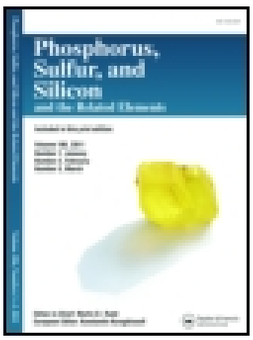

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Choline Hydroxide: An efficient and biodegradable catalyst for the synthesis of 2-amino-3-nitro-4*H*-chromene derivatives in an aqueous medium

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A shortened title of the article (running head): Synthesis of 2-amino-3-nitro-4*H*-chromene derivatives

Abstract

An expedient, eco-friendly and efficient procedure for the synthesis of novel 2-amino-3-nitro-4*H*-chromene derivatives has been developed through the reaction of various 2-hydroxybenzaldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine in the presence of the basic ionic liquid catalyst (choline hydroxide (ChOH)) at room temperature an aqueous medium. The advantageous of this method is a biodegradable and recyclable catalyst, mild, environmentally friendly and high products yields (83-96%) in short reaction times.

Keywords: Choline hydroxide, Green chemistry, 2-amino-3-nitro-4*H*-chromene derivatives, Aqueous medium.

Introduction

An economic and eco-friendly method for the synthesis of bioactive synthetic organic compounds remains as the primary objective in the current research endeavors. The introduction of new methods for the efficient assembling of functionalized intermediates obtained from simple precursors has become necessary due to the ever-increasing complexity of the organic target molecules. An appealing strategy to realize this end is the development of novel tandem reactions, where sequential transformations are performed without isolation or purification of intermediates in a single-step.[1] An especially critical aspect of research is finding and utilizing a single catalyst that promotes in tandem more than one chemical transformation in a selective manner.[2]

Oxygen heterocycles and their derivatives have attracted significant interest owing to their wide range of bioactivities in medicine, bio-organic, and pharmacy. Also, these molecules serve as an important ligands in various catalysts.[3] Among them, 2*H*-chromene and 4*H*-chromene, found in many naturally occurring compounds,[4] play pivotal role in pharmaceutical properties such as antioxidant, antileishmanial, antibacterial, antifungal, hypotensive, anticoagulant, antiviral, diuretic, antiallergenic, and antitumor activities.[5] In addition, 2-Amino-4*H*-chromene derivatives are widely employed as pigments, cosmetics,[6] laser dyes,[7] optical brighteners,[8] and potential biodegradable agrochemicals.[9] Fused chromenes were also used as anticancer,[10] antiviral,[11] anti-inflammatory,[12] and pesticidal compounds.[13] Additionally, due to their photosensitive properties they are also used as fluorescent compounds in laser technology and in monitoring of biomolecules.[14] The structures of a few biologically active 2-amino-4*H*-chromenes possessing anticancer activities are depicted in **Fig 1**.

Insert Figure 1 Here

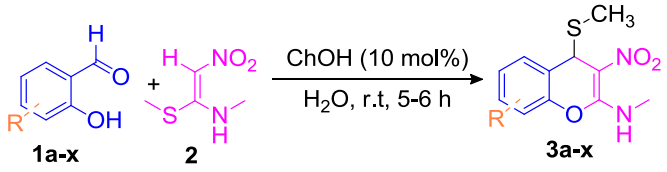
Due to such important biological properties of 2-amino-4*H*-chromenes, it remains as

an important challenging task to develop an easy and efficient method for their synthesis. An extensive survey of the literature revealed that various methods have been developed for the preparation of chromene derivatives.[15] Majority of the reports revealed that the chromene derivatives are synthesized via multicomponent reaction between aldehyde/2-hydroxybenzaldehydes (or isatin) and various deferent active methylene compounds such as barbituric acid, dimedone, cyclohexane-1,3-dione, malononitrile, and alkyl cyanoacetate. Generally synthesis of the chromene derivatives is promoted by bases. Rao et al.[16] have developed a base (DBU) that promoted the formation of two component 2-amino-3-nitro-4*H*-chromene derivatives without any active methylene compounds. This method shows varying degrees of limitations as well as successes. Prolonged reaction times, requirement of excess reagent or catalyst and relatively low yields based on this shows the need alternative milder and environmentally sustainable procedures for the synthesis of 2-amino-3-nitro-4*H*-chromene derivatives.

In recent years, major development has taken place in green chemistry using water and ionic liquids as an environmentally benign reaction media in place of traditional organic reaction media.[17] In this context, Choline hydroxide (ChOH) is an environmentally benign, easy to prepare base, which displays strong basicity. The activity of ChOH has been explored by various groups in organic synthesis due to its economical, easily available, recyclable, inexpensiveness and water compatibility. Recently, it has been used for the thiolysis of epoxides, and synthesis of α-hydroxyphosphonates, biscoumarins, pyrans, pyrimidines and other heterocyclic derivatives.[18]

To the best of our knowledge there are no reports on the synthesis of 2-amino-3-nitro-4*H*-chromene derivatives promoted by ChOH. As part of our ongoing research interest in the development of efficient, inexpensive, new methodologies.[19] We developed an eco-friendly method for synthesis of 2-amino-3-nitro-4*H*-chromene derivatives by the reaction of

substituted 2-hydroxybenzaldehyde and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine in presence of ChOH as catalyst in water at room temperature (**Scheme 1**).



