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Synthesis of ethyl-3-amino-1-aryl-1H-benzo[f]chromeme-2-carboxylate derivatives promoted by DMAP

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An efficient route, convenient and environmentally friendly procedure for the synthesis chromenes derivatives have been developed via a three-component coupling and one-pot reactions of various aromatic aldehyde with malononitrile or ethyl cyanoacetate and phenols in the presence N,N-dimethylpyridin-4-amine (DMAP) in reflux conditions. In simple reaction conditions, the use of DMAP is explored as an easy workup and a green catalyst for the one-pot three-component synthesis ethyl 3-amino-1-aryl-1H-benzo[*f*]chromene-2-carboxylate derivatives.

1. Introduction

Chromenes derivatives are very important biologicals that occur widely in natural products. Chromenes derivatives significant heterocycles that are known to have multiple biological activities[1] for instance, antibacterial,[2] antitumor,[3] sex pheromonal,[4] antimicrobial,[5] TNF-a inhibitory,[6] anticancer, [7]antifungal,[8] estrogenic,[9] antiviral[10] and anti-HIV.[11] Such compounds have also been applied in pigments, and insecticides[12] and therefore, a number of methods and catalysts have been reported for the synthesis of chromene derivatives such as, a [1-(n-butyl)-3-methylimidazolium hydroxide ([bmim]-OH)]/H_2O/reflux,[13] Triton B/EtOH/rt,[14] K_2CO_3/H_2O/MW irradiation,[15] MCM-41-NH_2/H_2O/80^oC,[16] CTACl/ H_2O/reflux,[17] CTABr/us/H_2O/rt,[18] $K_3PO_4.3H_2O$/solvent free,[19] piperazine/neat/ MW irradiation,[20] tetramethylguanidine/neat/rt,[21] $H_{14}[NaP_5W_{30}O_{110}]$/ H_2O/reflux,[22] $CuSO_4.5H_2O$/ H_2O/reflux,[23] methanesulfonic acid/CH_3CN/reflux,[24] KF-Al_2O_3/ EtOH/80^oC,[25]potassium phthalimide-N-oxyl/ H_2O/reflux,[26] the nanostructured diphosphate $Na_2CaP_2O_{7/}$ H_2O/reflux,[27] nano polypropylenimine dendrimer (DAB-PPI-G_1) /solvent free/110˚C,[28] DBU,[29] KF/solvent free/110˚C,[30] and $Ca(OH)_2$/MeOH/rt. [31]Many of the above methods have their own advantages. However, several of these methods suffer from certain drawbacks such as use of expensive catalyst, prolonged reactions times, use of volatile or hazardous organic solvents, tedious workup conditions, use of extra energy source,

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employment of large amount of catalyst and harsh reaction conditions. The present work represents a new method for the synthesis of chromene derivatives using DMAP as catalyst and co-solvent (additive), as a rapid convenient method with suitable yields. The point is which lead to higher purity of the products in compare with conventional method.

2. Results and Discussion

In continuation of our efforts toward the development of greener methodologies,[32-38] we report here in a simple, clean, and environmentally friendly process for the synthesis of ethyl-3-amino-1-aryl-1H-benzo[*f*]chromene-2-carboxylate derivatives by reaction of various aromatic aldehydes with malononitrile or ethyl cyanoacetate and phenols (α-naphthol or β-naphthol) in the presence DMAP, as catalyst and co-solvent (**Scheme 1**).

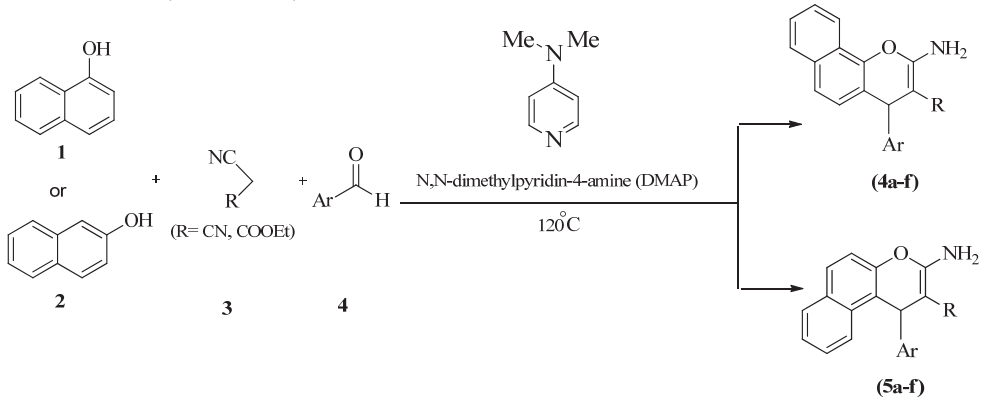
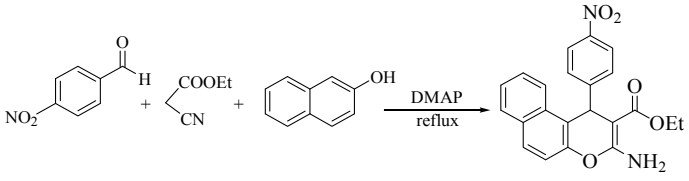


Fig. 1. One-pot synthesis of ethyl 3-amino-1-aryl-1H-benzo[*f*]chromene-2-carboxylate derivatives promoted by DMAP.

