A Simple Method for the Synthesis of Functionalised Chromenes via Vinylogous Michael Addition of α,α-Dicyanoalkenes on Iminocoumarin Derivatives

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Abstract: A one-pot synthesis of 2-amino-4*H*-chromenes was achieved in good yields from three-component reaction of salicylaldehyde, malononitrile, and α,α-dicyanoalkenes catalysed by triethylamine.

Key words: 2-amino-4*H*-chromenes, vinylogous Michael addition, α,α-dicyanoalkenes, multicomponent reactions

The development of novel C–C bond-construction methods is very important in synthetic organic chemistry. Over the past century, great advances have been made by employing nucleophilic carbanions from the deprotonation of an acidic C–H adjacent to one or more functional groups.[1] Nevertheless, the discovery of new synthons and synthetic strategies is still essential for the continuing expansion of synthetic protocols.

α,α-Dicyanoalkenes are materials which are readily available by the condensation of the corresponding carbonyl compounds and malononitrile. They were prepared more than a hundred years ago,[2] and inherently act as electron-deficient electrophiles.[3] The self-dimerisation of some α,α-dicyanoalkenes via intermolecular vinylogous addition and ring-closing processes by base catalysis has also been documented.[4] However, their potential as successful vinylogous donors in synthetic chemistry was not recognised until the independent publications by Jørgensen, Deng and Chen et al. in 2005.[5] In this letter we describe α,α-dicyanoalkenes as vinylogous donors in 1,4-addition reaction on iminocoumarin derivatives, thereby identifying α,α-dicyanoalkenes as very versatile synthons for the construction of multifunctional chromenes.

2-Aminochromenes are widely employed as pigments, cosmetics, agrochemicals and represent an important class of chemical entities being the major constituents of several natural products.[6] Fused chromenes exhibit a wide spectrum of biological applications as antimicrobial, antiviral,[7] mutagenicity, antiproliferative, sex pheromone, antitumor,[8] and central nervous system agents. Due to the unique pharmacological properties of 2-aminochromenes, the development of synthetic methods enabling facile access to this heterocycle, is desirable.

2-Aminochromenes are generally prepared by refluxing malononitrile, aldehyde, and activated phenol in the presence of hazardous organic bases like piperidine in organic solvents, ethanol, and acetonitrile for several hours.[9] A literature survey revealed several modified procedures using CTACl,[10] TEBA,[11] γ-alumina,[12] and K_2CO_3 in water under microwave irradiation for the synthesis of chromenes.[13] Moreover, enantioselective synthesis of 2-aminochromenes were also documented in the literature.[14]

As part of our ongoing research on the reactivity of α,α-dicyanoalkenes[15] and the synthesis of 2-amino chromenes via three-components reaction of salicylaldehyde and malononitrile with various reagents such as indole, Hantzsch dihydropyridine,[16] indium,[17] and triethyl phosphite,[18] we herein wish to report our investigation of a new multicomponent reaction involving salicylaldehyde, malononitrile, and α,α-dicyanoalkenes. To the best of our knowledge, this is the first report on α,α-dicyanoalkenes employed as Michael donors on iminocoumarins to synthesise functionalised chromenes.

The reactions were carried out by first mixing salicylaldehyde, malononitrile, and vinyl malononitrile (Figure 1) in ethanol in the presence of triethylamine (Scheme 1). All the reactions proceeded smoothly at room temperature to completion within 60 minutes and afforded the corresponding 2-amino-4*H*-chromenes in good yields. Out of all bases tested, including triethylamine, potassium carbonate, L-proline, urea, and sodium ethoxide, triethylamine was found to be the best catalyst (Table 1). Table 2 summarises our results on the one-pot reaction of various salicylaldehydes and malononitrile with α,α-dicyanoalkene derivatives (Scheme 2). Different salicylaldehydes either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as alkoxy group) gave expected products in good to high yields under the same reaction conditions.

