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Short communication

Optimization of CuAAC conditions for the synthesis of triazole-linked coumarin-isatin hybrid molecules

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Introduction

The design of hybrid molecules requires synthetic approaches that allow efficient and controlled connection of structurally distinct fragments. Click chemistry has therefore become an important tool in medicinal chemistry, particularly for the preparation of compounds in which different pharmacophoric units are joined through a stable and well-defined linker. Among click reactions, copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is one of the most widely applied transformations for the synthesis of 1,4-disubstituted 1,2,3-triazoles (Sharpless et al, 2025).

This reaction represents a significant improvement over the classical Huisgen 1,3-dipolar cycloaddition, which generally requires elevated temperatures, proceeds slowly, and affords a mixture of 1,4- and 1,5-disubstituted regioisomers. In contrast, CuAAC proceeds under milder conditions, with higher reaction efficiency and pronounced regioselectivity towards the 1,4-disubstituted triazole product (Meldal and Tornøe, 2008).

Despite its synthetic reliability, the practical outcome of CuAAC can be influenced by several experimental variables, including substrate solubility, solvent composition, copper source, reducing system, temperature, and reaction time. Therefore, optimization of these parameters is essential to enable the synthesis of triazole-linked coumarin-isatin hybrid derivatives.

Materials and methods

Optimization of the CuAAC was performed using selected 4-(ω-azidoalkoxy)-2*H*-chromen-2-one and 1-(prop-2-yn-1-yl)indoline-2,3-dione derivatives as representative azide and alkyne components. Equimolar amounts of both reactants were used in all experiments. The optimization was designed to evaluate the influence of solvent composition, catalyst/reducing-agent loading and reaction time.

N,N-dimethylformamide (DMF) was used as the principal organic solvent, while water was introduced through the aqueous $CuSO_4$/sodium ascorbate catalytic system. The tested DMF/H_2O ratios were 1:0, 10:1, 10:3, 2:1, and 1:1 (v/v). The $CuSO_4$/sodium ascorbate system was examined as an in situ source of Cu(I), with catalyst/reducing-agent loadings varied from 5/10 mol% to 10/20 mol%, respectively. Reaction progress was monitored at room temperature over defined time intervals.

For each optimization experiment, after completion of the reaction, the reaction mixture was poured onto crushed ice to induce precipitation of the product. The resulting solid was collected by vacuum filtration, washed with cold distilled water, and dried. The crude products were further purified

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by column chromatography using an *n*-hexane/ethyl acetate gradient as the mobile phase (Dimkovski et al., 2025). The structural identity of the purified compounds was initially confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analyses.

Results and discussion

The CuAAC conditions were optimized using compounds 6b1 and 6b4 as representative products. The initial experiment, performed in anhydrous DMF with 5 mol% $CuSO_4$/10 mol% sodium ascorbate, did not afford the desired triazole product even after 12 h, indicating that direct addition of the inorganic catalytic system into pure DMF was ineffective. When $CuSO_4$ and sodium ascorbate were pre-dissolved in water and introduced into the reaction medium, product formation was observed, confirming the importance of an aqueous phase for efficient in situ generation of Cu(I).

At 5 mol% $CuSO_4$/10 mol% sodium ascorbate, the tested DMF/H_2O ratios gave moderate yields after 6 h: 10:1 afforded 62% for 6b1 and 69% for 6b4, whereas higher water content decreased the yields to 54/51% at 10:3 and 51/30% at 2:1. Increasing the catalyst/reducing-agent loading to 10 mol% $CuSO_4$/20 mol% sodium ascorbate improved the reaction outcome. The best results were obtained in DMF/H_2O 10:1, giving 94% yield for 6b1 and 87% for 6b4 after 4 h. Notably, comparable yields were obtained after 0.5 h under the same solvent and catalyst conditions, affording 92% and 90%, respectively. In contrast, more aqueous systems were less efficient, particularly DMF/H_2O 1:1, which gave only 44% and 39% after 4 h.

Structural confirmation was primarily based on NMR and HRMS analyses. In the ^{1}H NMR spectra, successful cycloaddition was evidenced by the disappearance of the terminal alkyne proton of the propargylated isatin precursors, previously observed at δ 2.30–2.39 ppm, and the appearance of a characteristic singlet attributable to the triazole proton at δ 8.19–8.33 ppm. In addition, the propargylic methylene signal, initially detected at δ 4.52–4.64 ppm, shifted downfield after triazole formation, appearing at δ 4.91–4.99 ppm, further supporting the formation of the triazole-linked products.

The ^{13}C NMR spectra were consistent with the proposed structures, showing the disappearance of the acetylenic carbon resonances of the starting materials, typically observed at δ 73–76 ppm, together with the appearance of characteristic triazole carbon signals in the aromatic region. HRMS analysis provided additional confirmation of the molecular composition of the obtained derivatives, with experimentally observed molecular ion peaks in close agreement with the calculated exact masses. Together, these spectroscopic data confirmed the successful formation and structural integrity of the synthesized 1,4-disubstituted 1,2,3-triazole products.

Conclusion

The optimization study demonstrated that the efficiency of the CuAAC reaction strongly depends on the solvent composition and $CuSO_4$/sodium ascorbate loading. Among the evaluated conditions, the reaction proceeded most efficiently in DMF/H_2O 10:1 (v/v) using 10 mol% $CuSO_4$ and 20 mol% sodium ascorbate, affording the representative triazole products in high yields within a short reaction time. NMR and HRMS analyses confirmed the successful formation of the expected coumarin-triazole-isatin hybrids. Overall, the optimized protocol provides a simple, mild, and reproducible approach for the synthesis of coumarin–triazole–isatin hybrid molecules.

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