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Journal of Applied Chemical Research, 14, 3, 19-25 (2020)

One-pot Synthesis of 2-amino-4H-chromene Derivatives as Potential Antimicrobial Agents using DABCO-CuCl Complex as an Effective Catalyst

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(Received 14Nov. 2019; Final revised received 12Feb.2020)

Abstract

A new and efficient synthesis of 2-amino-4H-chromene derivativeswhich have remarkable pharmacological properties is developed by one-pot three-component efficient reaction between aldehydes, malononitrile, and α or β-naphthol in MeOH as solvent using DABCO-CuCl complex as an effective catalyst at room temperature. The structures of synthesized compounds were characterized by techniques of IR, ^{1}H-NMR, Mass and elemental analysis. This method provides an efficient improved pathway for the synthesis of chromenes in the terms of excellent yields, short reaction times and reusability catalyst.

Keywords: Multicomponent reactions (MCRs), DABCO-CuCl complex, Chromenes derivatives, One-pot synthesis, Antimicrobial agents.

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Introduction

Design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties are a major challenge of modern drug discovery. 2-amino-4H-Chromenes are an important class of heterocyclic compounds having important biological activities [1]. During the last decade, such compounds had shown interesting pharmacological properties including antimicrobial, antiviral, mutagenicity, antiproliferative, antitumor, cancer therapy and Central nervous system activity [2].In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [3].

The increasing attention during the last decades for environmental protection has led modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost whilst using nontoxic reagents, solvents and catalysts. One of the tools used to combine economic aspects with the environmental ones is the multicomponent reaction (MCR) strategy; this process consist of two or more synthetic steps which are carried out without isolation of any intermediate, thus reducing time, saving money, energy and raw materials [4].Widespread interest in the 4H-chromene containing structures has led to extensive study of their synthesis [5].Along this line, several procedures have been reported for the synthesis of 2-amino-4H chromene derivatives by refluxing malononitrile, aldehyde and activated phenol in the presence of hazardous organic bases like piperidine for several hours [6].

A literature survey revealed that several modified procedures using CTACl [7], TEBA [8], and γ alumina[9] as catalyst have been recently reported but all these methods require long refluxing hours.DABCO has been used recently as the most common catalyst in organic synthesis, for example, in the Baillys–Hillman reaction and the selective cleavage of esters [10,11]. One of the remarkable features of DABCO is its efficient activity under neat conditions or high-concentration conditions. Thus, we considered DABCO-CuCl complex (Figure 1) to be an ideal base for effecting one-pot synthesis of 4H-chromene derivatives. As a part of our work on one-pot multicomponent reactions (MCRs) and developing new selective and environmental friendly methodologies for the synthesis of various heterocyclic compounds, we describe herein the DABCO-mediated three-componenet coupling of naphthols, aromatic aldehydes and malononitrile in methanol at room temperature to afford 2-amino-4H-chromenes derivatives in excellent yields.

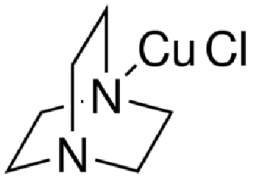


Figure 1. Structure formula (1,4-Diazabicyclo[2.2.2]octane)copper(I)chloride (DABCO-CuCl complex.

Experimental

Material and equipment

Chemicals were supplied from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. (USA). Melting points were taken as uncorrected using a digital Electrothermal melting point apparatus (*model 9100*, *Electrothermal Engineering Ltd*., Essex, *UK*). ^{1}H-NMR spectra were obtained using a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (Internal standard: TMS) and values were expressed in ppm. The IR spectra were recorded using a Thermo Nicolet FT-IR (model *Nexus-870,* Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrometer. Mass spectra were obtained using an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington, USA). The purity of compounds was confirmed by TLC. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. Elemental analyses were recorded using a Perkin-Elmer, CHN elemental analyzer model 2400 within ±0.4% of theoretical values for C, H and N. All products were characterized by spectra and physical data.

General procedure for the synthesis of 2-amino- 2-chromenes (Scheme 1)

A mixture of an appropriate benzaldehyde (1 mmol), malononitrile (79 mg, 1.1 mmol), α- or β-naphthol (172 mg, 1.2 mmol) and DABCO-CuCl complex (0.02 g), in methanol (5 mL) was stirred and refluxed for appropriate time as indicated in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and 0.5 ml of water was added; the precipitate was filtered and washed with methanol. The crude products were purified by re-crystallization in ethanol.