The structures of compounds **4a**–**m** were characterised by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.[19] The IR spectrum of **4a** showed absorptions at 3384, 3326, 2183 cm^{-1} indicating the presence of NH_2 and CN groups, respectively. In the ^{1}H NMR spectroscopy, the benzylic proton resonated at δ = 3.56 ppm with coupling constant 5.35 Hz and the two diastereotopic methylene protons were observed at δ = 3.18 and 3.31 ppm as two doublets of doublets with J_1 and J_2 values of 7.65, 5.35, 5.35, 8.4 Hz, respectively. The NH_2 protons resonated as sharp singlet at δ = 7.09 ppm which is exchangeable with D_2O and in the ^{13}C NMR spectrum, C-2 resonated at δ = 162.7 ppm. The structure of **4m** was additionally confirmed by X-ray diffraction analysis.[20]

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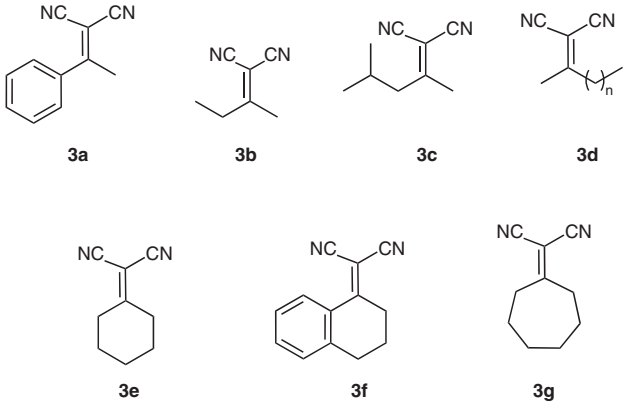
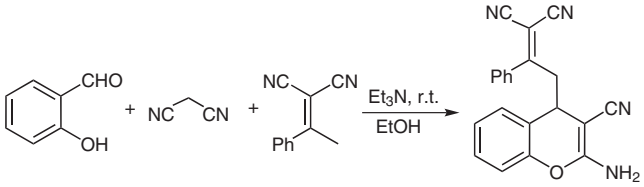


Figure 1 Structure of vinyl malononitriles



Scheme 1

Table 1 Screening of Catalysts

Entry	Base	Time (min)	Yield (%)
1	K_2CO_3	60	60
2	NaOEt	55	65
3	NH_2CONH_2	90	25
4	L-proline	60	75
5	Et_3N	35	78

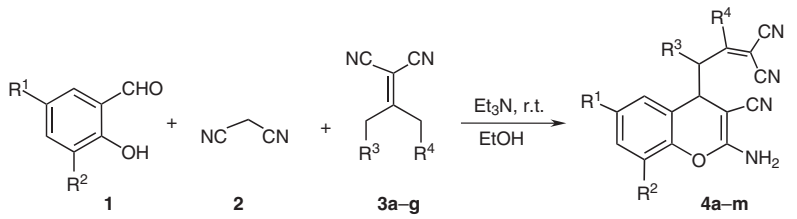
The chromenes **4a**–**h** were purified by column chromatography, whereas the chromens **4i**–**m** were isolated by simple filtration as inseparable mixture of diastereomers with a 50:50 ratio as determined by ^1H NMR spectroscopy. This method offers several advantages like milder reaction conditions, shorter reaction time, high yield, and simple experimental and isolation procedures making it an efficient route to the synthesis of 2-amino-4*H*-chromenes. Encouraged by these results, we extended the protocol replacing salicylaldehyde by 2-hydroxynaphthalene-1-carboxaldehyde (**5**) in order to synthesise fused chromene **6** under the same optimised conditions in 70% yield (Scheme 3).

