Formation of an unusually stable enol by conjugate addition of active methylene compounds to E-3-aryl-2-cyanopropenoates

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Abstract
The reactions of 4-hydroxycoumarin with substituted α-cyanocinnimate esters gives addition products that are entirely in the form of the enol tautomer, as demonstrated by the appearance of the doubly benzylic proton as a singlet rather than as a doublet (half an AB quartet).

Background and Significance
Despite its having been in clinical use as an oral anti-coagulant for over three decades, there are remarkably few papers describing the chemical transformation of the warfarin molecule. Thus, most chemically modified warfarin derivatives are synthesized a priori from a Michael acceptor (typically a substituted benzilicetone) and 4-hydroxycoumarin in the presence of a base. The Michael acceptor must be at least as reactive towards enolate nucleophiles as an enone to be successful: the reaction fails with cinnamate esters. We determined that one potentially useful approach to the modular synthesis of warfarin derivatives containing branched side chains involves the addition of 4-hydroxycoumarin to cyanocinnamate esters, followed by alkylation and functional group manipulation. However, cyanocinnamate esters have a history of yielding unexpected products in their reactions with nucleophiles. For example, the addition of hydroxylamine to alkyldienemalones leads to fragmentation, and the formation of oximes, and a similar fragmentation occurs when hydrazine is added to cyanocinnamate esters, with the result that the corresponding aldehyde azines are formed. We sought to prepare the cyanocacetate ester derivatives by conjugate addition of 4-hydroxycoumarin to a series of substituted E-3-aryl-2-cyanopropenoate esters. The goal of this work was to prepare a wide range of branched-chain, functionalized warfarin derivatives carrying variations in the alkyl side chain. We had expected that the product of the reaction would be a cyanoacetate ester that could then be alkylated under mild conditions, and subsequently decarboxylated to give a warfarin analogue.

Results and Discussion
The required cyanocinnamate esters were prepared by the Knoevenagel condensation of the appropriate aromatic aldehyde with ethyl cyanoacetate in toluene, using ammonium acetate or piperidine and acetic acid as the catalyst, and were obtained exclusively as the E isomers.

The conjugate addition of 4-hydroxycoumarin to these esters was accomplished by heating the pyridine solution of the Michael acceptor and 4-hydroxycoumarin for 2 days. In all cases, the conjugate addition proceeded well to give a good yield of the adduct.

The 1H NMR spectra of the products were all as anticipated with the exception that the doubly benzylic proton did not appear as a doublet, as had been expected, but as a singlet. At the same time, the resonance expected for the α proton of the saturated cyanoacetic ester was absent. The simplest rationalization for this was that the product was formed as an enol, and that the enol failed to tautomerize to the keto form. This was confirmed by the 13C NMR spectra of the adducts, which showed the presence of two additional sp2-hybridized carbon atoms in the molecule, and the absence of two expected sp3-hybridized carbon atoms.

The chemical shifts indicate that ester group, and not the cyano group is enolized; at this time we do not know the stereochemistry of the major enol. This is supported by the FT-IR spectra of the adducts. FT-IR spectra were recorded for both hydroxycoumarin adducts products (X = H and X = NO2); the latter showed a clear C≡N stretching vibration in the IR spectrum. The spectrum of the former compound did not exhibit a C≡N stretching vibration, but since this is not uncommon in nitriles (especially structurally complex nitriles), we do not necessarily assign the alternative enolization to this adduct on this basis.

Acknowledgements
The financial support of this research by grants from WiSys Technology Foundation, the University of Wisconsin System, and the UW-Eau Claire Office of Research and Sponsored Programs is gratefully acknowledged.