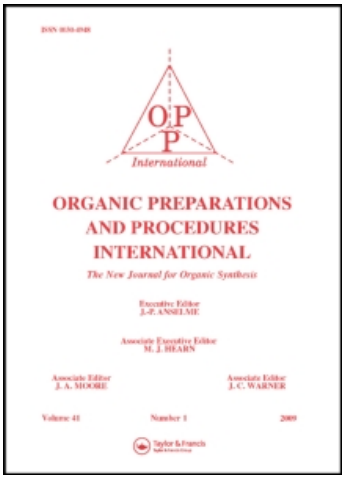

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AN EFFICIENT ONE STEP CONVERSION OF 3-FORMYLCHROMONES INTO 3-CYANOCHROMONES

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AN EFFICIENT ONE STEP CONVERSION OF 3-FORMYLCHROMONES INTO 3-CYANOCHROMONES

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(03/11/04)

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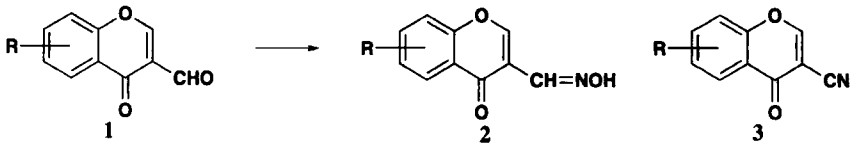
3-Cyanochromones constitute an important class of intermediates because of their use in the synthesis of anti-allergic substances.[1] The cyano group enhances the dienophilic nature of the carbon-carbon double bond of the cyclic enone system and thus 3-cyanochromones have been extensively used as dienophiles in the synthesis of compounds with selective acetylcholinesterase inhibiting activity.[2] Several methods have been reported for the synthesis of 3-cyanochromones (**3**) by dehydration of the corresponding aldoximes (**2**). These include refluxing for 12 hrs in alcohol in the presence of hydrochloric acid,[3] sodium formate in acetic acid[4] and acetic anhydride.[5] Sulfuric acid promoted elimination of methanol from O-methyloximes has also been reported for the synthesis of 3-cyanochromones.[6] Most of these methods involve i) prior preparation of oximes[5] and ii) dehydration, with the disadvantages of strongly acidic conditions,[4-6] expensive reagents,[6] long reaction times,[5] tedious isolation of products and low overall yields. The synthetic potential and medicinal interest of 3-cyanochromones and the difficulties encountered in the synthesis of 3-cyanochromones prompted a search of a convenient method.



a) R = H; b) R = 6-CH_3; c) R = 6-C_2H_5; d) R = 6-$(CH_3)_2CH$
e) R = 6-Cl; f) R = F; g) R = 6,7-diMe; h) R = 6-Cl, 7-CH_3

As a part of our ongoing program to develop a library of chromones,[7] we became interested in a more general synthesis of 3-cyanochromones. In the present work, substituted 3-formylchromones (**1**) were heated with hydroxylamine hydrochloride in refluxing acetonitrile in the presence of sodium iodide[8] to give 3-cyanochromones in good yields. In general, the aldoximes (**2**) are poorly soluble in most of the organic solvents thereby necessitating the use of strongly acidic conditions[4-6] in the dehydration step. Acetonitrile being a more dipolar solvent, allowed the dehydration of the oximes *in situ*, catalyzed by sodium iodide. The structures of all compounds reported in *Table 1* were established on spectral data and comparison of melting points with authentic samples.

The present method is simple, does not require the isolation of intermediate oximes, utilizes inexpensive and non-hazardous reagents with better yields.

