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Synthesis of 2-(alkylamino)-5-{alkyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylates using a multi-component reaction in water

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ABSTRACT

A simple synthesis of 2-(alkylamino)-5-{alkyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylates via a one-pot multi-component reaction is described. The reactive 1:1 zwitterionic intermediate generated from the addition of isocyanides to dialkyl acetylenedicarboxylates was trapped at room temperature by coumarin-3-carboxylic acids prepared in situ from a 2-hydroxy aromatic aldehyde and Meldrum's acid to afford the title compounds in good to excellent yields.

1. Introduction

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features, such as atom economy, straightforward reaction design and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[1j,k]

Furans, benzofurans, and their reduced forms are important core structures in many biologically active natural products. Moreover, they are useful building blocks in the total synthesis of natural products and pharmaceuticals.[2–5] Many naturally occurring furans have exhibited considerable biological activities, such as antitumor and cytotoxic properties,[6] as well as antimicrobial,[7] antispasmodic,[8] and several other potentially useful activities.[9,10] In addition, furans are also present in commercially important products, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers, flavoring and fragrance compounds.[10,11] This broad range of applications has made the development of new and efficient furan synthesis very valuable. Consequently, a variety of furan syntheses have been reported in the literature. Although a lot of strategies can be found for the synthesis of furans, convergent synthetic methods from simple and readily available starting materials without using transition-metal catalysis are still rare.[1g,2a,12–14]

Coumarinyl compounds have been extensively used in medicinal chemistry. Some examples have been shown to be highly potent human β-secretase inhibitors and are used in the treatment of Alzheimer's disease. Most of the synthetic medicines containing a coumarin, are prepared by the reaction between coumarin-3-carboxylic acids and amines.[15]

2. Results and discussion

As part of our current studies on the development of new efficient strategies for the preparation of interesting bioactive molecules and drug cores,[16] herein, we present a new synthetic method for the construction of 5-amido coumarinyl 2-aminofurans via a one-pot, isocyanide-based MCR involving commercially available starting materials. Thus, a mixture of salicylaldehyde **1a**, Meldrum's acid **2**, *tert*-butyl isocyanide **3a** (2 equiv) and dimethyl

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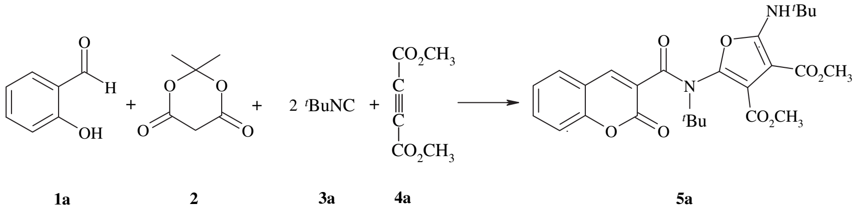
acetylenedicarboxylate (DMAD, **4a**) afforded dimethyl 2-(*tert*-butylamino)-5-{*tert*-butyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylate **5a** (Scheme 1).



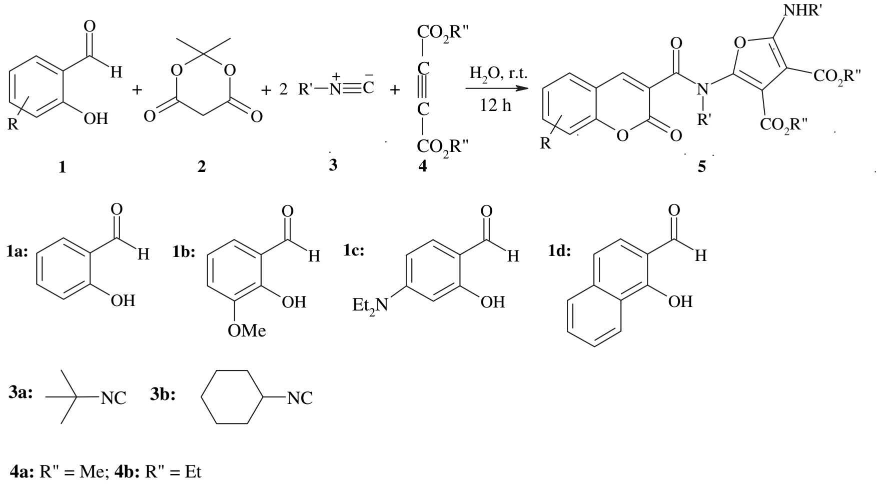
Scheme 1.

The reaction was carried out in some solvents under similar conditions at ambient temperature. As disclosed in Table 1, the maximum yield was observed in water (entry 1).

Table 1
Solvent effect in the multi-component synthesis of **5a**

Entry	Solvent	Time h	Yield of **5a** (%)
1	H_2O	12	87
2	CH_2Cl_2	12	70
3	$CHCl_3$	12	60
4	EtOH	12	68

In order to show the generality and scope of this new protocol, we used various 2-hydroxy aromatic aldehydes, dialkyl acetylenedicarboxylates, and isocyanides in water. The results are summarized in Scheme 2 and Table 2.



Scheme 2.

All the reactions were complete within 12 h. The ${}^1H$ NMR spectroscopic analysis of the reaction mixtures clearly indicated the formation of the corresponding 5-amido coumarinyl 2-aminofurans **5a**–**j** in good to excellent yields.

The structures of the isolated products **5a**–**j** were deduced on the basis of IR, ${}^1H$ and ${}^{13}C$ NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **5a** displayed the molecular ion (M^+) peak at m/z=498, which was consistent with the 1:1:2:1 adduct of salicylaldehyde, Meldrum's acid, *tert*-butyl isocyanide, and dimethyl acetylenedicarboxylate with the loss of water and an acetone molecule. The ${}^1H$ NMR spectrum of **5a** exhibited five single sharp lines readily recognized as arising from the two *tert*-butyl (δ=1.43 and 1.49 ppm) groups, two methoxy (δ=3.63 and 3.80 ppm) groups, and the coumarin vinylic H atom (δ=7.68 ppm). A fairly sharp singlet was seen for the amine NH group (δ=6.84 ppm) along with the characteristic signals with appropriate chemical shifts and coupling constants for the four aromatic protons. The ${}^1H$ decoupled ${}^{13}C$ NMR spectrum of **5a** showed 22 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section.

The ${}^1H$ and ${}^{13}C$ NMR spectra of compounds **5b**–**j** were similar to those of **5a**, except for the *N*-alkyl groups, ester functions and coumarin moieties, which exhibited characteristic signals with appropriate chemical shifts and coupling constants (see the Experimental section).

A mechanistic rationalization for this reaction is provided in Scheme 3. At first, the 2-hydroxy aromatic aldehydes **1** condense with Meldrum's acid **2** to produce intermediates **6**, which are readily converted in to coumarin-3-carboxylic acids **7** via an addition reaction and subsequent acetone elimination. Next, the reactive 1:1 zwitterionic intermediates **8**, generated in situ from the reaction between isocyanides **3** and dialkyl acetylenedicarboxylates **4**[17,1j,k] are protonated by **7**. Then, the positively charged ions **9** can be attacked by the carboxylate anions **10** to form imidoyl carboxylates **11**, which undergo a Mumm rearrangement[18] under the reaction conditions employed, to produce the α,β-unsaturated intermediates **12**. Finally cycloaddition of **12** and another isocyanide molecule gives iminolactone intermediates **13**, which tautomerize under the reaction condition to produce 2-aminofurans **5**.