A MILD AND FACILE METHOD FOR THE SYNTHESIS OF 3-CYANO-CHROMONES FROM OXIMES DERIVED FROM 3-FORMYLCHROMONES USING DIMETHYLFORMAMIDE - THIONYLCHLORIDE COMPLEX

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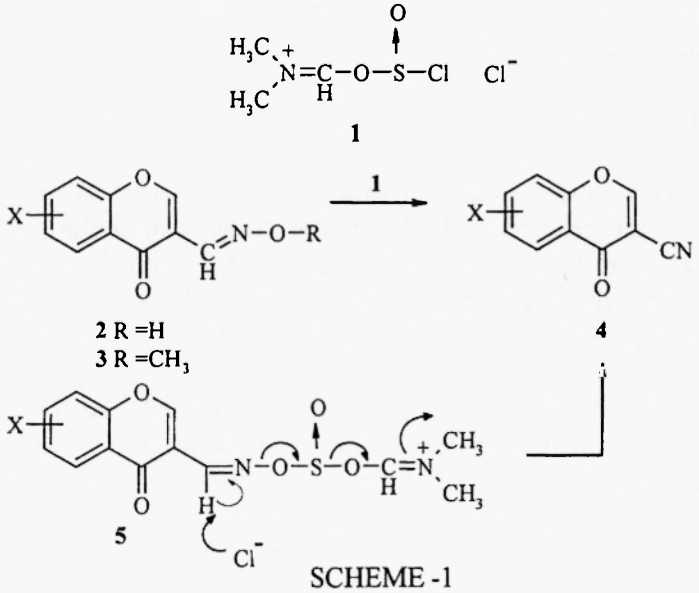
Abstract

A mild and facile method for the synthesis of 3-cyanochromones (**4**) from oximes (**2**) derived from 3-formylchromones using Dimethylformamide-thionylchloride complex (**1**) is herein reported.

Introduction

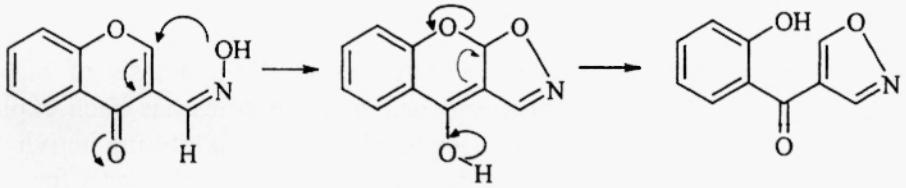
Chromone derivatives constitute an important class of compounds because of their natural abundance and also their application as pharmaceutical agents[1]. These are also used as antitumour agents with minimal side effects[2]. Recent reports indicate their prospects as anti HIV agents also[3], **Amlexanox** is a clinically useful anti allergic drug, the main intermediate in the synthesis of this drug is 6-isopropyl-3-cyanochromone which indicates the importance of 3-cyanochromones in the synthesis of biologically active compounds[4]. Thc use of 3-cyanochromones as dienophiles has been exploited in the synthesis of compounds with selective acetylcholinesterase inhibiting activity[5]. Since last one decade we are engaged in the development of library of chemicals for a number of chromone derivatives[6]. In view of this and the synthetic potential of cyanochromones, we report herein a mild and facile synthesis of 3-cyanochromones from oximes derived from 3-formylchromones using dimethylformamide-thionylchloride complex (**1**) (Scheme –1).



SCHEME -1

Results and Discussion

The most common method of making 3-cyanochromones (**4**) is by dehydration of the corresponding oximes (**2**) derived from 3-formylchromones. A variety dehydrating agents such as refluxing in alcohol in presence of hydrochloric acid[7], sodiumformate in acetic acid[8] and acetic anhydride[9] have been used. All these methods cannot be generalized as the reaction conditions change depending on the substitution pattern in the aromatic ring. This is largely due to the insolubility of the oximes in the reaction media. As a result the yields are poor, product isolation is difficult, require chromatographic separation and sometimes lead to side products like isoxazoles which are expected to form by the nucleophilic attack by the oxime hydroxy group on C_2 of chromone ring with concomitant opening of the chromone ring[10] (Scheme –2). To overcome this difficulty, recently Hsung et.al[11] reported a method of making cyanochromones via acid catalyzed elimination of O-methyloximes (**3**), with an intention to arrest the initial nucleophilic attack by the hydroxy group on C_2 thereby eliminating the possibility of isoxazole formation. However, this method requires the use of expensive O-methoxylamine hydrochloride. Thus, the methods so far reported in literature suffer from disadvantages like use of expensive reagents, strong acidic condition, require longer reaction periods low yields, involve difficult product isolation procedures.



