


Cite this: *RSC Adv.*, 2023, 13, 4754

Received 13th January 2023  
Accepted 20th January 2023

DOI: 10.1039/d3ra00251a

rsc.li/rsc-advances

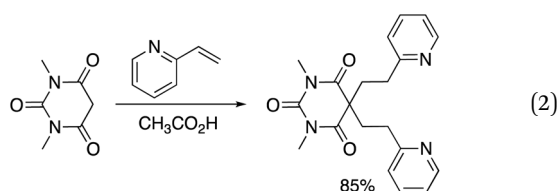
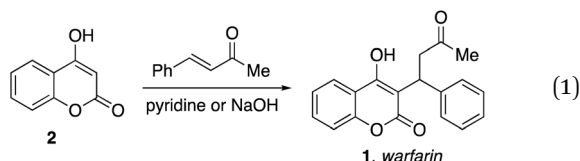
# Synthesis of warfarin analogs: conjugate addition reactions of alkenyl-substituted N-heterocycles with 4-hydroxycoumarin and related substrates†

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We have developed a procedure for the Michael addition of 4-hydroxycoumarins to vinyl-substituted N-heterocycles. The chemistry is also suitable for thiocoumarins and quinolinones. A mechanism is proposed involving nucleophilic attack at the vinyl-group of the protonated N-heterocycle.

## Introduction

Warfarin (**1**) is a clinically important anticoagulant drug.<sup>1</sup> It was first approved for use in the mid-1950s and warfarin is currently listed on the World Health Organization's List of Essential Medicines.<sup>2</sup> The substance is commonly prepared using a base-catalyzed reaction of 4-hydroxycoumarin (**2**) with benzalacetone (eqn (1)).<sup>3</sup> Enantioselective addition reactions have also been developed.<sup>4</sup> Our group recently described the Michael addition reactions of 1,3-dicarbonyl compounds with vinyl-substituted N-heterocycles (eqn (2)).<sup>5</sup> Based on this chemistry, we hypothesized that 4-hydroxycoumarins would exhibit similar nucleophilic reactivity with vinyl-substituted N-heterocycles. In the following Communication, we describe a convenient method for the synthesis of heterocycle-containing analogs of warfarin.



## Results and discussion

Using our previous methodology,<sup>5</sup> 4-hydroxycoumarin was reacted with 2-vinylpyridine and acetic acid in acetonitrile and the addition product **3** was isolated in 69% yield (Table 1). The product was exceptionally difficult to purify using chromatography, so a methodology was developed with crystallizing the product directly from the crude product mixture. Similar addition products (**3–8**) were prepared from substituted 4-hydroxycoumarins, including halogen, alkyl, and the methoxy-substituted systems. A modest yield of product **9** was obtained from 5-nitro-2-vinylpyridine and 4-hydroxycoumarin. The conversions were also accomplished with 4-vinylpyridine, providing compounds **10–14** in fair to good yields. The lower yields seem to be associated with systems that did not crystallize well from the crude product mixtures. For example, 4-hydroxycoumarin reacted with di-(4-pyridyl)ethylene but inefficient crystallization provided only a 39% isolated yield of compound **15**. Additionally, we found some systems slowly formed products from double addition reactions. These minor biproducts were identified from mass spectral analysis and NMR analysis of crude product mixtures. The data suggests C- and O-alkylation products (*i.e.* **16**). To suppress formation of these biproducts, some of the conversions were best conducted with equimolar ratios of the vinylpyridine and 4-hydroxycoumarin.

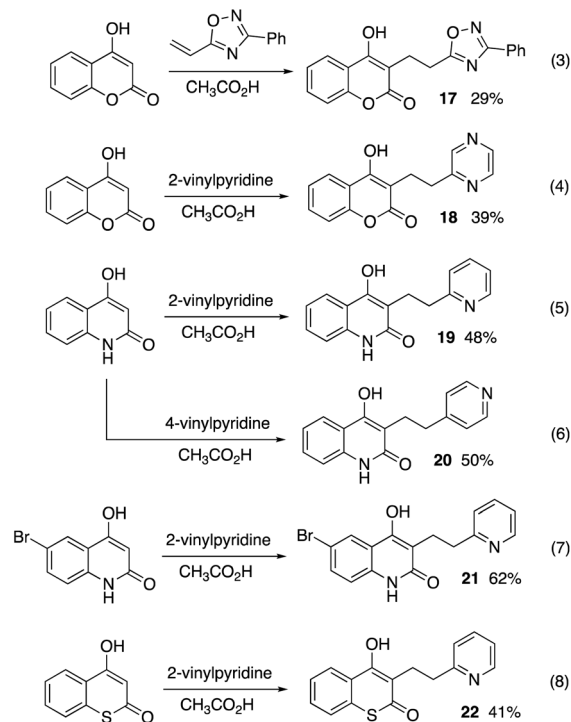
Over the past 50 years, several types of vinyl-substituted heterocycles have been shown to be reactive as Michael acceptors.<sup>6</sup> We have found that 4-hydroxycoumarin also reacts with other types of olefinic heterocycles. When 4-hydroxycoumarin is reacted with a vinyl-substituted 1,2,4-oxadiazole, product **17** is obtained, albeit in low isolated yield (Scheme 1, eqn (3)). Likewise, vinylpyrazine gives the adduct **18** in 39% yield from a reaction with 4-hydroxycoumarin (eqn (4)). The chemistry is also compatible with closely related nucleophiles. Thus, 4-hydroxyquinolin-2(1*H*)-one reacts with 2- and 4-vinylpyridine to give products **19–20** in fair yields (eqn (5) and (6)). Similarly, the brominated 4-hydroxyquinolin-2(1*H*)-one gives compound **21**

