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DABCO entrapped in agar-agar : A heterogeneous gelly catalyst for multi-component synthesis of 2-Amino-4*H*-Chromenes

R. S. Gaikwad
Department of Chemistry, Vidnyan Mahavidyalaya Sangola, Maharashtra, India

ABSTRACT

An efficient method for the multi-component synthesis of 2-amino-4H-chromenesby reaction of malanonitrile with various aldehydes and phenols in the presence of gel entrapped DABCO as catalyst is reported.

Keywords : Multi-component reactions, Gel Entrapped Base Catalysts, Recyclability.

I. INTRODUCTION

The rapid assembly of molecular diversity utilizing multi-component reactions (MCRs) has received a great deal of attention, most notably for the speedy synthesis of novel molecular libraries[1]. These methodologies are of particularly great utility when they lead to the formation of privileged medicinal and industrial scaffolds. 2-Amino-4*H*-chromene scaffolds are of significant medical relevance since theyhave widespread applications includingantiviral[2], antimicrobial[3], antiproliferative[4], mutagenicity[5], antitumor[6], sex pheromone[7] and central nervoussystem activity[8].Looking at their importance from pharmacological and industrial point of view, several methods for the multi-component synthesis of2-amino-4*H*-chromeneshave been reported. These method include both homogeneous as well as heterogeneous conditions, catalyzed by piperidine[9], aqueous K_2CO_3[10], triethyl amine[11], basic ionic liquid[12], CATBr[13], ammonium salt[14], NaOH[15], I_2/K_2CO_3[16], $TiCl_4$[17], $InCl_3$[18] and heteropolyacid[19] have been also employed. Although the literature on synthesis of2-amino-4*H*-chromene enjoys a rich array of versatile methodologies, new efficient approaches can be valuable additions to the contemporary arsenal of synthetic strategies.

The concept of gel entrapped base catalysts (GEBCs) combines the advantages of alkali and organic bases with those of heterogeneous supports[20]. These catalysts are prepared by immobilization of alkali or organic bases by entrapping them in an aqueous gel matrix of agar-agar which is a polymer composed of repeating agarobiose units alternating between 3-linked β-D-galactopyranosyl (G) and 4-linked 3, 6-anhydro-α-L-galactopyranosyl (LA) units **(Fig.1)**. This method reduces the amount of bases used and affords easy and efficient separation of products from the catalyst. Besides this, bases like alkalis when exposed to air, absorb moisture and are spoiled. On the contrary, the GEBCs do not absorb moisture on exposure to air and remain intact. The use of GEBCs in organic synthesis also provides excellent opportunity of recyclability and reusability which is seldom possible using bases alone as catalysts. However, despite their well recognized advantages, there have been only limited and sporadic

reports dealing with use of GEBCs in synthetic chemistry[21, 22.] The interesting properties of GEBCs spurred us to tap their barely exploited potential in organic synthesis.

In our continued interest in the applications of novel catalysts in organic synthesis[23], we report herein the synthesis of 2-amino-4*H*chromenes of phenols, aldehydes and malanonitrile in the presence of gel entrapped DABCO as a catalyst.

Results and Discussion

Initially, we focused our attention towards the synthesis of gel entrapped DABCO. A series of experiments were under taken in which different concentrations of DABCO (5-25 %) were dissolved in a varying amount of agar-agar in water. After a considerable experimentation, we found that 20 % *w/w* of agar-agar aqua gel containing 10 % DABCO resulted in the formation of soft gel that served as GEBC in the present work.gel entrapped DABCOwas white jelly like substance that could be cut into pieces. The changes in of physical nature of gel entrapped DABCO was studied in various solvents. The gel remained intact in ethanol, methanol, acetone, dichloromethane, toluene, 2-propanol and water.

Thermal behaviour of gel entrapped DABCO was studied by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (**Fig. 2**). The TGA/DSC curverevealed that the loss of water occurs initially upto ~150 ^{0}Cand is accompanied with endothermic peak in DSC curve. The thermal decomposition of DABCO embedded polymer matrix occurs in two distinct steps giving approximately weight loss 11 % in each step. It is also revealed from the DSC curve that these processes are exothermic. The decomposition iscompleted at the temperature 510 ^{0}C.