SCHEME -2

In view of the above drawbacks, the synthesis of cyanochromones by dehydration of aldoximes is still of continued interest and we report herein the use of N,N dimethyl chlorosulfitemethaniminium chloride[12,13] (**1**) obtained from dimethylformamide - thionyl chloride as dehydrating agent in the synthesis of 3-cyanochromones (**4**) from the corresponding oximes (**2**). This reagent is relatively unexplored and has been used in the activation of carboxylic acid groups in the synthesis of Cephalosporins[14] and as a dehydrating agent in the synthesis of azetidinones[15]. The reaction of 3-formylchromones[16] with hydroxylaminehydrochloride gives 3-hydroxyiminomethyl-chromones (**2**). These are reacted with the above reagent in dichloromethane at 0°, followed by stirring at room temperature for 3-4 hrs gave the title 3-cyanochromones (**4**) in 70-80% yields. The products are characterized by IR and ^{1}H NMR spectra[17] and the melting points were compared with authentic samples (Table –1).

In conclusion, the present method offers a convenient method for the synthesis of 3-cyanochromones, which involves mild reaction condition, simple work up procedure and excellent yields. The formation of **4** can be explained via the intermediate (**5**) obtained by the reaction of oxime (**2**) with the reagent (**1**).

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra recorded in KBr pellets. ^{1}H NMR spectra on a varian 200MHz instrument with TMS as internal standard, $CDCl_3$ as solvent unless otherwise mentioned. Chemical shifts are expressed in δ ppm.

General procedure for the preparation of N,N-dimethylchlorosulfitemethaniminium chloride[14] (**1**)

To a solution of toluene (50 ml) and dimethylformamide (0.01 mole), thionylchloride (0.011 mole) was added drop wise at 0°C. After 15 minutes the two phases were separated and the lower layer containing the reagent was taken and used in the next step.

General procedure for the preparation of 3-cyanochromones **4**

To a solution of oxime (**2**, 0.01 mole) in dichloromethane (100 ml), above reagent (**1**, 0.015 ml) was added at 0-5°C. The reaction mixture was stirred at room temperature for 3-**4** hrs and the reaction was monitored by TLC. At the end of the reaction, the reaction mixture was quenched with ice cold water, the organic layer washed with saturated $NaHCO_3$ solution followed by water, dried over anhydrous Na_2SO_4 and solvent removed to give **4** as crystalline solid. It was recrystallized from methanol.

All the compounds **4** reported in Table 1 were prepared as per the above procedure.

Table 1. Physical data of 3-cyanochromones[4]

Compound	X	m.p °C (lit)	Yield %
4a	H	176(177)	74
4b	6-CH_3	150(151)	77
4c	6-$(CH_3)_2CH$	119(118)	76
4d	6-CH_3CH_2	123(123)	85
4e	6-Cl,7-CH_3	231(232)	79
4f	6-Cl	211(210)	56
4g	6-F	171(172)	55
4h	6,7-diCH_3	207(207)	78

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17. Representative Spectra: **4a** (IR, KBr): 3089, 2242, 1667cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 7.44-7.6(m, 2H), 7.8(m, 1H), 8.2(dd, 1H), 8.82(s, 1H); **4b** (IR, KBr): 3073, 2240, 1665cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 2.48(s, 3H), 7.5(dd, 1H), 7.6(dd, 1H), 7.95(s, 1H), 8.82(s, 1H); **4c** (IR, KBr): 3079, 2236, 1665cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 1.30(dd, 6H), 3.10(octet, 1H), 7.46(dd, 1H), 7.65(dd, 1H), 8.05(d, 1H), 8.4(d, 1H); **4d** (IR, KBr): 3067, 2234, 1666cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 1.39(t, 3H), 2.8(q, 2H), 7.4(dd, 1H), 7.6(dd, 1H), 8.0(s, 1H), 8.4(s, 1H); **4e** (IR, KBr): 3070, 2240, 1667cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 2.55(s, 3H), 7.6(s, 1H), 8.05(s, 1H), 9.0(s, 1H).

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