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Facile syntheses of 2-substituted 3-cyanochromones

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ABSTRACT

A simple and general route to 3-cyanochromones containing various substituents on position 2 of the ring is developed. The method is based on condensation of 3-(2-hydroxyphenyl)-3-oxopropionitrile with acid chlorides or anhydrides in pyridine at room temperature.

3-Cyanochromones are of interest as antifungal agents[1] and novel telomerase inhibitors.[2] In addition, they are precursors of a number of 2-substituted chromone-3-carboxylic acids,[3] which are known as inhibitors of p56lCk tyrosine kinase,[4] and chromone-3-carbaldehydes,[5] which exhibit cytotoxic, anti-Helicobacter pylori, urease inhibitory, and anti-HIV activity.[6] The presence of the cyano group at position 3 allows further functionalization of chromones or the design of new heterocyclic compounds.[7–10]

Several routes to 3-cyanochromones are described in the literature, however, these methods only enable the synthesis of products with a limited set of substituents, particularly, at position 2 of the chromone. For example, 3-cyano derivatives were synthesized by substitution of chlorine in 3-chloro-2-phenylchromones with copper cyanide.[2,11–13] These reactions proceeded under reflux in *N*-methylpyrrolidone at 200–220 °C, and were limited by the availability of 3-halochromones. 3-Cyanochromones can also be synthesized by cyanation of 2-alkyl-3-bromochroman-4-ones with the use of the SmI_2/KHMDS/TsCN system at −78 °C, followed by oxidation of the resulting 2-alkyl-3-cyanochroman-4-ones with DDQ on reflux in 1,4-dioxane for 12 h to give 2-alkyl-3-cyanochrom-4-ones.[14] 2-Unsubstituted 3-cyanochromones were synthesized by refluxing a benzene solution of sulfuric acid and *O*-methyl oximes, which were produced by the reaction of chromone-3-carbaldehydes with *O*-methylhydroxylamine.[15]

In 2003, a method was developed for the synthesis of 3-cyano-2-phenylchromones (in 35–65% yields) involving the reaction of β-bromo-α-alkylthiocinnamonitriles with various substituted methyl salicylates followed by treatment with $AlCl_3$/$PhNO_2$ at 150 °C.[5] It should be noted that methods for the synthesis of 3-cyanochromones containing heterocyclic moieties at position 2 are lacking in the literature.

In the present study, we report a simple and general route to various 2-substituted 3-cyanochromones containing alkyl, aryl, or heterocyclic substituents at position 2 (Scheme 1). In the first step, readily available 2′-hydroxyacetophenone was converted into the corresponding dimethylaminomethylene derivative **2** in quantitative yield under reflux in DMF–DMA. Compound **2** was then refluxed in ethanol with hydroxylamine hydrochloride to give 2-(isoxazol-5-yl)phenol **3** in 80% yield. Upon treatment with aqueous-ethanolic NaOH solution at room temperature, the isoxazole ring in compound **3** was cleaved to form 3-(2-hydroxyphenyl)-3-oxopropionitrile (**4**) in 75% yield.[16] The synthesis of target nitriles **6a**,**b** was performed according to a method previously used by us for the synthesis of 3-acyl-2-hetarylchromones **10**.[17,18] In this method, β-diketone **7** (Scheme 2) underwent an aldol condensation with various aldehydes at room temperature or with slight heating to form a mixture of compounds **8** and **9**, which give 3-acyl-2-substituted chromones **10** upon oxidation with selenium dioxide in refluxing 1,4-dioxane. Using this approach we prepared condensation products **5** in 70–80% yield. The latter were easily oxidized to give compounds **6** in 52–75% yield.

It should be noted that the aldol condensation of aldehydes with nitrile **4** is complete in 15 min at room temperature,[19] which is much faster[20] compared to the corresponding reaction with diketones **7**, which is complete within 6–12 h. This fact is indicative of

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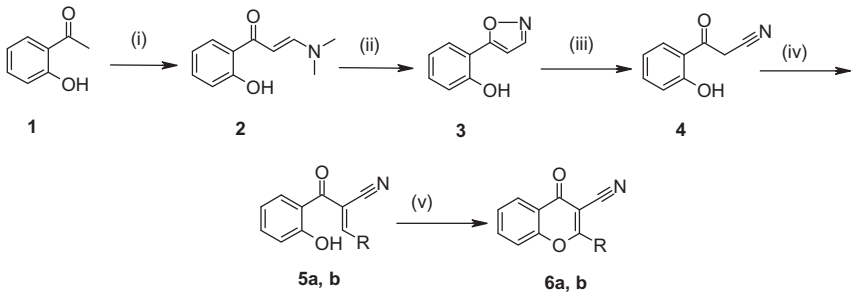
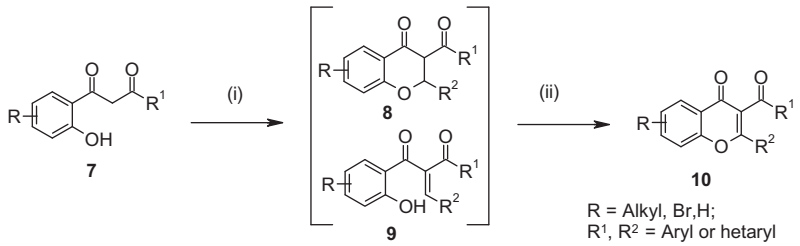
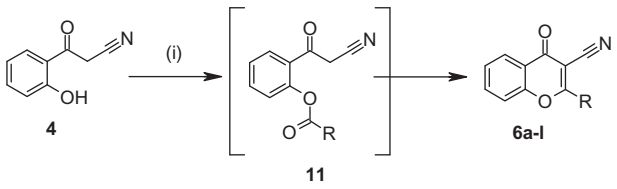