Scheme 1: Synthesis of 2-amino-3-nitro-4*H*-chromene derivatives

Result and discussion

To start with, a model reaction was performed with 2-hydroxybenzaldehyde **1a** (1.0 mmol), and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **2** (1.0 mmol) in the presence of various catalysts. To find out the influence of the catalyst, the two-component reaction was first carried out in water without a catalyst, which resulted in no reaction progress, even after 70 h at room temperature and 30 h at 80 ^{o}C (Table 1, entry 1). After that we attempted the reaction in the presence of organo-base catalysts. DABCO was able to catalyze the reaction in aqueous media (Table 1, entry 2) to afford the product **3a** with 62% yield. The use of DMAP, triethylamine, trimethylamine, piperidine and imidazole gave similar results (Table 1, entries 3 to 6). Under aqueous conditions, even pyridine exhibited some catalytic effect, albeit much slower (Table 1, entry 7). After that we investigated with different inorganic bases, such as K_2CO_3, $CaCO_3$, Cs_2CO_3 and $LiOH.H_2O$ which gave the desired product in the range 60% to 40% yields (Table 1, entry 9-12). Later we turned towards surfactants such as sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) (entries 13,14) these surfactant catalyst afforded the products with yields 60 % and 72 % after 24 h. Hence, there was no synthetic advantage in using surfactants for this chemical transformation. The bases were equally efficient in providing the desired product **3a** in good yield and a short reaction time, however, these basic catalysts are not reusable.

In order to overcome these problems, we turned our attention toward recyclable ILs. It is interesting to note that ChOH (10 mol%) act as remarkable catalysts in aqueous media

giving the best results in terms of yield and reaction rate (Table 1, entry 17). The higher yield of the product was obtained with ChOH because it acts as a homogeneous catalyst in an aqueous medium which helps to improve the solubility of the reactants through hydrogen bonding and hence increases the rate of the reaction. With ChOH as our optimal catalyst, we then systematically evaluated the solvent effect of this reaction using the reaction of 2-hydroxybenzaldehyde **1a** (1.0 mmol), and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **2** (1.0 mmol) as a model. The above reaction was carried out in conventional organic solvents such as DCM, CH_3CN, ethanol, THF and water. Water as a solvent provided the best yields compared to DCM, CH_3CN ethanol and THF (Table 1, entries 17 to 21). To determine the optimum catalyst ChOH loading, model reaction addition of 5 mol% ChOH afforded the product in low yield (Table 1, entry 22), an increase in the amount of ChOH to 10 mol% gave the desired product **3a** in 95% yield; further increase in the amount of catalyst 15 mol% did not increase the product yield. The results are summarized in **Table 1**.

Insert Table 1 Here

After the initial assessment of the optimum reaction conditions, we investigated the scope of the reaction by condensing (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **2** with various commercially available and also prepared substituted 2-hydroxybenzaldehydes having different electronically activating or deactivating substituent's to form a series of 2-amino-3-nitro-4*H*-chromene derivatives (**Table 2**). As illustrated in Table 2, 2-hydroxybenzaldehydes **1a-x** having either an electron-donating or electron-withdrawing group on the aromatic ring gave the corresponding 4*H*-chromene in good yields (Table 2, entries 3a–x). Obviously, the electron-rich 2-hydroxybenzaldehydes provided the desired products in slightly higher yields than the electron-poor 2-hydroxybenzaldehydes along with the shorter reaction time. Among them 2-hydroxybenzaldehydes 3a–3w which were examined, 3-methoxy-2-hydroxybenzaldehyde and 3-ethoxy-2-hydroxybenzaldehyde gave the most desirable results,

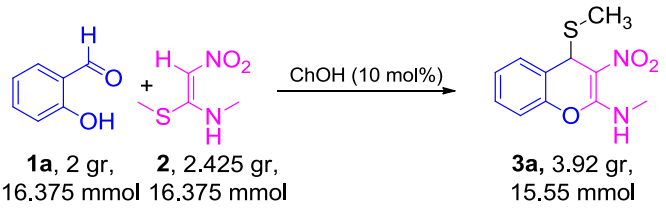
providing 4*H*-chromenes with high yield (Table 2, entry 3e and 3i). This can be attributed to the increased nucleophilicity of the hydroxy moiety in the 2-hydroxybenzaldehydes due to electron-donating substituents. It was observed that 2-hydroxybenzaldehydes having methyl, ethyl and *t*-butyl moiety (Table 2, entry 3f-3h and 3p) on the ring were equally compatible with the catalytic system and were easily introduced to the 4*H*-chromene skeleton with excellent yields. Electron-withdrawing groups such as chloro, bromo, and nitro on the 2-hydroxybenzaldehydes, also smoothly furnished the desired products in good yield (Table 2, entries 3b-3d and 3i-3o). 2-Hydroxybenzaldehydes with fused ring systems were also found to be active under the set of reaction conditions and resulted in adequate yield (entry 3k, Table 2).