We propose the plausible mechanism to account for the formation of **4a**–**m**. The process represents a typical cas-

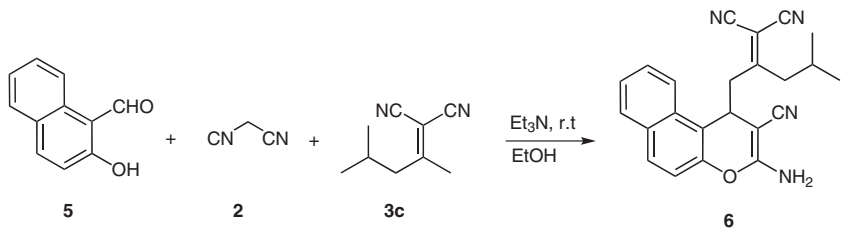
Table 2 Synthesis of 2-Amino-4*H*-chromenes

Entry	Salicylaldehyde		Vinyl malononitrile	Product	Time (min)	Yield (%)[a]
	R^1	R^2				
1	H	H	**3a**	**4a**	35	78
2	H	OEt	**3a**	**4b**	50	75
3	Br	H	**3a**	**4c**	45	80
4	H	H	**3b**	**4d**	40	70
5	Br	H	**3b**	**4e**	38	74
6	H	H	**3c**	**4f**	30	80
7	Br	H	**3c**	**4g**	34	77
8	H	H	**3d**	**4h**	55	65
9	H	H	**3e**	**4i**	30	88[b]
10	Br	H	**3e**	**4j**	36	85[b]
11	Br	Br	**3e**	**4k**	40	80[b]
12	H	H	**3f**	**4l**	50	75[b]
13	H	H	**3g**	**4m**	37	85[b]

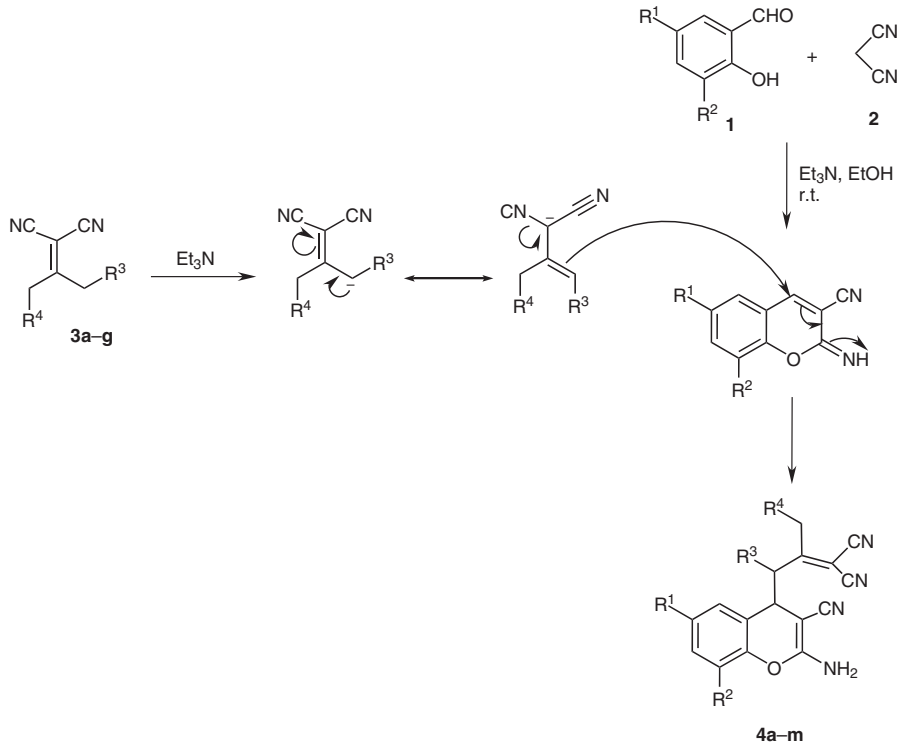
[a] Isolated yield.
[b] Obtained as racemic mixture.



Scheme 2



Scheme 3



Scheme 4 Plausible mechanism

cade reaction in which salicylaldehyde first condenses with malononitrile to form the Knoevenagel product[21] followed by cyclisation as a result of nucleophilic attack of the hydroxy group on the cyano group to form imino coumarin. The second step involves regioselective nucleophilic attack of vinyl malononitrile to produce 2-amino-4*H*-chromenes **4a**–**m** (Scheme 4).

