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Organic Reactions in Water: An Efficient Synthesis of Pyranocoumarin Derivatives

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Abstract: A mild and efficient protocol for the synthesis of pyrano[3,2-*c*]coumarins from 4-hydroxycoumarin through a one-pot reaction in water under phase-transfer conditions has been developed.

Key words: pyranocoumarin, isocyanide, PTC, water, green chemistry

Fused coumarin systems, in particular pyranocoumarins, are abundant in nature and constitute building blocks for many natural products found across the plant kingdom.[1] Naturally occurring pyranocoumarins exist either in linear form, such as xanthyetin, which was isolated from *Zanthoxylum americanum*,[2] or in angular form, such as khellactone, which was isolated from *Ligusticum elatum*[3] and *Peucedanum japonicum*[4] (Figure 1).

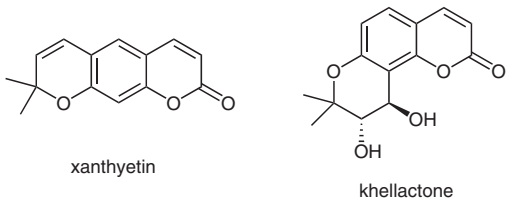
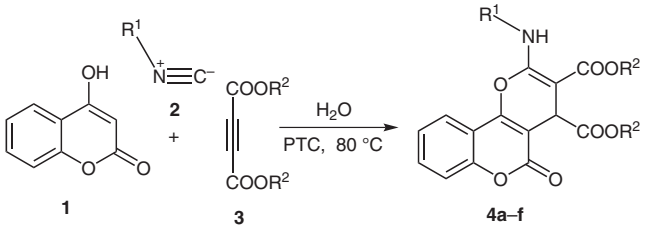


Figure 1

Pyranocoumarin derivatives have been found to possess antifungal, insecticidal, anticancer, anti-HIV, anti-inflammatory, antioxidant, and antibacterial activities.[5] They have also gained importance as photoactive drugs for skin disorders.[6] The pharmaceutical potency of this class of heterocycles has resulted in development of several methods for their synthesis.[7] The two main synthetic strategies employed for preparation of pyranocoumarins involve manipulation of 4-hydroxycoumarin to form pyrano[3,2-*c*]coumarins[7b] and manipulation of 7- or 8-hydroxycoumarin to obtain pyrano[2,3-*h*]coumarin[7d] or pyrano[3,2-*h*]coumarin[7e] derivatives. For example, Palmisano and co-workers[7b] have reported the synthesis of pyrano[3,2-*c*]coumarins from 4-hydroxycoumarin and conjugated aldehydes using ytterbium triflate as catalyst. Renaud and co-workers,[7a] in a recent report, have also prepared pyrano[3,2-*c*]coumarins by the same method, but they employed an acid catalyst that needed to be synthesized. As such, the development of mild and rapid strategies to synthesize pyranocoumarins is still desirable.

In recent years, isocyanide-based multi-component reactions (IMCRs) have gained much attention because of their synthetic potential to obtain a diverse array of heterocycles,[8] especially in drug discovery.[9] One of the fundamental challenges for organic chemists is to develop non-hazardous methodologies to perform organic reactions. In this respect, organic reactions in aqueous media have received much attention in recent years because water is a green alternative to organic solvents. The main disadvantage to using water as solvent is the frequently poor solubility of organic reactants. The use of phase-transfer catalysts (PTCs) often provides a suitable means to overcome this problem.[10]

In a continuation of our interest in developing green methodologies and the synthesis of diverse heterocyclic compounds of biological importance,[11] we report herein the synthesis of some pyrano[3,2-*c*]coumarin derivatives in aqueous medium. Thus, a three-component reaction of an isocyanide, dialkyl acetylenedicarboxylate and 4-hydroxycoumarin in water, in the presence of a phase-transfer catalyst at 80 °C, has been shown to give pyrano[3,2-*c*]coumarins in good yields (Scheme 1).