In the beginning, we chose three-component reaction *via* ethyl cyanoacetate (1 mmol), *p*-nitrobenzaldehyde (1 mmol), and 2-naphthol (1 mmol) **(5a)** as a model to determine the optimal reaction conditions. Reaction was performed in the presence of varying amounts of DMAP and at different temperatures. The best result is achieved in 0.5 mmol of DMAP at 120°C (**Table 1**, *Entry* 3). Also reaction was carried out in absence of the catalyst and was not observed product even after 5 h (**Table 1**, *Entry* 3). A summary of the optimization experiments is provided in **Table 1**.

Table. 1. Screening of the Reaction Conditions for the Synthesis of (5a).

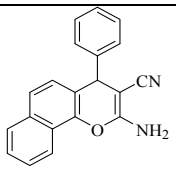
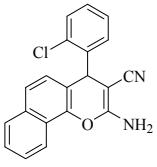
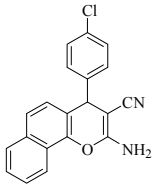
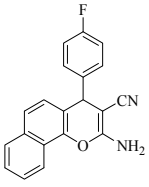
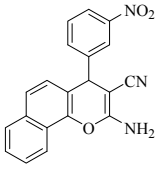
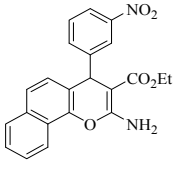


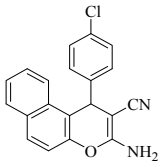
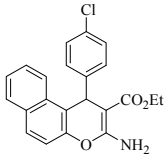
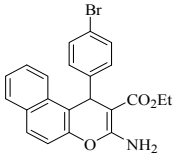
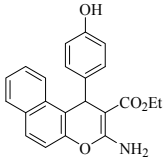
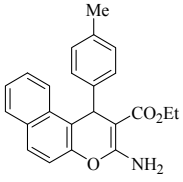
Entry	DMAP (mol %)	Temperature (°C)	Time (min)	Yield[1] (%)
1	10	100	20	76
2	10	110	20	80
3	10	120	20	91
4	10	130	20	85
5	15	120	20	90
6	5	120	20	81
7	10	rt	300	–[2]
8	–	120	300	–[2]

[1] Isolated yields; [2] No reaction.

After optimization of the reaction conditions, we studied the generality of these conditions to other substrates. By using this method, different kinds of various aromatic aldehydes compounds were reacted with malononitrile or ethyl cyanoacetate and phenols to produce the corresponding chromenes derivatives under reflux conditions (Table 2).

Table. 2. One-pot synthesis of ethyl-3-amino-1-aryl-1H-benzo[*f*]chromeme-2-carboxylate derivatives under reflux conditions.

Entry	Ar	Phenol	R	Products	Time (min)	Yield(%)[a]	Mp˚C	
							Found	Reported
1	C_6H_5	1-naphthol	CN	 **4a**	80	89	213-212	212-213[19]
2	2-ClC_6H_5	1-naphthol	CN	 **4b**	45	93	233-234	234-235[19]
3	4-ClC_6H_5	1-naphthol	CN	 **4c**	30	91	233-234	231-232[19]
4	4-FC_6H_5	1-naphthol	CN	 **4d**	100	79	230-231	231-232[19]
5	3-$NO_2C_6H_5$	1-naphthol	CN	 **4e**	35	91	208-210	212-213[19]
6	3-$NO_2C_6H_5$	1-naphthol	CO_2Et		25	90	198-200	198-200[14]

				4f				
7	4-ClC_6H_5	2-naphthol	CN		50	93	206-207	207-208[26]
				5a				
8	4-ClC_6H_5	2-naphthol	CO_2Et		30	86	187-188	NEW
				5b				
10	4-BrC_6H_5	2-naphthol	CO_2Et		15	93	203-204	204-206[28]
				5d				
11	4-OHC_6H_5	2-naphthol	CO_2Et		180	53	130-131	129-130[28]
				5e				
12	4-MeC_6H_5	2-naphthol	CO_2Et		30	90	197-198	NEW
				5f				

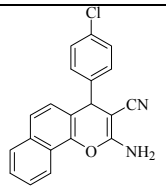
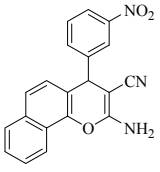
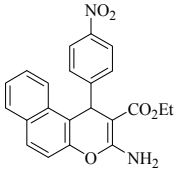
[1] Isolated yields

Finally, to show the merit of the present work, we summarized the results for the synthesis of chromenes derivatives obtained by other workers (Table 3). In contrast with other existing methods, the present methodology offers several advantages such as higher yields, a simple procedure, easy synthesis, simple work-up, does not require either hazardous acids or harsh reaction and greener conditions using DMAP as an efficient catalyst (Table 3).