EXPERIMENTAL SECTION

Mps were determined in open capillaries and are uncorrected. IR spectra were recorded as KBr pellets using Perkin Elmer System 2000 FT IR spectrometer. ^{1}H NMR spectra were recorded on a Varian 200 MHz instrument, in $CDCl_3$ with TMS as an internal standard and chemical shifts are expressed in δ (ppm). 3-Formylchromones required in the present work were prepared by Vilsmeier-Haack reaction on 2-hydroxyacetophenones according to the method reported by Nohara *et al.*[9]

General Procedure for 3-Cyanochromones (3a-h).- A mixture of 3-formylchromone (0.1 mole), hydroxylamine hydrochloride (8.34 g, 0.12 mole) and sodium iodide (7.45 g, 0.05 mole) was refluxed for 2 hrs. The progress of the reaction was monitored by TLC using hexane-ethyl acetate as solvent system (3:1). After completion of the reaction, it was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with water (100 mL) and the organic layer was extracted with dichloromethane (3 x 100 mL). It was washed with sodium sulfite solution (5%, 50 mL), water (2 x 50 mL), dried over Na_2SO_4, concentrated and the solid residue was recrystallized from methanol to give pure **3**.

TABLE. Yields, mps, Spectral Data of **3**

Cmpd	Yield (%)	mp (°C)	*lit.* mp (°C)	IR (cm^{-1})	^{1}H NMR Data (δ)
3a	81	175-177	(177)[4]	2242, 1667	7.44-7.6(m, 2H, ArH), 7.8(m, 1H, ArH), 8.2(dd, 1H, ArH), 8.82(s, 1H, C_2-H) – DMSO-d_6
3b	67	151-153	(152)[3]	2240, 1665	2.48(s, 3H, CH_3), 7.5(dd, 1H, ArH), 7.6(dd, 1H, ArH), 7.95(s, 1H, ArH), 8.82(s, 1H, C_2-H) – DMSO-d_6
3c	75	121-123	(123)[3]	2234, 1666	1.39(t, 3H, CH_2CH_3), 2.8(q, 2H, CH_2CH_3), 7.4(dd, 1H, ArH), 7.6(dd, 1H, ArH), 8.0(s, 1H, ArH), 8.4(s, 1H, C_2-H) – $CDCl_3$
3d	66	115-116	(118)[3]	2236, 1665	1.30(dd, 6H, $(CH)_2$), 3.1(octet, 1H, CH), 7.46(dd, 1H, ArH), 7.65(dd, 1H, ArH), 8.05(d, 1H, ArH), 8.4(d, 1H, C_2-H) – $CDCl_3$
3e	63	209-210	(210)[6]	2237, 1664	7.65(d, 1H, ArH), 7.8(dd, 1H, ArH), 8.1(d, 1H, ArH), 9.0(s, 1H, C_2-H) - DMSO-d_6
3f	69	172-174	(172)[6]	2238, 1665	7.5-7.6(m, 2H, ArH), 7.8(dd, 1H, ArH), 8.9(s, 1H, C_2-H) – DMSO-d_6
3g	65	204-206	(207)[7]	2240, 1667	2.55(s, 3H, CH_3), 7.6(s, 1H, ArH), 8.05(s, 1H, ArH), 9.0(s, 1H, C_2-H) – DMSO-d_6
3h	57	225-230	(232)[6]	2230, 1666	2.39(s, 3H, CH_3), 2.42(s, 3H, CH_3), 7.4(s, 1H, ArH), 7.84(s, 1H, ArH), 8.85(s, 1H, C_2-H) – DMSO-d_6

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AN EFFICIENT SYNTHESIS OF 2,3-DICYANOINDOLE

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In continuation of our studies of indoles substituted with electron-withdrawing groups at the C-2 and C-3 positions (i. e., nitro, phenylsulfonyl),[1] we became interested in 2- and 3-cyano- and 2,3-dicyanoindole. Due to its strong electron-withdrawing ability and small size, the cyano group could prove useful in activating the indole double bond to the chemistry we have been exploring.[1] Despite a simple structure, no practical syntheses of 2,3-dicyanoindoles exist, as the only two reports of these compounds originate from studies of the reaction of 2-chloro- and 2-(phenylsulfonyl)indoles with sodium azide (26–32%),[2a] the electrolytic oxidation of 1-