In summary, we have demonstrated a new, one-pot, three-component reaction that offers a simple method for the synthesis of new 2-amino-4*H*-chromenes from salicylaldehyde, malononitrile, and α,α-dicyanoalkenes catalysed by triethylamine. Investigation of the reaction using chiral bases is under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(19) **General Procedure for the Synthesis of 2-Amino Chromenes 4a–h from Salicylaldehyde, Malononitrile, and α,α-Dicyanoalkenes 3a–h – Representative Procedure for 2-Amino-4-(3,3-dicyano-2-phenylallyl)-4*H*-chromene-3-carbonitrile (4a)**

To a stirred mixture of salicylaldehyde (1 mmol) and malononitrile (1 mmol) in EtOH, vinyl malononitrile **3a** (1.5 mmol), and Et_3N (0.5 mmol) were added. The reaction mixture was stirred at r.t. for the appropriate time (Table 2). After complete conversion as indicated by TLC, the mixture was concentrated under vacuo and subjected to chromatographic purification over silica gel (Merck; 100–200 mesh; EtOAc–hexane, 3:7) to obtain chromene **4a** (78%).

Spectral Data of 2-Amino-4-(3,3-dicyano-2-phenylallyl)-4*H*-chromene-3-carbonitrile (4a, Table 2, Entry 1)

Pale pink solid; yield 78%. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.18 (dd, J_1 = 7.65 Hz, J_2 = 5.35 Hz, 1 H), 3.31 (dd, J_1 = 5.35 Hz, J_2 = 8.4 Hz, 1H), 3.56 (t, J = 5.35 Hz, 1 H), 6.93 (d, J = 7.6 Hz, 1 H), 7.09 (s, 2 H, D_2O exchangeable), 7.13 (t, J = 6.1 Hz, 4 H), 7.28 (t, J = 8.4 Hz, 1 H) 7.53 (m, 3 H) 7.65 (d, J = 7.6 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 35.6, 48.1, 52.7, 86.1, 113.2, 113.7, 116.5, 121.0, 122.8, 125.2, 128.8, 128.9, 128.9, 129.2, 129.4, 129.4, 132.6, 134.5, 149.6, 162.7, 177.0. IR (KBr): ν_{max} = 3384, 3326, 2183, 1653, 1423, 1050, 757 cm^{-1}. ESI-MS: 339 [M + 1]. Anal. Calcd (%) for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 75.97; H, 4.11; N, 15.71.

Spectral Data of 3-Amino-1-[2-(dicyanomethylene)-4-methylpentyl]-1*H*-benzo[*f*]chromene-2-carbonitrile (6)

Pale brown solid; yield 70%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.1 Hz, 3 H), 1.01 (d, J = 6.15 Hz, 3 H), 1.91 (m, 1 H), 2.42 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1 H) 2.59 (dd, J_1 = 6.85 Hz, J_2 = 6.15 Hz, 1 H), 2.85 (dd, J_1 = 9.2 Hz, J_2 = 3.8 Hz, 1 H), 3.00 (dd, J_1 = 3.8 Hz, J_2 = 8.45 Hz, 1 H), 4.55 (dd, J_1 = 4.6 Hz, J_2 = 4.6 Hz, 1 H), 5.00 (s, 2 H, D_2O exchangeable), 7.20 (d, J = 9.15 Hz, 1 H), 7.52 (t, J = 6.9 Hz, 1 H), 7.64 (t, J = 7.65 Hz, 1 H), 7.85 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 22.8, 29.2, 32.6, 43.2, 45.1, 56.5, 89.5, 111.7, 112.0, 115.1, 116.9, 119.6, 121.5, 125.7, 128.0, 129.3, 129.7, 130.0, 131.5, 147.7, 161.9, 180.1. IR (KBr): ν_{max} = 3434, 3327, 2959, 2183, 1643 cm^{-1}. ESI-MS: 369 [M + 1]. Anal. Calcd (%) for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.87; H, 5.11; N, 15.11.

(20) Crystallographic data for compound **4m** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication No. CCDC-796193. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

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