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SYNTHESIS OF 2-AMINO-4*H*-CHROMENES USING DIETHYLAMINE AS AN ORGANOCATALYST

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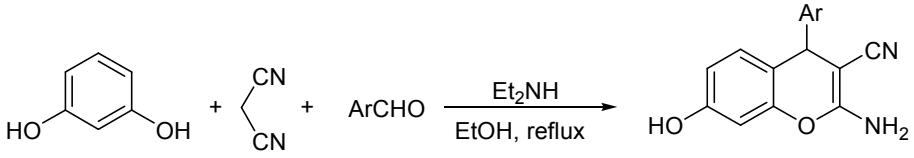
Abstract: Three-component one-pot synthesis of 2-amino-4*H*-chromenes,whichhavebeen reported from condensationofmalononitrile,aryl aldehydes andresorcinolin the presence of diethyleamine under refluxconditionsinethanol.

Key words:diethylamine; resorcinol; chromene;synthesis; multicomponent reaction

Introduction

Diethylamine has recently been demonstrated to be an efficient organocatalyst in the various organic transformations such assynthesis of chromenes,[1]Knoevenagel condensation[2] and aldol condensation-thia-Michael addition process. [3] Alsochromenes are an important class of compounds, widely present inplants, including edible vegetables and fruits.[4] Numerous bioactive natural productshave been identified, and the presence of the chromene-based structure has beenassociated with the capacity to prevent disease. [5] A number of methods have been reported for the synthesis of 2-amino-4*H*chromenes using resorcinol, malononitrile and aldehyde. Various catalyst such as piperidine, [6]triethyl amine, [7]K_2CO_3,[8]CTABr[9] and basic ionic liquid[10] have been used for such kind of multicomponent reaction. Recently Makeremand et al. reported electrochemically induced multicomponent condensation of resorcinol, malononitrile and aldehyde in propanol in an undivided cell in the presence of NaBr as an electrolyte. [11]Many of the methods reported for the synthesis of these compounds [12-15] are associated with the use of hazardous organic solvents, long reaction time, use of toxic amine-based catalysts, and lack of general applicability. Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity, and general applicability. Thus, development of an inexpensive, mild, general, and reusable catalyst for MCRs remains an issue of interest

In this study, malononitrile,resorcinol and aromatic aldehydes in the gained considerable attention in presence of diethyl amine under reflux condition in ethanol was subjectedfor the synthesis of 2-amino-4*H*-chromenesin good-to-excellent yields, regarding to fully simple and efficient route, using less hazardous solvent and easy separation(Scheme 1).



Scheme 1

Results and discussion

The first efforts were focused on the evaluation of catalytic amount of the catalyst on rate and the yields of obtained 2-amino-4*H*-chromenes by reacting resorcinol, 4-chlorobenzaldehyde, malononitrileand diethyl amine in refluxing ethanol. The results on these reactions claimed that 15 mol% of the catalyst is the best in terms of yield and reaction time (entry 4, table 1).

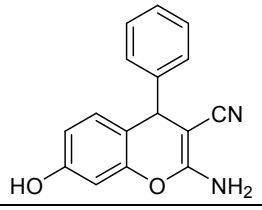
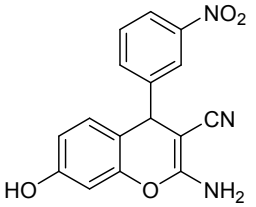
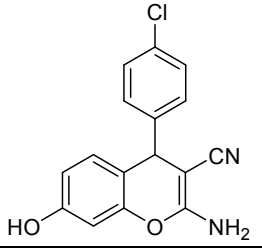
Table1 One-pot synthesis of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile.

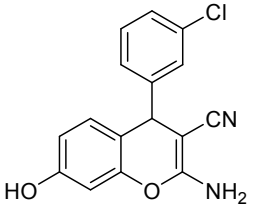
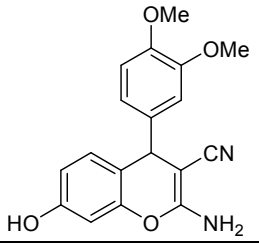
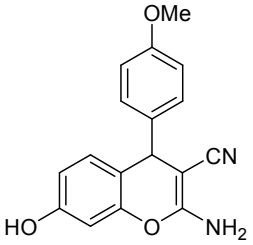
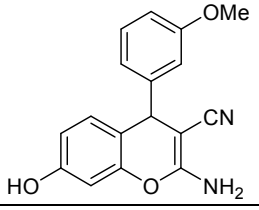
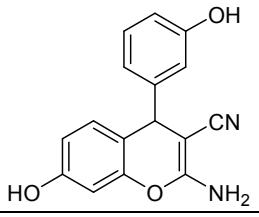
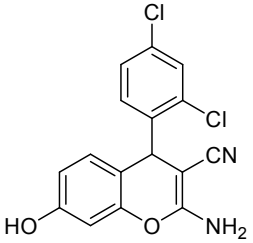
Entry	Catalyst / mol%	τ /h	Yield %[a]
1	free	48	-
2	5	5.0	78
3	10	5.0	86
4	15	4.5	96