Scheme 1

For example, treatment of cyclohexyl isocyanide with dimethyl acetylenedicarboxylate and 4-hydroxycoumarin in water at 80 °C, in the presence of 10 mol% tetrabutylammonium bromide, gave dimethyl 2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (**4a**) in 70% yield after four hours. The reaction was studied by replacing cyclohexyl isocyanide with *n*-butyl isocyanide, benzyl isocyanide and dimethyl acetylenedicarboxylate with diethyl acetylenedicarboxylate. The crude product mixture could easily be separated from the reaction medium by simple filtration. However, it was ob-

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served that some unreacted 4-hydroxycoumarin always remained, which could be separated by column chromatography. ^{1}H and ^{13}C NMR spectra of the crude products showed the formation of a single product **4**, and no side product was detected. The reaction also proceeded smoothly when 4-hydroxy-6-methyl-2*H*-pyran-2-one was employed in place of 4-hydroxycoumarin (Scheme 2). The generality of this method is illustrated with respect to three different isocyanides and two dialkyl acetylenedicarboxylates, and the results are summarized in Table 1. The various products **4a**–**l**, thus obtained, were characterized by IR, ^{1}H and ^{13}C NMR spectroscopic analyses and by mass spectrometric analysis.

Table 1 Synthesis of Pyrano[3,2-*c*]coumarins **4**

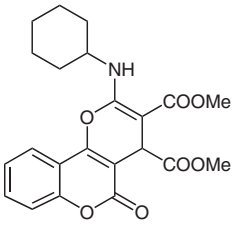
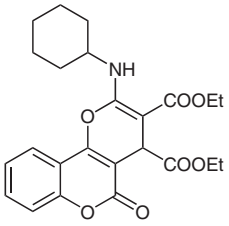
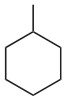
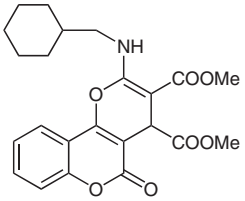
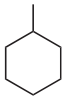
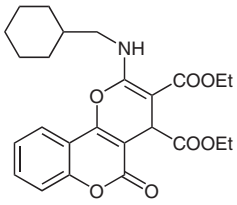
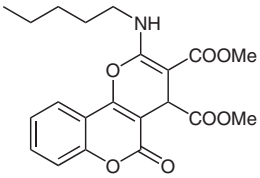
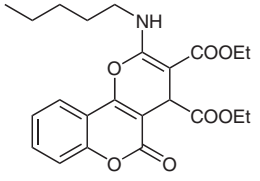
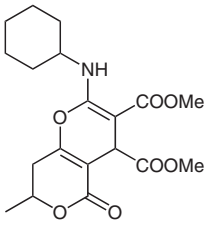
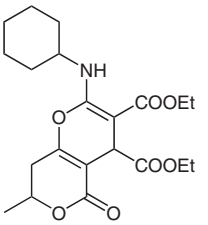
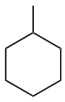
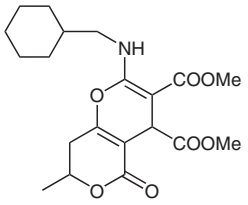
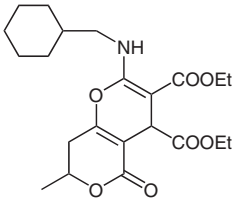
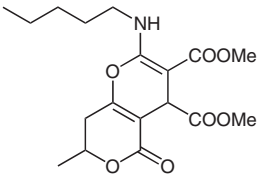
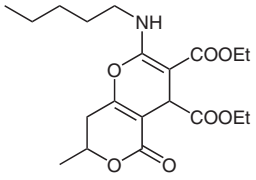
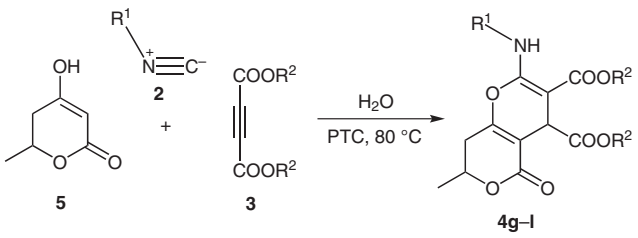
Entry	**1** or **5**	R^1	R^2	Product		Time (h)	Yield (%)
1	**1**		Me		**4a**	3	75
2	**1**		Et		**4b**	3.5	70
3	**1**		Me		**4c**	4	70
4	**1**		Et		**4d**	4.5	72
5	**1**		Me		**4e**	4	75
6	**1**		Et		**4f**	4	77