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ra00251a>

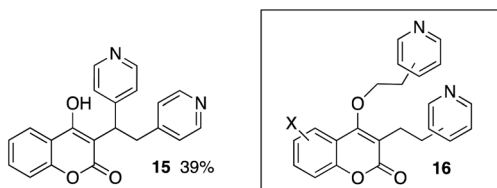


**Table 1** Products and yields from the reactions of 4-hydroxycoumarins with vinylpyridines

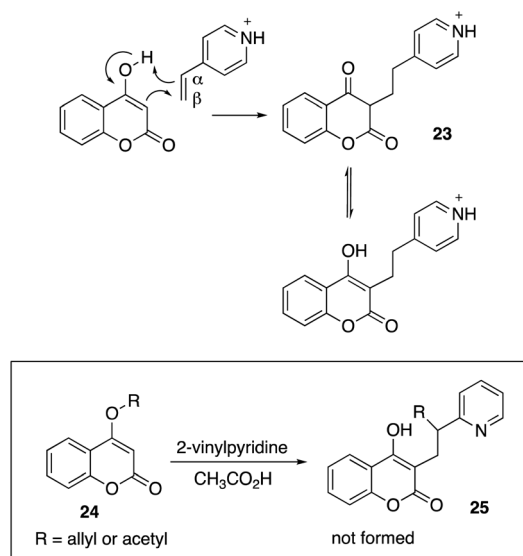
**Scheme 1** Addition reactions with varied heterocycles.

carbon – giving intermediate **23** which rapidly isomerizes to the pyridinium salt of the observed product. Working from the proposed mechanism, we sought to determine if other electrophiles or groups could be transferred to the  $\alpha$ -carbon, besides a simple proton. Compounds **24** were prepared, but unfortunately neither the acetyl or allyl groups were observed to migrate and give products **25**.

from 2-vinylpyridine (eqn (7)). The adduct (**22**) from 4-hydroxy-2H-thiophene-2-one is also formed in fair yield from 2-vinylpyridine (eqn (8)).



As acid-promoted addition reactions, it is suggested that the acid protonates the N-heterocycle and enhances the electrophilic reactivity of the vinyl group (Scheme 2). We propose a mechanism involving nucleophilic attack of the enol group at the electrophilic vinyl group. As the enol transfers electron density into the vinyl group, negative charge accumulates at the  $\alpha$ -carbon. This leads to a simultaneous proton transfer to the  $\alpha$ -

**Scheme 2** Proposed mechanism for the addition reaction and an unsuccessful application of the chemistry.

## Conclusions

In summary, we have found that 4-hydroxycoumarins react with vinyl-substituted N-heterocycles using an acid promoter. The enol groups of 4-hydroxycoumarins are sufficiently nucleophilic to undergo Michael additions to vinyl-substituted pyridines, pyrazine, and 1,2,4-oxadiazole. Similar reactivity has been demonstrated with 4-hydroxyquinolin-2(1H)-one and 4-hydroxy-2H-thiophene-2-one. This work and other recent studies further demonstrates the utility of Michael addition as a useful route to functionalized heterocycles.<sup>7</sup>

## Author contributions

The experimental work was carried out by B. G. and the conceptual work was done by D. A. K.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The support of the NIGMS-NIH (1R15GM126498-01) is gratefully acknowledged. We also acknowledge the generous support from the NSF MRI program (award no. CHE-1726931) for the purchase of a high-resolution mass spectrometer and an NMR instrument (award no. CHE-2117776). We thank Northern Illinois University for the support of the Molecular Analysis Core Facility.

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