In the literature report by using base catalyst, condensation reaction of (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine with 4-alkoxy-2-hydroxybenzaldehyde did not take place.[16] The same substrates (4-methoxy-2-hydroxybenzaldehyde and 4-ethoxy-2-hydroxy-aldehyde) reacted under the optimized conditions (ChOH, 10 mol%) and given good yields (Table 2, entries 3u and 3v). The reaction of benzyloxy substituted at the 4th-position of 2-hydroxybenzaldehydes also gave the corresponding 4*H*-chromenes 3q, 3r, 3s, 3t in 90%, 88%, 87% and 89% yield respectively under the optimized reaction conditions (Table 2, entries 3q, 3r, 3s and 3t). It is noteworthy that, any substituted 2-hydroxybenzaldehyde smoothly furnished the desired products under the optimized conditions

Insert Table 2 Here

To further demonstrate the practicality and efficiency of the developed reaction sequence, a scale-up reaction was performed. Gram-scale synthesis of *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine (**3a**, 3.92 g) could be achieved under the optimized reaction conditions in 95% yield from 2-hydroxybenzaldehyde as the starting material (Scheme 2). This gram scale reaction yield was relatively similar to the submillimolar scale

reaction. It concludes that the present methodology is a practical and scalable synthetic entry to synthesize highly functionalized the 2-amino-3-nitro-4*H*-chromene derivative.



1a, 2 gr, 16.375 mmol **2**, 2.425 gr, 16.375 mmol **3a,** 3.92 gr, 15.55 mmol

Scheme 2: Gram-scale Synthesis of 4*H*-chromene derivative **3a**

The syntheses of all the 4*H*-chromene derivatives were confirmed using ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra, the –NH– proton signals appeared as a broad singlet in the region of 10.46–10.05 ppm. The Ar–CH proton signals also appeared as a singlet in the region of 6.13–5.39 ppm. *N*-methyl protons appeared as a doublet in the region of 3.32–3.21 ppm, and also a sharp signal for *S*-methyl protons appeared as a singlet in the region of 1.96–1.81 ppm, confirming product formation;[16] the remaining proton signals were observed in the expected regions. In the ^{13}C NMR spectra, the Ar–CH carbon signals were observed in the region of 41.28–37.66 ppm, confirming the formation of 4*H*-chromenes. A detailed description of the spectral data for all compounds (3a–3w) is provided in the experimental section.

Experimental

Material and methods

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies and used without further purification. NMR spectra were recorded in parts per million (ppm) in $CDCl_3$ or DMSO-d_6 on a Jeol JNM ECP 600 or Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Standard abbreviations were used to denote signal multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and brs = broad singnal) and the coupling constants are given in hertz (Hz). Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an

Electrothermal-9100 (Japan) instrument and are uncorrected. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra of products 3b-3x (Figure S 1 – S 40)

Procedure for the preparation of ChOH[18b]

ChOH was synthesized according to a literature procedure. Choline chloride (7 mmol) was dissolved in methanol (15 mL), KOH (7 mmol) was added slowly at room temperature, and the mixture was heated at reflux for overnight. After mixture cooling to room temperature, the reaction mixture was filtered to remove solid KCl, concentrated to remove methanol until the weight of the residue remained constant, and used without further purification. ChOH was characterized using a mass spectrum, it is provided in the Supporting information. The massspectra showed good agreement with the reported results. The mass spectrum clearly showed the exact molecular weight of the ChOH.[18b] MS (FAB, m/z): $[M+H]^+$ calcd for $C_5H_{15}NO_2$, 122.11; found 122.09.

Synthesis of N-Methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (3a)

The ChOH 10 mol% in water (3 mL) was added to a mixture of 2-hydroxybenzaldehyde (**1a**, 1.0 mmol) and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**2**, 1.0 mmol) (1 mmol) in a 10 mL reaction flask equipped with a magnetic stirrer. The resulting mixture was stirred for the appropriate time at room temperature. After completion of the reaction (confirmed by TLC, hexanes: EtOAc 1:1), the solid product was filtered and washed with water. The obtained crude product was recrystallized from ethanol to yield the pure product. The same method was adopted for the synthesis of all the targeted products **3a-x**.

Spectral characterization

*N-Methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3a**):* Yellow solid; Yield: 95%, m.p. 154–155 °C (152–153 °C)[16] ; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.29 (brs, 1H), 7.43 (dd, J = 7.6, 1.6 Hz, 1H), 7.30 (td, J = 7.8, 1.7 Hz, 1H), 7.25 (td, J = 7.5, 1.2 Hz, 1H), 7.13 (dd, J =

8.1, 1.0 Hz, 1H), 5.50 (s, 1H), 3.23 (d, *J* = 5.2 Hz, 3H), 1.88 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.15, 148.99, 129.31, 128.87, 126.32, 122.59, 115.88, 105.98, 40.52 (Ar-CH), 28.13, 12.50; HRMS (ESI, m/z): calcd for $C_{11}H_{12}N_2O_3S$ ($M+H^+$) 252.0569, found: 252.0574.