Table 1 Synthesis of Pyrano[3,2-*c*]coumarins **4** (continued)

Entry	**1** or **5**	R^1	R^2	Product		Time (h)	Yield (%)
7	**5**		Me		**4g**	1.5	80
8	**5**		Et		**4h**	2	78
9	**5**		Me		**4i**	2	75
10	**5**		Et		**4j**	1.5	77
11	**5**		Me		**4k**	2	72
12	**5**		Et		**4l**	2	75

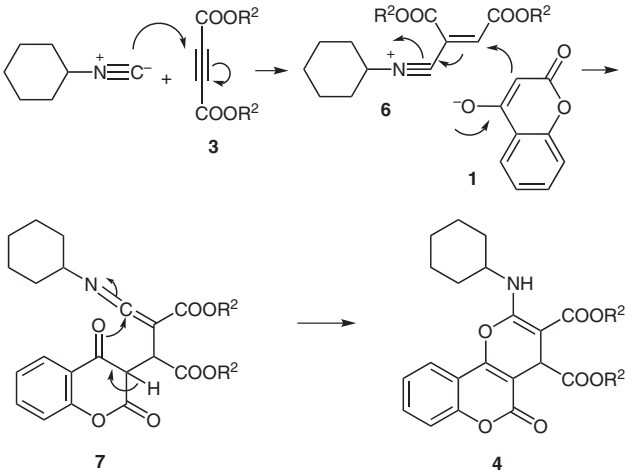


Scheme 2

The ^{1}H NMR spectrum of dimethyl 2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (**4a**) showed the characteristic signal for the NH group at δ = 8.70 ppm, the two methoxy groups as singlets at δ = 3.71 and 3.74 ppm and other signals at δ = 1.37–2.09 (cyclohexyl ring protons), 3.78–3.87 (NCH), 4.73 (olefinic methane), and 7.30–7.72 (aromatic protons) ppm. The ^{13}C NMR spectrum showed 22 distinct peaks at δ = 24.41, 24.46, 25.3, 33.4, 33.7, 36.3, 50.6, 51.2, 52.7, 72.1, 102.9, 113.5, 117.1, 121.9, 124.6, 132.7, 152.7, 154.9, 158.2, 160.7, 169.3, 173.1 ppm. The IR spectrum showed absorptions at 3265 cm^{-1} due to the NH group and at 1733, 1686, and 1659 cm^{-1} due to the carbonyl groups. The mass spectrum revealed a strong molecular ion peak at *m*/*z* =

413 [M+]. In a similar way, other annulated 4*H*-pyran derivatives **4b–l** were synthesized and characterized from their spectroscopic data.

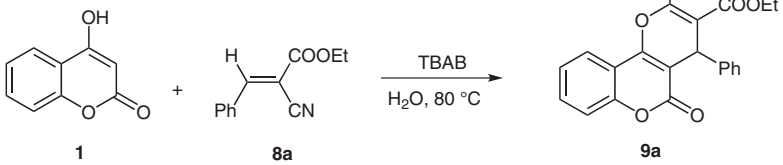
Although the mechanism of the reaction has not been established experimentally, it is proposed that the reaction is initiated by formation of a highly reactive 1:1 zwitterionic intermediate **6** from the alkyl isocyanide and dialkyl acetylenedicarboxylate. This intermediate then undergoes an addition reaction with 4-hydroxycoumarin (**1**), followed by cyclization to generate the corresponding pyrano[3,2-*c*]coumarin (**4**; Scheme 3).