Selected spectral data

2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile **(4a)**

IR (KBr) (ν_{max}, cm^{-1}): 3465, 3318, 3010, 2910, 2200, 1660, 1600, 1550, 1450, 1370, 1267, 1100, 1022, 811, 744; ^{1}H-NMR ($CDCl_3$) (ppm): 4.90 (s, 1H, H-4), 7.10 (s 2H, NH_2), 7.07–7.12 (m, 6H, H-5, 2′, 3′, 4′, 5́), 7.56–7.66 (m, 3H, H-6,8,9), 7.94 (d, 1H, J= 8. 4, H-7), 8.23 (d, 1H, J = 8. 4, H-10); Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.66; H, 4.90; N, 9.53. MS: m/z (regulatory intensity): 298 (100), 299 (23).

2-amino-4-(4-nitro-phenyl)-4H-benzo[h]chromene-3-carbonitrile **(4e)**

IR (KBr) (ν_{max}, cm^{-1}): 3450, 3320, 2170, 1660, 1600, 1575,1530, 1500, 1352, 1270, 1190, 1100, 800, 770; δ_H (ppm): 5.12 (s, 1H, H-4), 7.29 (s, 2H, NH_2), 7.05 (d, 1H, J=8.6, H-5), 7.5–7.7 (m, 3H, H-6,8,9), 7.52 (d, 2H, H- 2′, 6′), 7.90 (d, 1H, J= 8.4, H-7), 8.15 (d, 2H, H-3′, 5′), 8.27 (d, 1H, J= 8.6, H-10); Anal. Calcd. for $C_{20}H_{13}N_3O_3$: C, 69.96; H, 3.82; N, 12.24. Found: C, 70.16; H, 3.90; N, 12.43. MS: m/z (regulatory intensity): 343 (100), 344 (23).

Reusability of DABCO-CuCl

In the following, the reusability of DABCO-CuCl investigated. At the end of the reaction, the catalyst recovered by a simple filtration, washed with methanol, dried and subjected to a second run of the reaction process. To assure that the catalysts were not dissolved in methanol, they were weighed after filtration and before use and reuse for the next reaction. In Table 1, the comparison of efficiency of DABCO-CuCl in synthesis of **4a** after five times is reported. As shown in Table 2 the first reaction using recovered DABCO-CuCl afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields were gradually decreased.

Table 1. Reuse of the DABCO-CuCl for synthesis of 2-amino- 2-chromene (**4a**).

Entry	Time(h)	Yield(%)[a]
1	1.5	95
2	2	94
3	3	92
4	4	85
5	4.5	80

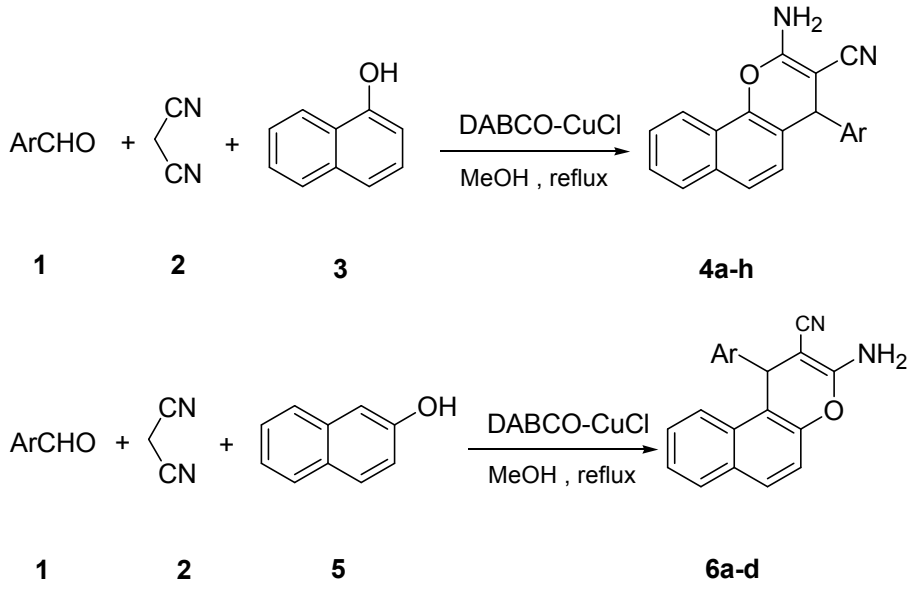
(a) Isolated yields

Results and Discussion

Based on previous studies to develop new and heterogeneous catalyst systems for fine chemical preparation,we have studied the one-pot three-component condensation reaction of aldehydes, malonitrile and α- or β-naphthol using DABCO-CuCl complex as available, green and inexpensive

catalyst in good yields for synthesizing of 2-amino-4H-chromenes. Synthesis of the target compounds is outlined in Scheme 1.

