excess of H_2O_2 did not significantly influence the higher productivity due to oxidation of coumarin ring.



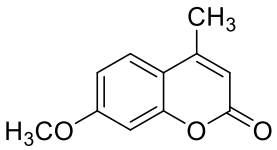
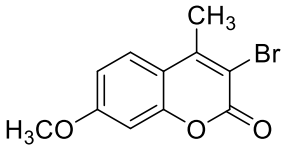
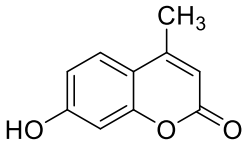
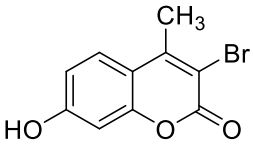
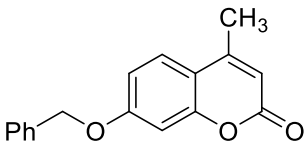
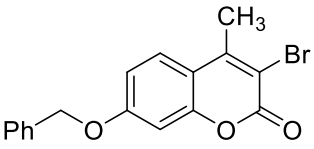
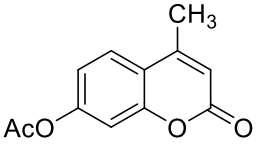
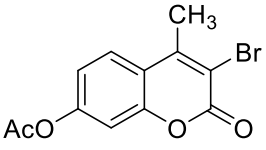
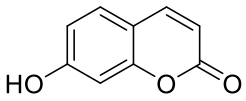
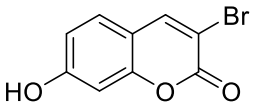
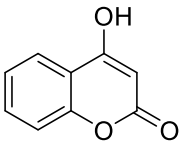
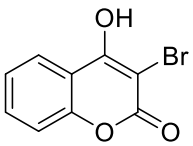
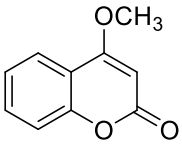
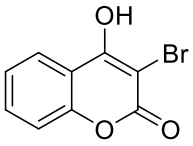
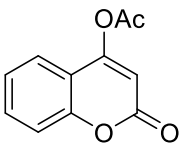
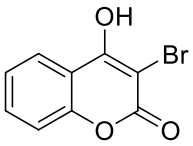
Scheme 1: optimization of the reaction conditions

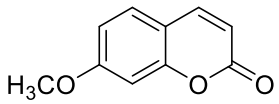
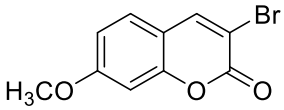
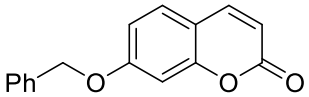
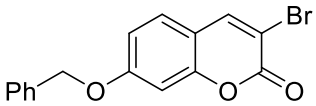
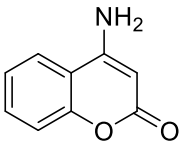
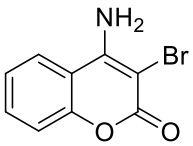
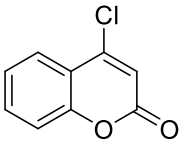
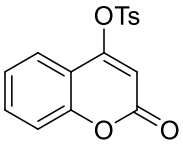
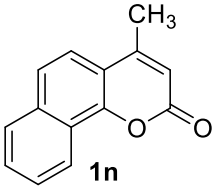
Table 1: Selective bromination of 4-methyl-7-methoxy coumarin

Entry	Substrate	KBr	30% H_2O_2 w.r.t. KBr	% Yield
1.	1 equiv.	1 equiv.	1 equiv.	30%
2.	1 equiv.	2 equiv.	1 equiv.	40%
3.	1 equiv.	2.5 equiv.	1 equiv.	40%
4.	1 equiv.	2.5 equiv.	2 equiv.	72%
5.	1 equiv.	**3 equiv.**	**2 equiv.**	**92%**
6.	1 equiv.	6 equiv.	3 equiv.	28%
7.	1 equiv.	3 equiv.	8 equiv.	25%