*6-Chloro-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3b**):* Yellow solid; Yield: 88%, m.p. 187–189 °C (185–187 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (brs, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.26 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 5.43 (s, 1H), 3.22 (d, *J* = 5.2 Hz, 3H), 1.89 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.79, 147.43, 131.45, 129.03, 128.95, 124.39, 117.30, 105.32, 40.34 (Ar-CH), 28.19, 12.57; HRMS (ESI, m/z): calcd for $C_{11}H_{11}ClN_2O_3S$ ($M+H^+$) 286.0179, found: 286.0175.

*6-Bromo-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3c**):* Yellow solid; Yield: 90%, m.p. 156–158 °C (154–157 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (brs, 1H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 5.44 (s, 1H), 3.22 (d, *J* = 5.2 Hz, 3H), 1.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.76, 147.99, 131.94, 131.92, 124.85, 118.87, 117.62, 105.40, 40.27 (Ar-CH), 28.17, 12.63; HRMS (ESI, m/z): calcd for $C_{11}H_{11}BrN_2O_3S$ ($M+H^+$) 329.9674, found: 329.9680.

*N-Methyl-4-(methylthio)-3,6-dinitro-4H-chromen-2-amine (**3d**):* Yellow solid; Yield: 85%, m.p. 189–191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.16 (brs, 1H), 8.36 (d, *J* = 2.6 Hz, 1H), 8.20 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 5.54 (s, 1H), 3.26 (d, *J* = 5.2 Hz, 3H), 1.96 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.15, 152.47, 145.62, 125.30, 124.70, 124.39, 117.13, 105.02, 40.38 (Ar-CH), 28.35, 13.04; HRMS (ESI, m/z): calcd for $C_{11}H_{11}N_3O_5S$ ($M+H^+$) 297.0419, found: 297.0415.

*8-Methoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3e**):* Yellow solid; Yield: 96%, m.p. 146–148 °C (144–146 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.22 (brs, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.49 (s, 1H), 3.91 (s, 3H), 3.25 (d, *J* = 5.2 Hz, 3H), 1.89 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ

159.84, 147.25, 138.33, 125.88, 123.44, 119.91, 110.65, 105.66, 55.97, 40.39 (Ar-CH), 27.95, 12.26; HRMS (ESI, m/z): calcd for $C_{12}H_{14}N_2O_4S$ ($M+H^+$) 282.0674, found: 282.0680.

*N,6-Dimethyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3f**):* Yellow solid; Yield: 94%, m.p. 154-157 ºC (154–157 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (br s, 1H), 7.21 (s, 1H), 7.10 (br d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 5.44 (s, 1H), 3.22 (d, J = 5.2 Hz, 3H), 2.36 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.10, 146.98, 136.06, 129.52, 129.26, 121.95, 115.45, 105.93, 40.47 (Ar-CH), 28.08, 20.81, 12.23; HRMS (ESI, m/z): calcd for $C_{12}H_{14}N_2O_3S$ ($M+H^+$) 266.0725, found: 266.0719.

*6-Ethyl-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3g**):* Yellow solid; Yield: 93%, m.p. 163–166 ºC (163–166 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.22 (br s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.48 (s, 1H), 3.22 (d, J = 5.1 Hz, 3H), 2.66 (q, J = 7.5 Hz, 2H), 1.87 (s, 3H), 1.2 (t, J = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.10, 147.01, 142.32, 128.2, 128.01, 121.90, 115.50, 105.80, 40.51 (Ar-CH), 28.10, 27.92, 15.53, 12.30; HRMS (ESI, m/z): calcd for $C_{13}H_{16}N_2O_3S$ ($M+H^+$) 280.0882, found: 280.0888.

*6-Tert-butyl-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3h**):* Yellow solid; Yield: 93%, m.p. mp 166-170 ºC (166–170 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 5.50 (s, 1H), 3.22 (d, J = 5.4 Hz, 3H), 1.88 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.21, 149.30, 146.72, 125.80, 125.71, 121.52, 115.20, 106.11, 40.70 (Ar-CH), 34.51, 31.30, 27.92, 12.50; HRMS (ESI, m/z): calcd for $C_{15}H_{20}N_2O_3S$ ($M+H^+$) 308.1195, found: 308.1191.

*8-Ethoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3i**):* Yellow solid; Yield: 95%, m.p. 163–165°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 7.1 Hz, 1H), 6.84 (dd, J = 8.1, 0.9 Hz, 1H), 5.47 (s, 1H), 4.10 (q, 7.0 Hz, 2H), 3.25 (d, J = 5.2 Hz, 3H), 1.88 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ

160.08, 146.84, 138.69, 126.06, 123.64, 119.98, 111.89, 105.91, 64.66, 40.63 (Ar-CH), 28.05, 14.90, 12.48; HRMS (ESI, m/z): calcd for $C_{13}H_{16}N_2O_4S$ ($M+H^+$) : 296.0831, found: 296.0838.