[a] Reaction condition: 4-Chloro benzaldehyde (1 mmol), resorcinol (1.0 mmol), malononitrile (1 mmol) and ethanol (5 ml) under reflux conditions.

On the basis of the optimization of the reaction conditions, the scope of this diethyl amine-catalyzed multicomponent reaction was explored. Not only electron-rich aryl aldehydes, but also electron-deficient aryl aldehydes in the reactions resulted 2-amino-4*H*-chromenes in 87–96% yields (Table 2). Comparatively, the rate of the reaction electron-deficient aryl aldehydes is faster than electron-rich aryl aldehydes.

Table 2 2-Amino-4H-Chromenes using diethylamine

Entry	ArCHO	Product	τ /h	Yield%	M.p (°C)	
					Found	Reported[ref.]
1	C_6H_5CHO		5	95	232-234	234-236 [8]
2	3-Nitro-C_6H_4CHO		4.5	93	191-193	188-192 [16]
3	4-Cl-C_6H_4CHO		4.5	96	162-164	160-162 [11]

4	3-Cl-C_6H_3CHO		5	94	106-108106-109 [17]
5	3,4-DiMeO-C_6H_3CHO		4.5	91	213-215 215-217 [16]
6	4-MeO-C_6H_4CHO		4.5	92	110-112112-114[11]
7	3-MeO-C_6H_4CHO		5	87	183-184 -
8	3-OH-C_6H_4CHO		5	90	215-217 215-217 [17]
9	2,4-DiCl-C_6H_3CHO		4.5	96	254-257 256-258 [17]

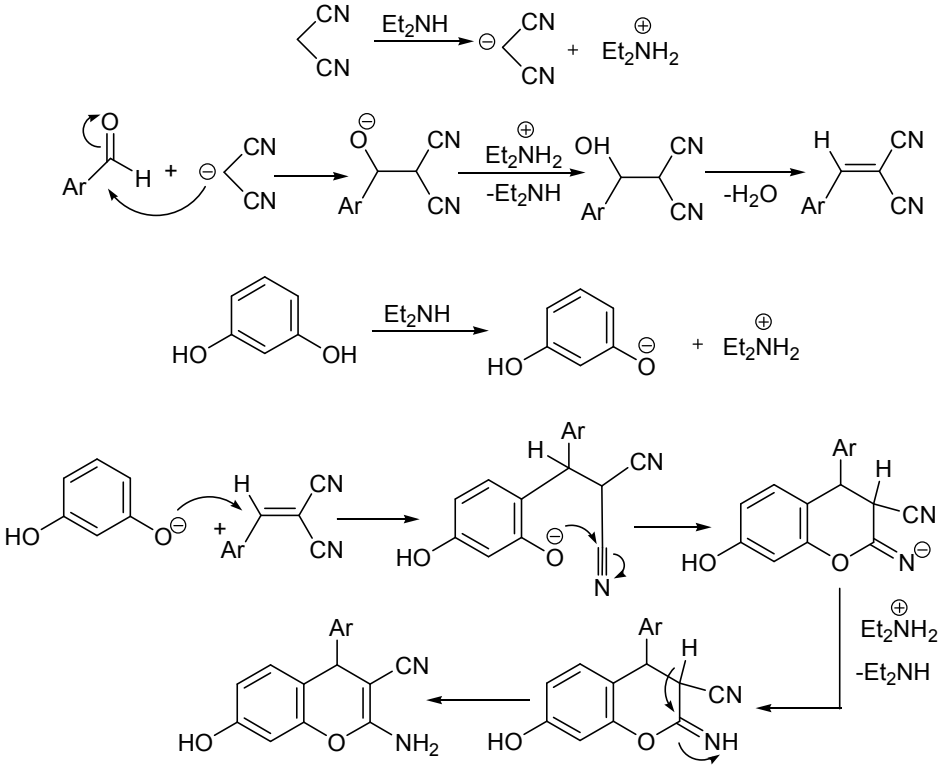
To show the fairly advantages of using diethylamine as a catalyst in the synthesis of 2-amino-4-phenyl-7-hydroxy-4*H*-chromene-3-carbonitrile, our protocol was compared with previously reported methods (Table 3). From the results given in Table 3, the advantages of this work are evident regarding the yields of the reactions which are very important in chemical industry especially when it is combined by easy separation and reusability of the catalyst.