Various substituted coumarins were brominated using a green bromination method (Table 2), demonstrating high selectivity for bromine incorporation at the C-3 position. The resulting solid products were isolated post-reaction with high purity, allowing for their use without further purification in most cases. The presence of electron-donating groups on the coumarin moiety facilitated the reaction, whereas electron-withdrawing groups completely suppressed bromination. In the case of 4-hydroxycoumarin (**1f**), bromination resulted in a product with significant impurities that could not be fully removed even by using column chromatography. To address this, a modified protocol was implemented, involving the bromination of 4-methoxycoumarin (**1g**) and 4-acetoxycoumarin (**1h**) followed by overnight in-situ hydrolysis at room temperature. Both **1g** and **1h** yielded the same product, 3-bromo-4-hydroxycoumarin (**2f**), with high yield and excellent purity.

Table 2: Selective bromination of coumarin derivatives using 3 equiv. KBr-H_2O_2 (1:2 equivalent ratio) in aq. AcOH at room temperature

Entry	Substrate	Time (hrs.)	Yield (%)	Product
1.	 **1a**	2	92	 **2a**
2.	 **1b**	2	98	 **2b**
3.	 **1c**	2	80	 **2c**
4.	 **1d**	2	78	 **2d**
5.	 **1e**	2	62	 **2e**
6.	 **1f**	2	75	 **2f**
7.	 **1g**	24	77	 **2f**
8.	 **1h**	24	78	 **2f**

Entry	Substrate	Time (hrs.)	Yield (%)	Product
9.	 **1i**	2	70	 **2i**
10.	 **1j**	2	70	 **2j**
11.	 **1k**	2	90	 **2k**
12.	 **1l**	24	-	No product
13.	 **1m**	24	-	No product
14.	 **1n**	24	-	No product

3. Conclusion

In this article, a novel, environmentally friendly method for the selective bromination of coumarin derivatives is presented. The described approach is highly efficient and exhibits remarkable selectivity, often yielding crystalline products directly from the reaction mixture without the need for additional purification steps. The process utilizes commonly available and cost-effective laboratory reagents, ensuring broad accessibility and economic feasibility. Furthermore, the procedure is characterized by mild reaction conditions and a non-hazardous nature, enhancing its suitability for sustainable chemical practices. Using this method, a diverse

range of selectively brominated coumarins was successfully synthesized, demonstrating its versatility and potential for broad application in synthetic organic chemistry.

Typical Experimental Procedure

Preparation of 3-bromo-4-methyl-7-methoxycoumarin (1b): To the aqueous acetic acid solution (6:1 v/v mixture of AcOH and H_2O) of KBr (0.1877gm, 3 equiv.) 4-methyl-7-methoxycoumarin (0.1 gm, 1 equiv.) was taken. Then 30% H_2O_2 solution (0.35ml, 2 equiv.) was added to the mixture dropwise in three portions & the whole mixture was stirred for 2 hours at room temperature in absence of sun light. Then the mixture was poured into the crushed ice for 30 minutes, the yellowish white solid formed was filtered & washed with cold water then the product was dried and crystallized from ethanol. M.P. =143 °C, Yield = 92 %.

Preparation of 3-bromo-4-hydroxycoumarin (2f) from 4-acetoxycoumarin (1h): To the aqueous acetic acid solution (6:1 v/v mixture of AcOH and H_2O) of KBr (1.8gm, 3 equiv.), 4-acetoxycoumarin (1gm, 1 equiv.) was taken and stirred for 10 minutes to make a clear solution. Then 30% H_2O_2 solution (3.325 ml, 2 equiv.) was added to the mixture dropwise in three portions and the mixture was stirred for 3 hours at room temperature in absence of sun light. Then the mixture was kept in rest for 24 hours in absence of sun light. The yellowish crystalline solid product was separated out from the acetic acid medium and the product was filtered and washed with cold distilled water. The product was re-crystallised from MeOH. M.P. = 122 °C, Yield = 78 %.

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