To choose the most appropriate medium in this heterocyclization reaction, the catalyst-assisted reaction was examined in EtOH, glycol, tetrahydrofuran (THF), DMF and MeOH as solvents. The reaction in MeOH resulted in higher yields and shorter reaction time than others. Therefore, MeOH was chosen as the solvent of this reaction.



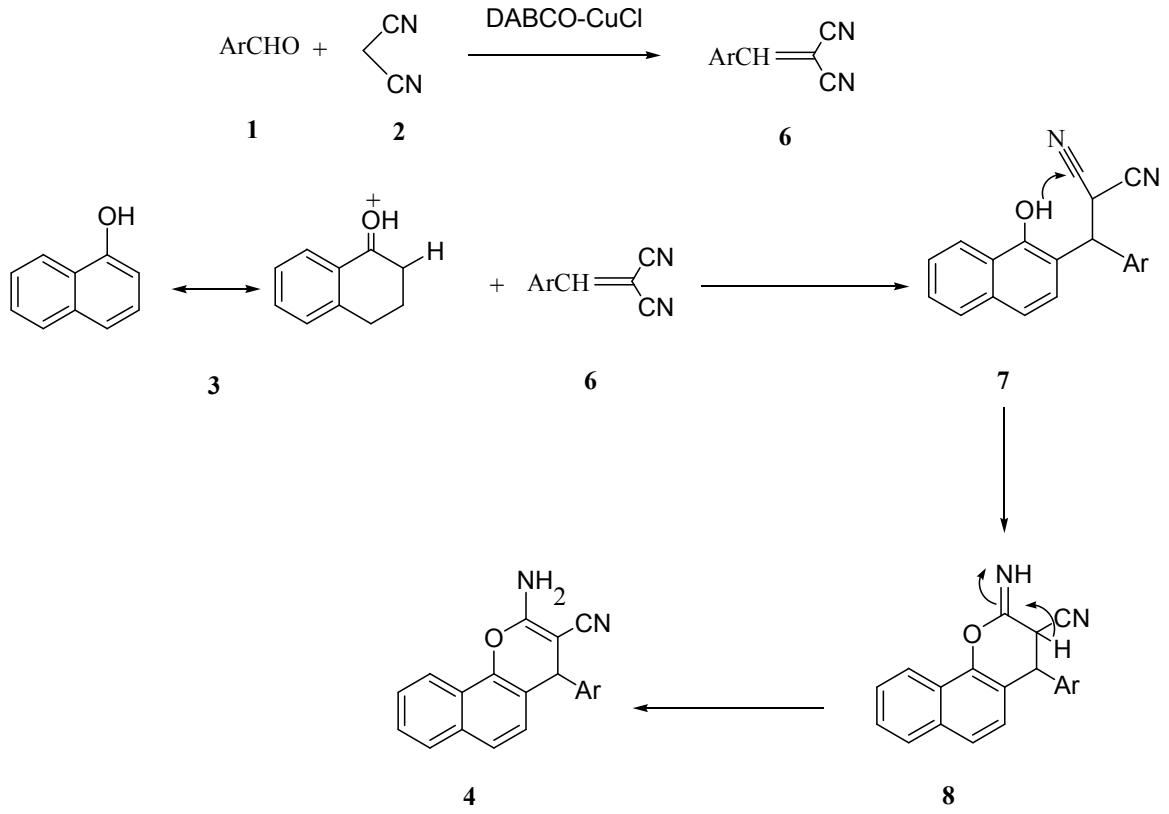
Scheme 1. Synthesis of substituted 2-amino-4H-chromene.

It is noteworthy to mention that, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in high yields in relatively short reaction times. The results are shown in Table 2.

Table 2. Synthesis of substituted 2-amino-chromenes catalyzed by DABCO-CuCl complex.