Scheme 1. Reagents and conditions: (i) DMF–DMA reflux, 1 h; (ii) $NH_2OH{\cdot}HCl$, EtOH, reflux, 2 h; (iii) NaOH, EtOH/H_2O (1:3), rt 24 h; (iv) thiophene-2-carboxaldehyde or furfural, piperidine, EtOH, rt, 15 min; (v) SeO_2, 1,4-dioxane, reflux.



Scheme 2. Reagents and conditions: (i) R^2CHO, piperidine, EtOH, rt (6–12 h) or heating (0.5–3 h); (ii) SeO_2, 1,4-dioxane, reflux.



Scheme 3. Reagents and conditions: (i) RCOCl, pyridine, rt 1–3 h.

the higher activity of the methylene group in nitrile derivatives **4** compared to that in diketones **5**. This encouraged us to synthesize esters **11** in expectation of spontaneous cyclization to cyanochromones **6a–l** (Scheme 3).

In fact, the acylation of nitrile **4** with acid chlorides in pyridine at room temperature afforded the target nitriles in 49–90% yields. It should be noted that the reaction products did not require chromatographic purification and pure products could be obtained by simple crystallization, for example, from ethanol. The method is versatile and enabled the synthesis of various 3-cyanochromones **6a–l**, including previously unavailable 2-hetaryl-substituted examples **6a–c**, in good to high yields (Table 1).

Table 1
Isolated yields and melting points of compounds **6a–l**[a].

Entry	R	Product	Mp (°C)	Yield (%)
1	Furan-2-yl	**6a**	166–168	82
2	Thien-2-yl	**6b**	198–200	64
3	5-Methylthien-2-yl	**6c**	149–151	60
4	Ph	**6d**	165–166	90
5	2-Cl-C_6H_4	**6e**	150–152	67
6	4-Cl-C_6H_4	**6f**	203–205	78
7	2-F-C_6H_4	**6g**	189–191	63
8	4-F-C_6H_4	**6h**	209–211	70
9	2-Me-C_6H_4	**6i**	165–167	61
10	Me	**6j**	192–194	65 (70)[b]
11	Et	**6k**	123–125	(54)[b]
12	CH_2Ph	**6l**	189–190	49

[a] The corresponding acid chloride (1.05 mmol) was added to nitrile **4** (1 mmol) in pyridine (1.5 mL). After stirring at rt, the mixture was poured into water. The precipitate that formed was washed with water, dried, and if required, crystallized from ethanol.

[b] The yields in the acylation with the use of acid anhydrides under reflux conditions are given in parentheses.

In summary, we have developed a general and simple method for the synthesis of a range of 2-alkyl-, 2-aryl-, and 2-hetaryl-3-cyanochromones in good to excellent yields. The method does not require the use of expensive reagents or chromatographic purification of the reaction products.

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Supplementary data

Supplementary data (characterization data of synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.031. These data include MOL files and InChiKeys of the most important compounds described in this article.

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16. 3-(2-Hydroxyphenyl)-3-oxopropanenitrile (**4**). Mp 108–109 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 11.36 (s, 1H), 7.54–7.58 (m, 2H), 6.94–7.05 (m, 2H), 4.17 (s, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 192.68 (C═O), 162.76 (C-OH), 138.18 (C-4′), 129.45 (C-6′), 119.80 (C-5′), 119.2 (C-3′), 117.70 (C-1′), 113.40 (CN), 29.70 (C-2).
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19. General procedure for the preparation of **5**: One drop of piperidine was added to a mixture of ketonitrile **4** (322 mg, 0.2 mmol) and furfural (0.2 g, 0.208 mmol) or thiophene-2-carboxaldehyde (0.24 g, 0.208 mmol) in EtOH. After stirring for 15 min, the precipitate that formed was filtered, washed with cold EtOH, and dried in air. A pure yellow product was obtained.
3-Furan-2-yl-2-(2-hydroxybenzoyl)acrylonitrile (**5a**). Yield 380 mg (80%); mp 118–120 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 11.34 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.96 (s, 1H), 7.81 (s, 1H), 7.53–7.58 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 3.1 Hz, 1H).
2-(2-Hydroxybenzoyl)-3-(thien-2-yl)acrylonitrile (**5b**). Yield 70%; mp 112–114 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): 11.33 (s, 1H), 8.28 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 3.4 Hz, 1H), 7.87 (d, J = 4.8 Hz 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.28 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H).
General procedure for the oxidation of **5**. SeO_2 (2 mmol) was added to a solution of **5a** or **5b** (1 mmol) in 1,4-dioxane and the resulting mixture was refluxed until completion of the reaction (TLC monitoring). Column chromatographic separation afforded products **6a** and **6b** in 75% and 52% yields, respectively.
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