Scheme 3

After the successful application of phase-transfer conditions (PTCs) in the synthesis of pyranocoumarin derivatives from isocyanides and dialkylisocyanides, we wished to explore further the potential of this method. Therefore, we performed a three-component reaction of 4-hydroxycoumarin, ethyl cyanoacetate and *p*-nitrobenzaldehyde under identical reaction conditions. In this case, we observed formation of biscoumarin instead of the expected pyranocoumarin product. This could be because the highly reactive CH-acidic 4-hydroxycoumarin traps the aldehyde before it can react with the ethyl cyanoacetate.

We next carried out the reaction in two steps. First, we synthesized an ylidine nitrile by using a Knoevanagel condensation between ethyl cyanoacetate and *p*-nitrobenzaldehyde and then reacted the ylidine nitrile with 4-hydroxycoumarin in water under PTC conditions. Gratifyingly, we obtained the pyranocoumarin derivative **9a** in excellent yield within a short reaction time (Scheme 4).



Scheme 4

The ^{1}H NMR spectrum of **9a** revealed the presence of the NH_2 group at δ = 6.56 ppm as a singlet, the CH group at δ = 5.02 ppm as singlet, methyl protons at δ = 1.15 ppm as a triplet and methylene protons at δ = 4.02 ppm as a quartet. The ^{13}C NMR spectrum showed peaks at δ = 165.4, 158.5, 157.5, 156.6, 151.5, 137.6, 134.4, 129.4, 128.2, 127.2, 121.9, 111.3, 83.7, 65.1, 40.6, 19.0 ppm. The IR spectrum showed absorptions at 3419 and 3310 cm^{-1} due to the NH_2 group and at 1723 and 1691 cm^{-1} due to the carbonyl groups. The mass spectrum revealed a strong molecular ion at *m*/*z* = 408.6 [M+]. Finally, the structure of compound **9a** was confirmed by single-crystal X-ray diffraction (Figure 2).[12] The generality of the reaction was checked by reacting different ylidine nitriles with 4-hydroxycoumarin (Scheme 5). In all cases, the reaction occurred smoothly and excellent yields of the products were obtained. Furthermore, the reaction was clean and formation of side products was not observed. The results obtained are summarized in Table 2.

In summary, we have developed an efficient and clean protocol for the synthesis of pyrano[3,2-*c*]coumarin derivatives from 4-hydroxycoumarin in aqueous medium, in

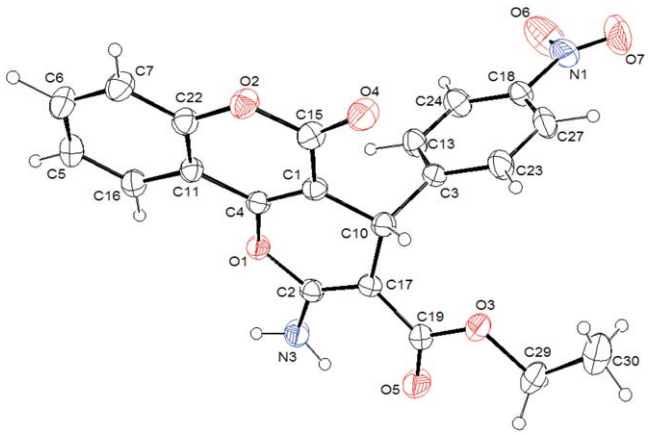
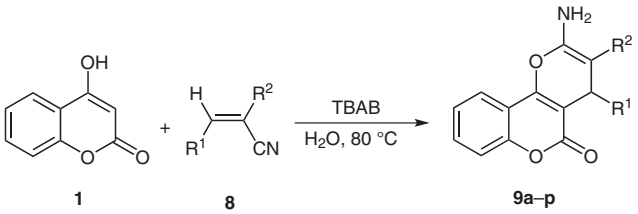