N^7,N^7-Diethyl-N^2-methyl-4-(methylthio)-3-nitro-4H-chromene-2,7-diamine ***(3j):*** Yellow solid; Yield: 90%, m.p. 140–143°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.41 (brs, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.54 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 5.40 (s, 1H), 3.35 (q, *J* = 7.5 Hz, 4H), 3.22 (d, *J* = 5.2 Hz, 3H), 1.86 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.38, 154.67, 150.24, 129.60, 110.00, 106.88, 106.25, 97.24, 45.59, 44.48, 40.37, 28.08, 12.52; HRMS (ESI, m/z): calcd for $C_{15}H_{21}N_3O_3S$ ($M+H^+$) 323.1304, found: 323.1309.

N-Methyl-1-(methylthio)-2-nitro-1H-benzo[f]chromen-3-amine ***(3k):*** Yellow solid; Yield: 91%, m.p. 195–197°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.26 (brs, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.53 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 6.13 (s, 1H), 3.28 (d, *J* = 5.2 Hz, 3H), 1.81 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.93, 146.82, 131.74, 130.13, 129.76, 128.82, 127.71, 126.15, 123.75, 115.44, 114.60, 106.39, 37.66 (Ar-CH), 28.18, 12.03; HRMS (ESI, m/z): calcd for $C_{15}H_{14}N_2O_3S$ ($M+H^+$) 302.0725, found: 302.0720.

6,8-Dichloro-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine ***(3l):*** Yellow solid; Yield: 83%, m.p. 206–208°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 5.44 (s, 1H), 3.28 (d, *J* = 5.2 Hz, 3H), 1.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.36, 143.57, 131.25, 129.29, 127.24, 125.99, 122.47, 105.08, 40.55 (Ar-CH), 28.44, 12.88; HRMS (ESI, m/z): calcd for $C_{11}H_{10}Cl_2N_2O_3S$ ($M+H^+$) 319.9789, found: 319.9795.

8-Bromo-6-chloro-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine ***(3m):*** Yellow solid; Yield: 85%, m.p. 209–211°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 5.45 (s, 1H), 3.30 (d, *J* = 5.3 Hz, 3H), 1.95 (s,

3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.57, 144.67, 132.14, 131.65, 127.98, 125.98, 110.74, 105.20, 40.73 (Ar-CH), 28.63, 12.98; HRMS (ESI, m/z): calcd for $C_{11}H_{10}BrClN_2O_3S$ ($M+H^+$) 363.9284, found: 363.9279.

*6,8-Dibromo-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3n**):* Yellow solid; Yield: 86%, m.p. 196–198°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.06 (brs, 1H), 7.66 (d, *J* = 1.0 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 5.44 (s, 1H), 3.30 (d, *J* = 5.2 Hz, 3H), 1.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.53, 145.14, 134.82, 130.93, 126.37, 118.78, 111.02, 105.24, 40.59 (Ar-CH), 28.64, 12.98; HRMS (ESI, m/z): calcd for $C_{11}H_{10}Br_2N_2O_3S$ ($M+H^+$) 407.8779, found: 407.8786.

*6-Bromo-8-methoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3o**):* Yellow solid; Yield: 91%, m.p. 193–195°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.15 (brs, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 5.39 (s, 1H), 3.90 (s, 3H), 3.23 (d, *J* = 5.2 Hz, 3H), 1.89 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.64, 148.07, 137.68, 125.12, 122.67, 118.40, 114.39, 105.29, 56.50, 40.32 (Ar-CH), 28.20, 12.51; HRMS (ESI, m/z): calcd for $C_{12}H_{13}BrN_2O_4S$ ($M+H^+$) 359.9779, found: 359.9774.

*6,8-Di-tert-butyl-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3p**):* Yellow solid; Yield: 93%, m.p. 173–175°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.46 (brs, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 5.49 (s, 1H), 3.32 (d, *J* = 5.3 Hz, 3H), 1.88 (s, 3H), 1.47 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.29, 148.61, 145.87, 136.29, 124.25, 123.82, 122.34, 106.12, 41.28 (Ar-CH), 34.97, 34.83, 31.46, 30.05, 29.34, 12.75; HRMS (ESI, m/z): calcd for $C_{19}H_{28}N_2O_3S$ ($M+H^+$) 364.1821, found: 364.1827.

*7-(Benzyloxy)-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3q**):* Yellow solid; Yield: 90%, m.p. 144–146°C (144 °C)[16]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (brs, 1H), 7.44 – 7.39 (m, 4H), 7.37 – 7.34 (m, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 5.45 (s, 1H), 5.08 (s, 2H), 3.21 (d, *J* = 5.2 Hz, 3H), 1.86 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.08, 159.06, 149.57, 136.20, 130.03, 128.86, 128.45, 127.63, 114.59, 113.67, 106.35, 101.96, 70.58, 40.23 (Ar-CH), 28.16, 12.38; HRMS (ESI, m/z): calcd for $C_{18}H_{18}N_2O_4S$ ($M+H^+$) 358.0987, found: 358.0994.