Our next task was to demonstrate the catalytic activity of gel entrapped DABCO in thesynthesis of 2-amino-4*H*-chromenes (**Scheme 1**). As a trial case, equimolar mixture of phenol, benzaldehyde and malanonitrile (5 mmol each) was stirred in the presence of 1 gm of various GEBCs in ethanol at ambient temperature till the completion of reaction as monitored by thin layer chromatography. The reaction proceeded efficiently yielding the corresponding of2-amino-4*H*-chromene 10 minutes. In order to check the generality of this methodology, a series of2-amino-4*H*-chromeneswere prepared by reaction of malanonitrile with various phenols and aryl aldehydes. The results are summarized in (**Table 1**). With both electron-poor and electron-rich benzaldehydes, the corresponding products were obtained in good to excellent yields. The reaction of the sterically hindered 2-substitued benzaldehydes even gave higher yields highlightening the general applicability of the protocol. Further, we have also studied the reaction in absence of catalyst. It is worthy of note that in blank experiment no reaction was observed under similar conditions in the absence of gel entrapped DABCO. The striking feature of all the reactions was the isolation of products. It was interesting to observe that after specified time, the product precipitates out of the reaction mixture that can be isolated simply by filtration. The product obtained after sufficient washing with water was found to be practically pure.The identity of all the compounds was ascertained on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy data. The physical and spectroscopic data are in harmony with the proposed structures.

In the GEBCs, the reagent entrapped in the gel may leach into the solvent. To study the leaching of DABCO in solvent, 1 gm gel entrapped DABCOwas stirred in 5 mL of ethanol at room temperature. The catalyst was filtered and water (3 mL) was added to the filtrate. The DABCO leached out was then determined by titrating against 0.1 N hydrochloric acid solution using methyl red as an indicator. It was observed that only 5 % DABCO leached out

from gel into ethanol. Using the amount of DABCO same as that leached out, the reaction between phenol, benzaldehyde and malanonitrile did not gave quantitative yield of the corresponding product. This clearly demonstrated that catalysis was solely due to intact gel entrapped DABCOrather than leached DABCO.

The plausible mechanism for the formation of 2-amino-4*H*-chromenesusing gel entrapped DABCO is shown in (**Fig 3**) Initially, the catalyst facilitates the formation of dicyanoolefin (**5**) by Knoevenagel condensation between aryl aldehyde and malanonitrile as well as generation of phenolate anion (**6**) from phenol. The addition of phenolate anion to dicyanoolefin results in the formation (**7**) which on cyclization furnishes imine (**8**) that results in the formation of 2-amino-4*H*-chromene (**4 a-l**).

The recovery and reuse of catalysts is highly preferable for the large scale operations and industrial point of view. To check the possibility of GEC recycling, the reaction of phenol, benzaldehyde and malanonitrile using gel entrapped DABCOin ethanol was studied. After completion of the reaction, the catalyst was separated from reaction mixture, washed with ethanol and reused in another reaction with identical substrates. The catalyst showed a remarkable recyclability as the corresponding yields started at 96 % and reached 90 % at fifth run(**Fig. 3**).

Experimental

Melting points were determined in an open capillary and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avon 300 MHz spectrometer using DMSO/$CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on a Shimadzu QP2010 GCMS with an ion source temperature of 280 ^{0}C. The thermal gravimetric analysis (TGA) curves were obtained by using the instrument STA 1500 in the presence of static air at a linear heating rate of 10 ^{0}C/min from 25 ^{0} to 1000 ^{0}C. All chemicals were obtained from local suppliers and used without further purification.

Preparation of gel entrapped DABCO

To a boiling mixture of agar-agar (5 gm) in water (35 mL) was added a mixture of base (2.5 gm) in water (2.5 mL). The resultant solution was boiled with stirring for five minutes and cooled in ice bath to yield the desired gel entrapped DABCOcatalyst.

General procedure for the multi-component synthesis of 2-amino-4H-chromenes

A mixture of phenol (5 mmol), aldehyde (5 mmol) and malanonitrile (5 mmol) was stirred in the presence of gel entrapped DABCO(1 gm) in 5 mL of ethanol at ambient temperature till the completion of the reaction as monitored by TLC. The resulting crude product was filtered off, washed with water and recrystallized from ethanol to afford pure products.