Table 3 The synthesis of 2-amino-4-phenyl-7-hydroxy-4*H*-chromene-3-carbonitrile using variety of catalysts was compared.

Entry	Catalyst / mol%	Solvent	τ /h	*t* / °C	Yield %	Ref.
1	DBU (5mol%)	EtOH	2- 4	50, MV	91	11
2	Mg Al/HT[a] (15Wt %)	H_2O	4	60	95	18
3	NaBr (50 mol%)	n-PrOH	4	r.t -50 mA	83	16
4	Diethyl amine (15mol%)	EtOH	5	reflux	95	This work

[a]Hydrotalcite

A probable mechanism for the synthesis may be postulated as shown below (Scheme 2).



Scheme 2

Experimental

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm-1. ^{1}HNMR spectra were obtained on Bruker DRX- 300 MHZ NMR instrument. All products were characterized and compared with those of authentic sample in literature.

Synthesis of 2-amino-4*H*-chromenes.General procedure:Amixtureof an malononitrile(1mmol), aromatic aldehyde (1mmol) and resorcinol(1mmol),anddiethyl amine(15mol%) in Ethanolwasstirredat reflux conditions foranappropriatetime.Aftercompletionofthereaction which was monitored by TLC, thecatalystwasfiltered offandthemixturewascooledtoroomtemperature.Theprecipitatedcrude productwasthenremovedbyrecrystallized from absoluteethanoltogivepureproduct.

Physical and spectral data

***Compound*(1)**: 2-Amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene. Yield: 95 %; m.p.232-234 °C; IR (KBr, cm^{-1}): 3427 (-OH stretching), 3378(-NH stretching of amine), 3055 (-C-H stretching of aromatic ring), 2962 (-C-H stretching of aliphatic), 2192 (-CN stretching), 1619(-C=C stretching of aliphatic ring), 1581(-C=C stretching of aromatic ring), 1092 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.66 (1H, s, OH), 6.40-7.33 (8H, m, ArH), 6.86 (2H, s, NH_2), 4.60 (1H, s, CH).

***Compound* (2)**: 2-Amino-3-cyano-7-hydroxy-4-(3-nitrophenyl)-4*H*-chromene. Yield: 93%; m.p. 191-193°C. IR (KBr, cm^{-1}):3438 (-OH stretching), 3329(-NH stretching of amine), 3071(-C-H stretching of aromatic ring),2977 (-C-H stretching of aliphatic), 2194 (-CN stretching), 1643(-C=C stretching of aliphatic ring), 1582(-C=C stretching of aromatic ring), 1532 (NO_2, stretching-asymmetry, 1351 (NO_2, stretching-symmetry), 1078 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.77 (1H, s, OH), 6.44-8.10 (7H, m, ArH), 7.02(2H, s, NH_2), 4.90 (1H, s, CH).

***Compound*(3)**: 2-Amino-3-cyano-7-hydroxy-4-(4-chlorophenyl)-4*H*-chromene.Yield: 96%;m.p. 162-164°C; IR (KBr, cm^{-1}): 3461 (-OH stretching), 3341(-NH stretching of amine),3065(-C-H stretching of aromatic ring), 2989 (-C-H stretching of aliphatic), 2192 (-CN stretching), 1640(-C=C stretching of aliphatic ring), 1585(-C=C stretching of aromatic ring), 1089 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.71(1H, s, OH), 6.39-7.58 (7H, m, ArH), 6.90 (2H, s, NH_2), 4.65 (1H, s, CH).