7-(4-Nitrobenzyloxy)-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine ***(3r)****:* Yellow solid; Yield: 87%, m.p. 193–195°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.29 (brs, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 5.46 (s, 1H), 5.19 (s, 2H), 3.22 (d, *J* = 5.2 Hz, 3H), 1.88 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.01, 158.41, 149.65, 147.95, 143.60, 130.30, 127.77, 124.11, 115.56, 113.39, 106.30, 102.21, 69.24, 40.22 (Ar-CH), 28.15, 12.52; HRMS (ESI, m/z): calcd for $C_{18}H_{17}N_3O_6S$ ($M+H^+$) 403.0838, found: 403.0833.

7-(4-Fluorobenzyloxy)-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine ***(3s)****:* Yellow solid; Yield: 87%, m.p. 167–169°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (brs, 1H), 7.42 – 7.38 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.88 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 5.45 (s, 1H), 5.03 (s, 2H), 3.21 (d, *J* = 5.2 Hz, 3H), 1.86 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.78 (d, *J* = 246.9 Hz), 160.06, 158.87, 149.58, 131.96 (d, *J* = 3.3 Hz), 130.08, 129.54 (d, *J* = 8.4 Hz), 115.81 (d, *J* = 21.7 Hz), 114.78, 113.58, 106.32, 101.98, 69.92, 40.21 (Ar-CH), 28.15, 12.39; HRMS (ESI, m/z): calcd for $C_{18}H_{17}FN_2O_4S$ ($M+H^+$) 376.0893, found: 376.0899.

7-((Naphthalen-1-yl)methoxy)-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine ***(3t)****:* Yellow solid; Yield: 90%, m.p. 198–200°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.30 (brs, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.95 – 7.83 (m, 2H), 7.62 – 7.52 (m, 3H), 7.49 (dd, *J* = 8.2, 6.7 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 5.51 (s, 2H), 5.47 (s, 1H), 3.21 (d, *J* = 5.1 Hz, 3H), 1.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.12, 159.17, 149.65, 135.14, 133.97, 131.58, 130.09, 129.53, 128.98, 126.86, 126.77, 126.21, 125.46, 123.61, 114.90, 113.72, 106.42, 102.14, 69.32, 40.31 (Ar-CH), 28.14, 12.52;

HRMS (ESI, m/z): calcd for $C_{22}H_{20}N_2O_4S$ ($M+H^+$) 408.1144, found: 408.1139.

*7-Methoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3u**):* Yellow solid; Yield: 90%, m.p. 142–144°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (brs, 1H), 7.33 (d, J = 8.6 Hz, 1H), 6.82 (dd, J = 8.6, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 5.45 (s, 1H), 3.83 (s, 3H), 3.22 (d, J = 5.2 Hz, 3H), 1.86 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.11, 159.95, 149.63, 130.00, 114.27, 112.98, 106.41, 100.94, 55.82, 40.22 (Ar-CH), 28.15, 12.34; HRMS (ESI, m/z): calcd for $C_{12}H_{14}N_2O_4S$ ($M+H^+$) 282.0674, found: 282.0680.

*7-Ethoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3v**):* Yellow solid; Yield: 89%, m.p. 142–144°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (brs, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.81 (dd, J = 8.6, 2.5 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 5.44 (s, 1H), 4.26 – 3.87 (m, 2H), 3.21 (d, J = 5.2 Hz, 3H), 1.85 (s, 3H) 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.06, 159.90, 149.58, 129.95, 114.22, 112.93, 106.36, 100.89, 64.64, 40.61 (Ar-CH), 28.03, 14.88, 12.46; HRMS (ESI, m/z): calcd for $C_{13}H_{16}N_2O_4S$ ($M+H^+$) 296.0831, found: 296.0836.

*7-Butoxy-N-methyl-4-(methylthio)-3-nitro-4H-chromen-2-amine (**3w**):* Yellow solid; Yield: 89%, m.p. 124–126°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (brs, 1H), 7.31 (d, J = 8.6 Hz, 1H), 6.80 (dd, J = 8.6, 2.5 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.45 (s, 1H), 3.97 (t, J = 6.5 Hz, 2H), 3.22 (d, J = 5.2 Hz, 3H), 1.85 (s, 3H), 1.80–1.75 (m, 2H), 1.53 – 1.47 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.15, 159.53, 149.60, 129.90, 113.96, 113.46, 106.45, 101.39, 68.34, 40.25 (Ar-CH), 31.26, 28.13, 19.33, 13.96, 12.34; HRMS (ESI, m/z): calcd for $C_{15}H_{20}N_2O_4S$ ($M+H^+$) 324.1144, found: 324.1150.