Spectral data of representative compounds

2-Amino-4-aryl-3-cyno-7-hydroxy-4*H*-chromene(**4a**):IR (KBr): υ 3429, 3211, 2193, 1651, 1505, 1447 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 4.50 (s, 1H), 6.40 (s, 1H, ArH), 6.48 (d, 1H, J=8.3 Hz, ArH), 6.80 (d, 1H, J=9.2 Hz, ArH), 6.85 (s, 2H, NH_2), 7.15-7.21 (m, 3H, ArH), 7.30 (t, 2H, J=7.1 Hz, ArH), 9.68 (s, 1H, ArOH); ^{13}C NMR (75 MHz, DMSO): 57.74, 102.80, 112.69, 113.52, 121.00, 126.75, 127.75, 128.58, 129.84, 146.18, 149.24, 157.37, 160.30; MS (EI): m/z = 264 (M^{+}).

2-Amino-3-cyno-4(phenyl)-4*H*-benzochromene(**4b)**:IR (KBr): υ 3448, 3304, 3010, 2910,2204, 1649, 1633, 1550, 1450, 1375, 1267, 1100, 1022 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 4.79 (s, 1H), 6.88 (brs, 2H, NH_2), 7.14 (d, 1H, J=8.3 Hz, ArH), 7.21-7.28(m, 5H, ArH), 7.45-7.56(m, 3H, ArH), 7.77 (d, 1H, J=8.3 Hz, ArH), 8.21(d, 1H, J=8.3 Hz, ArH) ; ^{13}C NMR (75 MHz, DMSO): 57.06, 78.61, 79.05, 79.49, 117.90, 121.36, 123.38, 124.08, 126.39, 126.65, 126.81, 127.14, 127.76, 128.04, 128.85, 133.14, 145.85, 160.45; MS (EI): m/z＝298 (M^+).

Conclusion

In conclusion, a novel and highly efficient methodology for the multi-component synthesis of 2-amino-4*H*-chromene by reaction of malanonitrile with various aldehydes and phenols in the presence of gel entrapped DABCO. The method offers several significant advantages, such as high conversions, easy handling, clean reaction profile and short reaction time, which make it a useful and an attractive addition to the existing methodologies.

Acknowledgements

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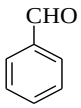
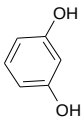
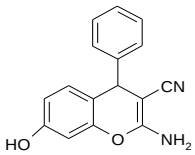
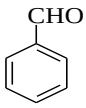
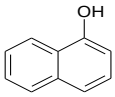
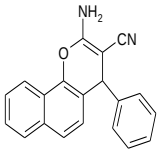
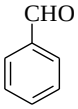
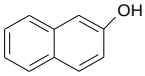
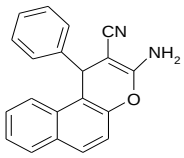
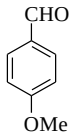
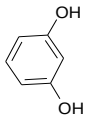
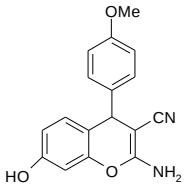
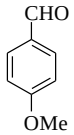
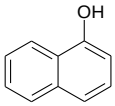
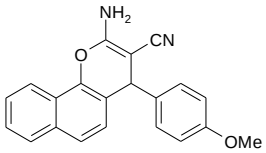
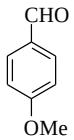
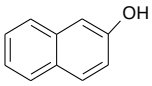
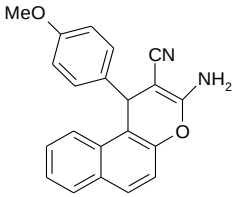
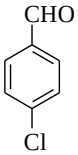
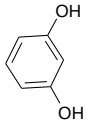
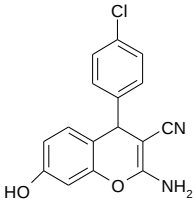
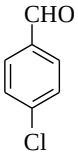
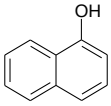
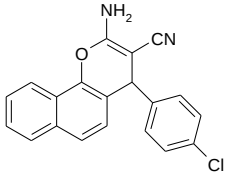
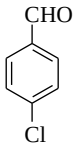
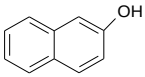
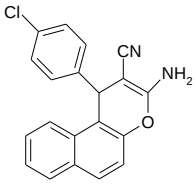
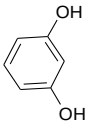
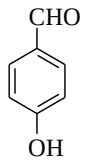
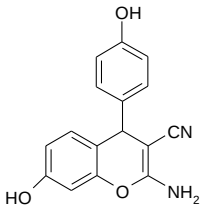
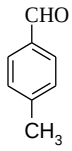
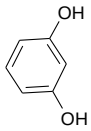
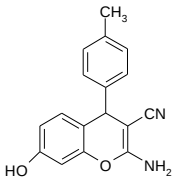
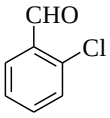
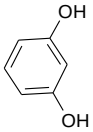
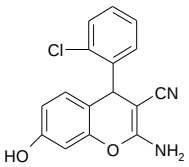
1	 2a	 3a	 4a	10	96	235 (234-236)[24]
2	 2b	 3b	 4b	10	92	209 (210-211)[25]
3	 2c	 3c	 4c	10	93	280 (278-280)[25]