Entry	R	Substrate	product	Time (min)	Yield (%)	m.p. (°C) Observed	Reported
1	C_6H_5	α-naphthol	4a	30	95	209	210-211[12]
2	3-$NO_2C_6H_4$	α-naphthol	4b	30	96	212	212-214[12]
3	4-$MeOC_6H_4$	α-naphthol	4c	30	92	194-195	195-196[13]
4	4-ClC_6H_4	α-naphthol	4d	30	96	231-232	231-232[12]
5	4-$NO_2C_6H_4$	α- naphthol	4e	30	95	242	239-241[12]
6	4-MeC_6H_4	α-naphthol	4f	30	91	207-209	205-206[13]
7	3-ClC_6H_4	α-naphthol	4g	30	94	218-220	229-230[12]
8	2-ClC_6H_4	α-naphthol	4h	30	93	237-238	236-237[12]
9	C_6H_5	β-naphthol	6a	30	95	280--281	280-282[12]
10	4-$NO_2C_6H_4$	β-naphthol	6b	30	96	186-187	185-186[12]
11	4-ClC_6H_4	β-naphthol	6c	30	92	208-209	206-208[12]
12	2-ClC_6H_4	β-naphthol	6d	30	96	260-262	259-261[12]

A plausible mechanism for this reaction has been suggested in Scheme2. In first step, the aldehyde (**1**) condenses with malononitrile (**2**) to afford a-cyanocinnamonitrile derivative (**6**). Then the phenol ortho C-alkylation happens using the electrophilic C=C double bond and results in the intermediate (**7**). The intermediate (**7**) was cyclized by the nucleophilic attack of OH group on the cyano (CN) moiety and gave the intermediate (**8**). Finally, the expected products (**4**) were obtained.



Scheme 2. Mechanism for the synthesis of substituted 2-amino-chromenes.

Conclusion

In conclusion, DABCO-CuCl complex can serve as an efficient catalyst for the synthesis of 2-amino-4H-chromenes. A simple experimental and work-up procedure,cleaner reaction, mild reaction conditions and also high yields of products are all advantages of this method which makes it useful and noteworthy for the synthesis of these compounds.

References

[1] G.R. Green, J.M. Evans, A.K. Vong, *In Comprehensive HeterocyclicChemistry II*; Pergamon Press: Oxford, Vol. 5, pp 469 (1995).

[2] B.D. Rupnar, P.B. Rokade, P.D. Gaikwad, P.P. Pangrikar, *Inter. J. Chem. Environ. Bio. Sci.*,2, 83 (2014)

[3] C.S. Konkoy, D.B. Fisck, S.X. Cai, N.C. Lan, J.F.W. Keana, *WO 0075123,Chem. Abstr*., 134, 29313a (2000).

[4] (a) N. Hall, *Science*, 266, 32 (1994); (b) A. Domling, E. Herdtweck, I. Ugi, *Acta. Chem. Scand*., 52, 107 (1998).

[5] L. Moa, S. Ahadi, A. Bazgir, *Tetrahedron Lett.* 51(48), 6270 (2010).

[6] A.G.A. Elagamay, F.M.A.A. El-Taweel, *Indian J. Chem. B*., 29, 885 (1990).

[7] R. Ballini, G. Bosica, M. L. Conforti, R. Maggi, A. Mazzacanni, P. Righi, G. Sartori, *Tetrahedron*, 57, 1395 (2001).

[8] D.Q. Shi, S. Zhang, Q.Y. Zhuang, S.J. Tu, H.W. Hu, *Youji Huaxue*., 23, 809 (2003).

[9] R. Maggi, R. Ballini, G. Sartori, R. Sartorio, *Tetrahedron Lett*., 45, 2297 (2004).

[10] (a) D. Basavaiah, A.J. Rao, T. Satyanarayana, *Chem. Rev.,* 103, 811 (2003); (b) V. Kannan, *Synlett,* 2, 1120 (2004).

[11] L.A. Paquette, Encyclopedia of Reagents for Organic Synthesis; John Wiley & Sons: Chichester, 1494 (1995).

[12] T.-Sh. Jin, J.-Ch. Xiao, S.-J. Wang, T.-Sh. Li, *Ultrason. Sonochem*., 11, 393 (2004)

[13] M.R. Poor Heravi, M.R. Amirloo, *Iran. Chem. Commun.,* 3, 62 (2015).