*N-methyl-4-(methylthio)-3-nitro-7-(octyloxy)-4H-chromen-2-amine (**3x**):* Yellow solid; Yield: 88%, m.p. 119–120°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (brs, 1H), 7.31 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.6, 2.5 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.45 (s, 1H), 3.95 (t, J = 6.5 Hz, 2H), 3.21 (d, J = 5.2 Hz, 3H), 1.85 (s, 3H), 1.81-1.76 (m, 2H), 1.49 – 1.41 (m, 2H), 1.39 –

1.23 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.15, 159.53, 149.60, 129.90, 113.96, 113.46, 106.45, 101.39, 68.66, 40.25 (Ar-CH), 31.94, 29.45, 29.36, 29.22, 28.13, 26.13, 22.80, 14.25, 12.34; HRMS (ESI, m/z): calcd for $C_{19}H_{28}N_2O_4S$ ($M+H^+$) 380.177, found: 380.177.

Recycling of choline hydroxide

Choline hydroxide (10 mol %) was added to a stirred solution of 2-hydroxybenzaldehyde (1a, 1.0 mmol) and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (2, 1.0 mmol) (1 mmol) in water (3 mL). The reaction was stirred at r.t. After completion of the reaction (confirmed by TLC, hexanes: EtOAc 1:1), the solid product was filtered. Filtrate choline hydroxide was washed with dry diethyl ether (2X2 mL). Fresh 2-hydroxybenzaldehyde (1a, 1.0 mmol) and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (2, 1.0 mmol) were added to the IL phase for the second run of the reaction. The third run was performed as described for the second run.

Conclusion

In conclusion, we have demonstrated an efficient and eco-friendly protocol for the synthesis of *N*-Methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine derivatives in an aqueous medium through the choline hydroxide ionic liquid catalyzed reaction of 2-hydroxybenzaldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine. This new method is endowed with advantages such as low cost, use of non-toxic catalyst, green reaction medium, easy work-up process, environmentally benign reaction conditions and good yields. The procedure provides access to compounds that are useful in heterocyclic synthesis.

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Supporting Information

Experimental detail, ^{1}H and ^{13}C NMR spectra have been provided in supporting information.

Fig.1. Selected examples of pharmaceutically active 2-amino-4*H*-chromene derivatives

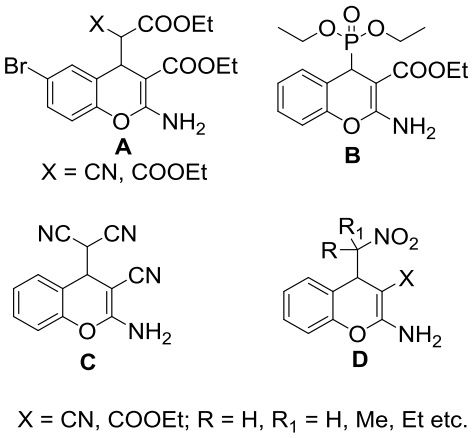
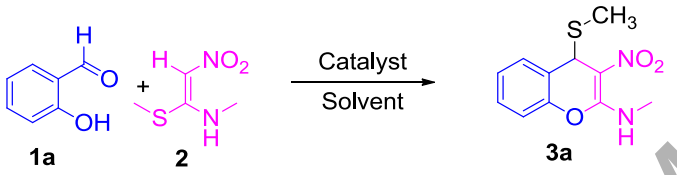


Table 1: Effect of various catalysts on the synthesis of compound **3a** at room temperature.[a]



Entry	Catalyst	mol %	Solvent	Time (h)	Yield (%)[b]
1	-[c]	-	H_2O	70 (30[d])	Nr[e]
2	DABCO	20	H_2O	16	62
3	DMAP	20	H_2O	24	58
4	Triethylamine	30	H_2O	24	60
5	Trimethylamine	20	H_2O	17	55
6	Piperidine	20	H_2O	19	70
7	Pyridine	20	H_2O	17	Traces
8	Imidazole	20	H_2O	15	80
9	K_2CO_3	20	H_2O	16	79[d]
10	$CaCO_3$	20	H_2O	24	60[d]

11	Cs_2CO_3	10	H_2O	24	72[d]
12	$LiOH.H_2O$	20	H_2O	40	52 (60)[d]
13	SDS[f]	20	H_2O	24	59
14	CTAB[g]	20	H_2O	24	72
15	ChCl:Urea	10	-	6	Nr[e]
16	ChCl	40	H_2O	4	Traces
17	ChOH	10	H_2O	5	95
18	ChOH	10	CH_2Cl_2	5	40
19	ChOH	10	CH_3CN	6	50
20	ChOH	10	Ethanol	6	57
21	ChOH	10	THF	6	71
22	ChOH	5	H_2O	5	85
23	ChOH	15	H_2O	5	92

[a]Reaction conditions: 2-hydroxybenzaldehyde (1, 1 mmol), (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (2, 1 mmol), solvent (3 mL), R.T.

[b]Yield of the isolated product.

[c]No catalyst.