4	 2d	 3d	 4d	10	92	112 (112-114)[24]
5	 2e	 3e	 4e	10	90	191 (190-192)[25]
6	 2f	 3f	 4f	10	91	182 (182-183)[25]
7	 2g	 3g	 4g	10	89	158 (160-162)[24]
8	 2h	 3h	 4h	10	85	230 (231-232)[25]
9	 2i	 3i	 4i	10	86	205 (206-208)[25]
10				10	89	248 (248-250)[24]

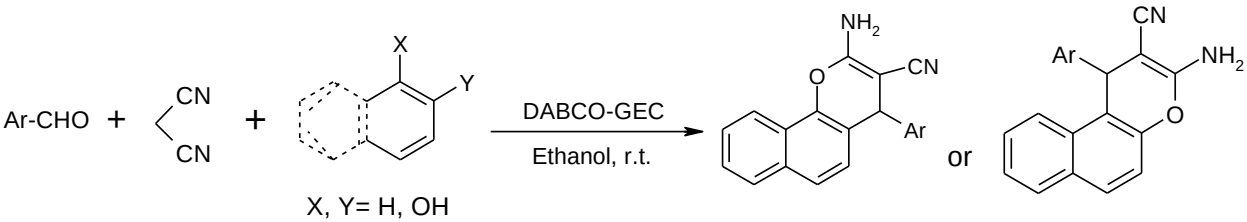
	 2j	3j	 4j			
11	 2k	 3k	 4k	10	88	183 (180-182)[24]
12	 2l	 3l	 4l	10	90	95 (96-98)[24]

[a]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

[b]Isolated yields.

[c]Literature values in parenthesis.

Table 1. Gel entrapped DABCOcatalyzed synthesis of 2-amino-4*H*-chromenes[a]



Scheme 1: Multi-component synthesis of2-amino-4*H*-chromenes using gel entrapped DABCO

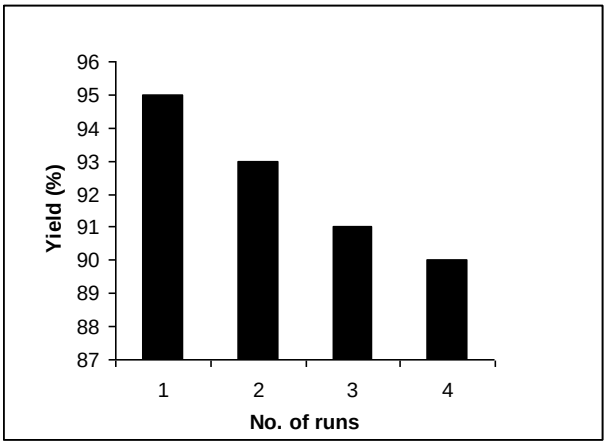


Fig. 3: Recyclic use of gel entrapped DABCO in of2-amino-4*H*-chromene synthesis