***Compound* (4)**: 2-Amino-3-cyano-7-hydroxy-4-(3-chlorophenyl)-4*H*-chromene.Yield: 96%;m.p. 106-108 °C; IR (KBr, cm^{-1}): 3472 (-OH stretching), 3373 (-NH stretching of amine), 3065 (-C-H stretching of aromatic ring), 2989 (-C-H stretching of aliphatic), 2192 (-CN stretching), 1634(-C=C stretching of aliphatic ring), 1587(-C=C stretching of aromatic ring), 1065 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.94(2H, s, NH_2), 9.731(1H, s, OH), 6.382-7.305 (7H, m, ArH), 4.739 (1H, s, CH).

***Compound* (5)**:2-Amino-3-cyano-7-hydroxy-4-(3,4-dimethoxyphenyl)-4*H*-chromene.Yield: 91%;m.p. 213-215°C; IR (KBr, cm^{-1}): 3424 (-OH stretching), 3370 (-NH stretching of amine), 3077 (-C-H stretching of aromatic ring), 2993 (-C-H stretching of aliphatic), 2190 (-CN stretching), 1631(-C=C stretching of aliphatic ring), 1588(-C=C stretching of aromatic ring), 1147 (C-O stretching), 1055 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.66 (1H, s, OH), 6.45-7.12 (6H, m, ArH), 6.38 (2H, s, NH_2), 4.55 (1H, s, CH), 3.69 (6H, s, OCH_3).

***Compound* (6)**:2-Amino-3-cyano-7-hydroxy-4-(4-methoxyphenyl)-4*H*-chromene.Yield: 92%;m.p. 110-112°C; IR (KBr, cm^{-1}): 3439 (-OH stretching), 3340 (-NH stretching of amine),3056 (-C-H stretching of aromatic ring), 2968 (-C-H stretching of aliphatic), 2190 (-CN stretching), 1641(-C=C stretching of aliphatic ring), 1591(-C=C stretching of aromatic ring), 1143 (C-O stretching), 1090 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.66(1H, s, OH), 6.43-7.10(8H, m, ArH), 6.82 (2H, s, NH_2), 4.55 (1H, s, CH), 3.32 (3H, s, OCH_3).

***Compound*(7)**:2-Amino-3-cyano-7-hydroxy-4-(3-methoxyphenyl)-4*H*-chromene. Yield: 87%;m.p. 183-184°C; IR (KBr, cm^{-1}): 3445 (-OH stretching), 3339 (-NH stretching of amine), 3038 (-C-H stretching of aromatic ring), 2985 (-C-H stretching of aliphatic), 2190 (-CN stretching),1641(-C=C stretching of aliphatic ring), 1587(-C=C stretching of aromatic ring),1072 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.68 (1H, s, OH), 6.45-7.23 (7H, m, ArH), 6.80 (2H, s, NH_2), 4.57 (s, 1H, CH), 3.70 (3H , s, OCH_3).

***Compound*(8)**: 2-Amino-3-cyano-7-hydroxy-4-(3-hydroxyphenyl)-4*H*-chromene.Yield: 90%;m.p. 183-184°C; IR (KBr, cm^{-1}): 3440 (-OH stretching), 3360 (-NH stretching of amine), 3088 (-C-H stretching of aromatic ring), 2952 (-C-H stretching of aliphatic), 2192 (-CN stretching), 1687(-C=C stretching of aliphatic ring), 1600 (-C=C stretching of aromatic ring), 1092 (-C-N stretching); ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 9.68 (1H, s, OH), 6.391-7.085 (7H, m, ArH), 6.849 (2H, s, NH_2), 4.490 (s, 1H, CH).

Compound (**9**): 2-Amino-3-cyano-7-hydroxy-4-(2,4-dichlorophenyl)-4*H*-chromene. Yield: 96%;m.p. 254-257°C; IR (KBr, cm^{-1}): 3461(-OH stretching), 3388 (-NH stretching of amine), 3060 (-C-H stretching of aromatic ring), 2934 (-C-H stretching of aliphatic), 2177(-CN stretching), 1647(-C=C stretching of aliphatic ring), 1587(-C=C stretching of aromatic ring), 1042 (-C-N stretching);^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm):9.78 (1H, s, OH), 6.397-7.571 (6H, m, ArH), 6.986 (2H, s, NH_2), 5.12 (1H, s, CH).

Conclusion

Disclosed work has demonstrated a protocol for the catalytic synthesis of 2- amino-4*H*-chromenes which proceeds efficiently in ethanol under reflux conditions. The reaction conditions are mild and the reaction gives excellent yields of products. This method does not involve the use of volatile organic solvents, and thus, is an environmentally friendly process.

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