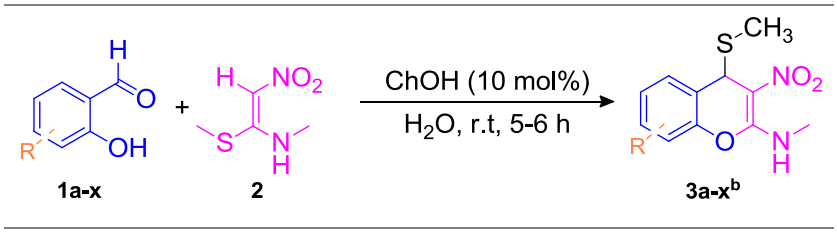
[d]Reaction at 80 ^oC.

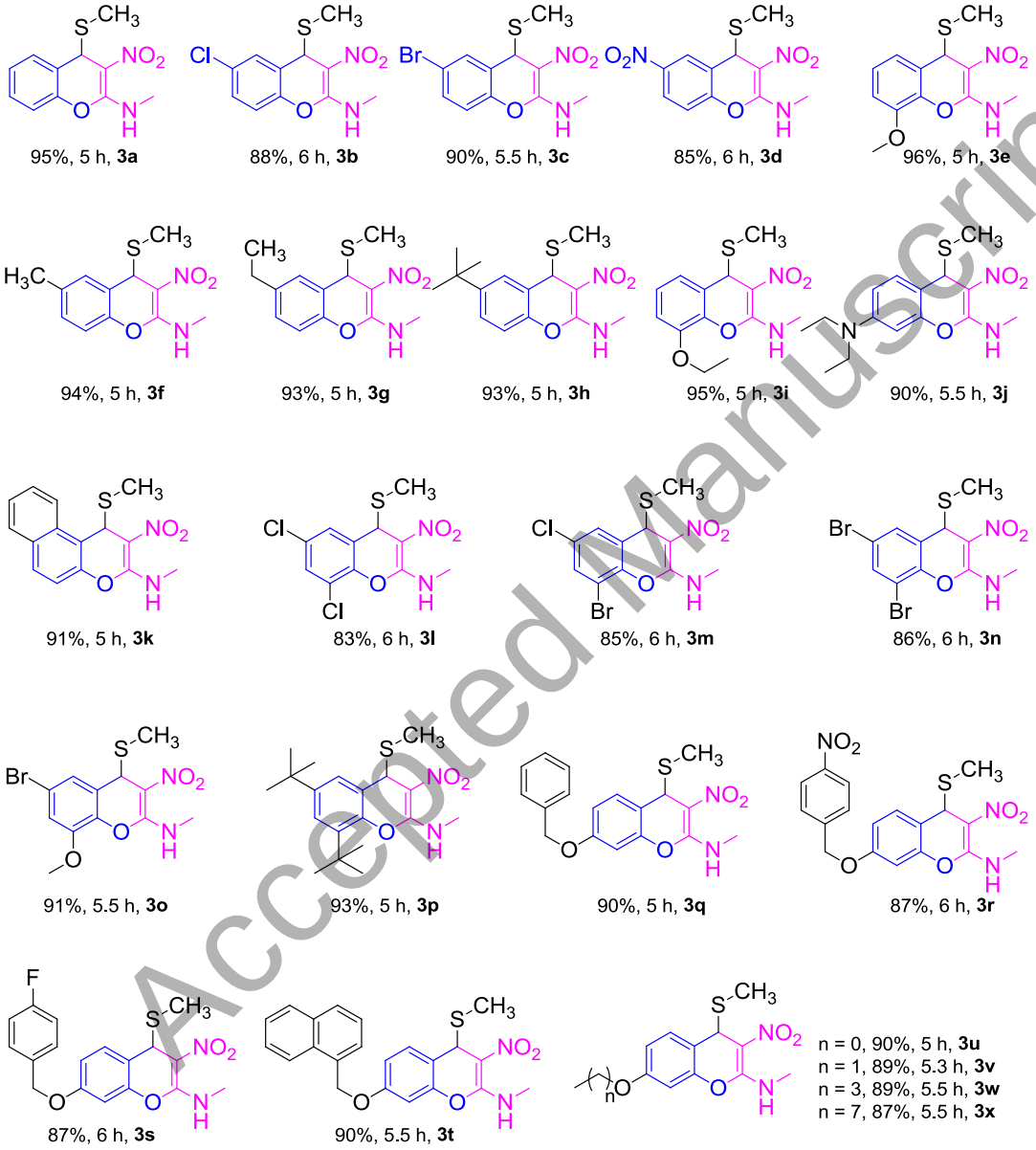
[e]No reaction.

[f]Sodium dodecyl sulfate (SDS).

[g]Cetyltrimethylammonium bromide (CTAB).

Table 2: Synthesis of 2-amino-3-nitro-4*H*-chromenes **(3a–x)** from different substituted 2-hydroxybenzaldehyde (**1a–x)** and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **2**.[a]





[a]Reaction conditions: 2-hydroxybenzaldehyde (1, 1 mmol), (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (2, 1 mmol), ChOH (10mol%) H_2O (3 mL), R.T; [b]Yield of the isolated product.