3. Conclusions

In summary, we have developed an efficient and environmentally friendly method for the synthesis of 2-amino-2-chromenes in high yield, by use DMAP, as catalyst and co-solvent (additive). In contrast to the existing methods using potentially hazardous catalysts/additives, these procedures provide several advantages such as cleaner reactions, does not require either hazardous acids or harsh reaction, easier work-up, and an eco-friendly and promising strategy.

Table. 3. Comparison of methods for the synthesis of chromenes derivatives.

Entry	Conditions	Time (min)	Yield (%)
 **4c**	DMAP/120˚C (this work)	30	91
	$K_3PO_4.3H_2O$/100 ºC /solvent-free[19]	7	50
	potassium phthalimide-N-oxyl /water/reflux[26]	10	93
 **4e**	DMAP/120˚C (this work)	35	91
	Methanesulfonic acid/CH_3CN/reflux[24]	240	90
	CTABr/H_2O/ultrasonic/rt[18]	40	93
	$Na_2CaP_2O_7$/water/reflux[27]	300	85
	KF/110˚C/ solvent-free[30]	5	89
 **5c**	DMAP/120˚C (this work)	45	93
	KF-Al_2O_3/EtOH/80 ºC [25]	300	86
	CTABr/H_2O/ultrasonic/rt[18]	150	80
	$K_3PO_4.3H_2O$/100 ºC /solvent-free[19]	6	78
	Nano polypropylenimine dendrimer (DAB-PPI-G1) /110 ºC / Solvent-free[28]	4	5

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4. Experimental

4.1. Generel

All the chemicals required for the synthesis of cheromene derivatives were purchased from Merck Company. A Bruker (DRX-400 AVANCE) NMR instrument was used to record the ^1H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature; chemical shifts have been expressed in ppm. The IR spectra were recorded on a Shimadzu 8400 instrument (the samples as KBr disks for the range 400-4000 cm^{-1}). Melting points were recorded with Electrothermal 9100 apparatus. Thin-layer chromatography was performed on Kieselgel 60 GF_{254} and visualization was accomplished by UV Lamp or iodine flask. Elemental analysis was carried out on a Thermo Finnigan Flash EA microanalyzer, and the results were found to match satisfactorily with the calculated and observed values.

4.2. General procedure for the synthesis of cheromene derivatives (4a-f and 5a-f).

To a mixture of various aldehydes, 1-naphthol or 2-naphlhol (5 mmol), ethyl 2-cyanoacetate or malononitril (5 mmol) and DMAP (0.5 mmol) in reflux conditions was stirred magnetically at 120℃

for an appropriate time as mentioned in Table 2. Completion of the reaction was indicated by TLC (hexane:ethyl acetate, 8:2), after completion, appropriate amounts of hot EtOH (96%) was added and the mixture stirred for 10 min. Next, the resulting crude product was poured into crushed ice and the solid product, which separated was filtered, recrystallized from ethanol (96%, 3 ml) to get pure cheromene derivatives (4a-f and 5a-f).

4.3 Physical and Spectral Data for *New Compounds*

Ethyl 3-amino-1-(4-chloro phenyl)-1H-benzo[f]chromene-2-carboxylate (5b). White crystals, M.p. 187-188°C; IR (KBr, cm^{-1}): 3328-3467, 3078, 2977, 1670, 1639, 1504, 1072, 1222 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, 3H, CH_3), 4.23 (m, 2H, CH_2), 5.58 (s, 1H, CH), 6.33 (br, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 14.6, 36.7, 59.7, 79.9, 159.9, 169. Anal. Calcd. For $C_{22}H_{18}ClNO_3$ (379.8): C, 69.57; H, 4.78; N, 3.69; O, 12.64; Cl, 9.33; Found: C, 69.40; H, 4.86; N, 3.55; O, 12.57.

Ethyl 3-amino-1-p-tolyl-1H-benzo[f]chromene-2-carboxylate (5f). White crystals, M.P. 197-198 °C; IR (KBr, cm^{-1}): 3332-3467, 3013, 2927, 1670, 1639,1504, 1072,1222 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.2 (m, 2H, CH_2), 5.5 (s, 1H, CH), 6.3 (br, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ ppm: 14.6, 21, 36.7, 59.7, 80.5, 160, 169.3; Anal. Calcd. For $C_{23}H_{21}NO_3$ (359.4): C, 76.86; H, 5.89; N, 3.90; O, 13.35; Found: C, 76.64; H, 5.93; N, 3.78; O,13.16.

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