Figure 2 ORTEP diagram of compound **9a** drawn with 30% probability ellipsoids



Scheme 5

Table 2 Synthesis of Pyrano[3,2-*c*]coumarins **9**

Entry	Product	R^1	R^2	Time (min)	Yield (%)
1	**9a**	4-$O_2NC_6H_4$	COOEt	15	88
2	**9b**	Ph	COOEt	15	90
3	**9c**	4-$MeOC_6H_4$	COOEt	20	80
4	**9d**	4-MeC_6H_4	COOEt	20	83
5	**9e**	4-FC_6H_4	COOEt	15	86
6	**9f**	2-furyl	COOEt	20	82
7	**9g**	2-thienyl	COOEt	20	80
8	**9h**	4-ClC_6H_4	COOEt	15	85
9	**9i**	4-ClC_6H_4	CN	22	80
10	**9j**	4-$MeOC_6H_4$	CN	20	82
11	**9k**	4-$O_2NC_6H_4$	CN	15	85
12	**9l**	Ph	CN	20	90
13	**9m**	4-MeC_6H_4	CN	20	85
14	**9n**	2-furyl	CN	25	80
15	**9o**	2-thiophenyl	CN	25	79
16	**9p**	4-FC_6H_4	CN	15	92

the presence of a phase-transfer catalyst.[13] The use of water as the reaction medium makes the process economical and environmentally friendly. The methodology offers further advantages such as short reaction time, mild reaction conditions, operational simplicity and an easy work-up procedure, which makes it an attractive strategy for the synthesis of pyranocoumarin derivatives.

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(12) CCDC-784897 contains the supplementary crystallographic data for compound **10a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) (a) **Typical procedure for the synthesis of 4a–l**:
A mixture of alkyl isocyanide (1 mmol), dialkyl acetylenedicarboxylate (1 mmol) and 1,3-dicarbonyl compound (1 mmol) in H_2O (5 mL), in the presence of TBAB (10 mol%) was stirred at 80 °C until the reaction was complete as indicated by TLC. The crude solid product was filtered, washed with H_2O, dried and purified by column chromatography (EtOAc–hexane, 3:7). The products thus obtained were characterized by their IR, NMR spectroscopic and mass spectrometric data. Dimethyl 2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (**4a**): White solid; mp 198–200 °C; IR ($CHCl_3$): 3264.9 (N–H), 1732.6, 1686.3, 1659.4 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–2.09 (m, 10 H, 5 × CH_2), 3.71 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.78–3.87 (m, 1 H, NCH), 4.73 (s, 1 H, CH), 7.30–7.72 (m, 4 H, ArH), 8.70 (s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.41, 24.46, 25.3, 33.4, 33.7, 36.3, 50.6, 51.2, 52.7, 72.1, 102.9, 113.5, 117.1, 121.9, 124.6, 132.7, 152.7, 154.9, 158.2, 160.7, 169.3, 173.1. GC/MS: *m*/*z* = 413 [M$^+$] (b) **Typical procedure for the synthesis of 9:** An equimolar mixture of ylidine malononitrile **8** (1 mmol) and 4-hydroxycoumarin (1 mmol) in H_2O (5 mL), in the presence of TBAB (10 mol%) was stirred at 80 °C until the reaction was complete as indicated by TLC. The solid product was filtered, washed with water, dried and purified by recrystallization (EtOH–$CHCl_3$, 1:1). The products thus obtained were characterized by their IR, NMR spectroscopic and mass spectrometric data (**9a**): Yellow crystal; mp 240–243 °C; IR (KBr): 3430, 3340 (NH_2), 1714 (CO), 2181 (CN) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3 H), 4.08 (q, 2 H), 5.03 (s, CH, 1 H), 6.56 (br s, NH_2, 2 H), 7.33–8.13 (m, 8 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 35.8, 60.2, 106.4, 113.1, 117.0, 122.3, 123.4, 124.3, 124.6, 129.5, 132.7, 146.7, 151.7, 152.7, 153.6, 158.0, 160.5, 168.2; LCMS (ESI): *m*/*z* = 408 [M$^+$].