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Short communication

Competitive formation of symmetrical coumarin dimers during the *o*-alkylation of 4-hydroxycoumarin with α,ω-dibromoalkanes

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Introduction

Coumarin derivatives represent privileged heterocyclic scaffolds in medicinal chemistry, owing to their structural diversity, synthetic accessibility, and broad applicability in the design of biologically active molecules (Pereira et al., 2018). Among common functionalization strategies, *O*-alkylation of 4-hydroxycoumarin with α,ω-dibromoalkanes affords 4-(ω-bromoalkoxy)-2*H*-chromen-2-one intermediates with alkyl linkers of different lengths. These intermediates are synthetically useful, as the terminal bromide enables further transformation and incorporation into more complex coumarin-based derivatives (Derr et al., 2020).

Despite its practical value, this transformation may be complicated by the bifunctional nature of the dibromoalkane reagent. After initial monoalkylation, the remaining terminal bromide of the bromoalkoxy intermediate may undergo a second nucleophilic substitution with another molecule of 4-hydroxycoumarin alkoxide, yielding symmetrical coumarin-alkyl-coumarin dimers. This short communication describes the occurrence of these dimeric side products during 4-hydroxycoumarin *O*-alkylation and their differentiation from the corresponding monoalkylated derivatives by NMR spectroscopy and mass spectrometry.

Materials and methods

The 4-(ω-bromoalkoxy)-2*H*-chromen-2-one derivatives were synthesized by base-mediated *O*-alkylation of 4-hydroxycoumarin with the appropriate α,ω-dibromoalkane. Briefly, 4-hydroxycoumarin was dissolved in anhydrous DMF, treated with anhydrous K_2CO_3, and subsequently reacted with the corresponding dibromoalkane at room temperature. After completion, the reaction mixture was poured onto crushed ice, and the resulting precipitate was filtered, washed with cold water, dried, and purified by column chromatography using ethyl acetate/n-hexane as the mobile phase (Dimkovski et al., 2025). Reaction progress was monitored by TLC under UV light at 254 nm, while the isolated fractions were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry, while TLC visualization at 254 nm was employed for reaction monitoring.

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Results and discussion

TLC monitoring of the *O*-alkylation reactions showed two UV-active products of comparable intensity at 254 nm, corresponding to the expected monoalkylated bromoalkoxy coumarin derivative and an additional product. After chromatographic separation, both fractions were obtained in comparable yields, approximately 35–45%, indicating that the latter was not a trace impurity, but the consequence of a competitive alkylation pathway under the reaction conditions.

The first-eluting fractions were assigned to the desired 4-(ω-bromoalkoxy)-2*H*-chromen-2-one derivatives, as confirmed by ^{1}H and ^{13}C NMR spectroscopy and supported by mass spectrometric analysis. In the representative bromopropoxy derivative, the ^{1}H NMR spectrum exhibited the characteristic aliphatic pattern of a non-symmetrical -$OCH_2CH_2CH_2Br$ linker. The terminal methylene groups appeared as two distinct triplets at δ 4.29-4.32 ppm and δ 3.62–3.65 ppm, assigned to the –OCH_2- and –CH_2Br protons, respectively. The central methylene group resonated as a multiplet at δ 2.50–2.44 ppm, reflecting vicinal coupling with both adjacent methylene groups. Together, these three aliphatic resonances provide clear spectroscopic evidence for the introduction of a bromopropoxy linker onto the coumarin oxygen.

In contrast, the second-eluting fractions were assigned to symmetrical coumarin dimers formed through further nucleophilic substitution of the terminal bromide by a second molecule of 4-hydroxycoumarin alkoxide. This structural assignment is supported by the simplification of the aliphatic region in the ^{1}H NMR spectra: whereas the monoalkylated bromopropoxy intermediate contains three chemically distinct methylene environments, the corresponding dimer displays only two linker resonances because the two terminal –OCH_2- groups become chemically equivalent. The terminal -OCH_2- protons therefore resonate as a single triplet, while the central methylene group appears as the remaining aliphatic signal, observed as an apparent triplet or unresolved multiplet depending on spectral resolution. This pattern is consistent with the formation of coumarin–alkyl–coumarin dimeric product.

The ^{13}C NMR spectra provided additional support for the structural assignment. While the monoalkylated bromopropoxy intermediate displayed three distinct aliphatic carbon resonances corresponding to the non-equivalent –OCH_2-, central –CH_2–, and -CH_2Br carbons of the linker, the symmetrical dimer showed only two aliphatic linker signals. This reduction in the number of carbon resonances confirms the chemical equivalence of two terminal –OCH_2- groups and is consistent with replacement of the terminal bromide by a second coumarin unit.

Mass spectrometric analysis further supported the structural assignment by showing ion signals consistent with the calculated molecular mass of the dimeric products, together with the absence of the characteristic bromine isotopic pattern expected for the monoalkylated bromoalkoxy derivatives.

Conclusion

The base-mediated *O*-alkylation of 4-hydroxycoumarin with α,ω-dibromoalkanes afforded the desired 4-(ω-bromoalkoxy)-2*H*-chromen-2-one intermediates, but was accompanied by the competitive formation of symmetrical coumarin–alkyl–coumarin dimers. The comparable isolation of both products confirms that dimerization is a significant side pathway under these conditions, emphasizing the need for careful TLC monitoring, chromatographic separation, and spectroscopic confirmation.

References

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