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Three-component process for the synthesis of 2-amino-2-chromenes in aqueous media

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Abstract—The reaction of an aldehyde, malononitrile and a phenol in water at reflux in the presence of cetyltrimethylammonium chloride (CTACl) as catalyst affords a one-pot synthesis of 2-amino-2-chromenes.

1. Introduction

The increasing attention during the last decades for environmental protection has led both modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost whilst using non-toxic 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 consists of two or more synthetic steps which are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials.[1]

As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of fine chemicals,[2] we performed the synthesis of 2-amino-chromenes through a three-component reaction employing water as the reaction medium. In fact, as clearly stated by R. A. Sheldon, it is generally recognised that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water".[3] The use of water as the reaction medium represents a remarkable benefit since this green solvent is highly polar and therefore immiscible with most organic compounds; moreover the water soluble catalyst resides and operates in the aqueous phase and separation of the organic materials is thus easy. A further advantage is that many organic reactions like the Claisen rearrangement, the aldol condensation, the benzoin condensation and the Diels–Alder cycloaddition exhibit rate enhancement in water.[4]

2-Amino-chromenes are an important class of compounds found as the main components of many naturally occurring products employed as cosmetics and pigments[5] and utilised as potential biodegradable agrochemicals.[6] These compounds are generally prepared by reacting malononitrile, an aldehyde and an activated phenol in organic solvents (i.e. acetonitrile, ethanol) and in the presence of organic bases like piperidine, which are frequently utilised in stoichiometric amounts.[7]

2. Results and discussion

Based on our previous studies on the use of water as solvent for carrying out carbon–carbon forming reactions under both homogeneous and heterogeneous catalysis,[8] we now report the three-component reaction of aromatic aldehydes **1**, malononitrile **2** and phenols **4** in water at reflux and in the presence of a catalytic amount of cetyltrimethylammonium chloride (CTACl) for 6 h, allowing the 'one-pot' formation of 2-amino-2-chromenes **6** in 60–93% overall yield.

The complete process represents an example of the one-pot and sequential steps reaction (often referred to as tandem or cascade reaction) where reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade.[9] Thus the benzylidenemalononitrile **3** containing the electron-poor C=C double bond is quantitatively produced by fast Knoevenagel addition of malononitrile to the aromatic aldehyde. As we previously reported, the reaction easily occurs in protic solvents including water without adding any catalyst,

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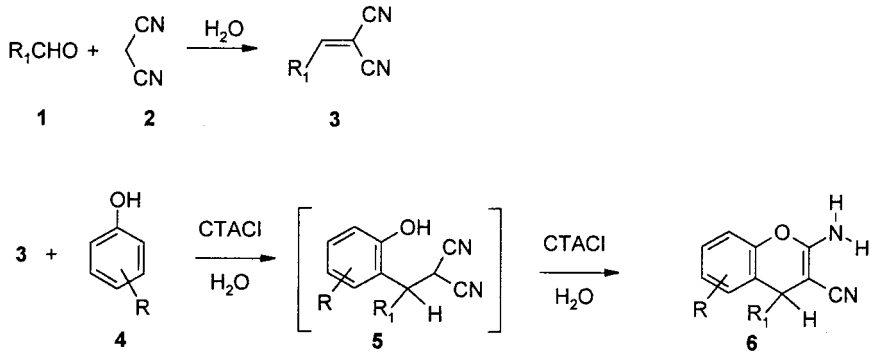


Scheme 1. Supposed reaction mechanism for the synthesis of 2-amino-2-chromene.

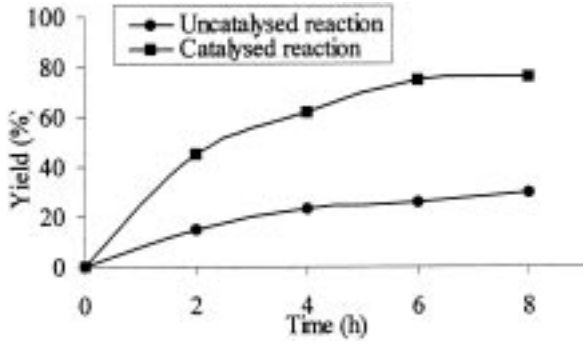


Figure 1. Reactivity of benzylidenemalononitrile with β-naphthol in the presence or not of CTACl as a function of time.

although it results in a net dehydration.[10] The second step that requires the presence of CTACl presumably involves, as also previously reported,[7a] the phenol *ortho C*-alkylation by reaction with the electrophilic C=C double bond giving the intermediate **5**. This is contrary to the mechanism of the reaction of phenols and α,β-unsaturated carbonyl compounds, where the C=C double bond reacts with the phenolic oxygen.[11] Successively the phenolic OH group undergoes fast nucleophilic addition to the CN moiety[12] producing the final 2-amino-2-chromene **6** (Scheme 1).

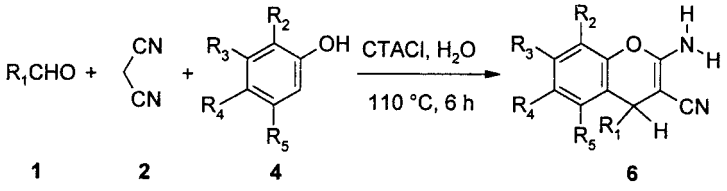
The second step has been investigated by carrying out a model reaction between benzylidenemalononitrile **3** (previously prepared by reaction of benzaldehyde with malononitrile) and β-naphthol in water with or without addition of CTACl.

As shown in Fig. 1 the rate of the reaction is markedly affected by the catalyst. In fact the uncatalysed reaction affords the corresponding 2-amino-2-chromene **6g** in 30% yield after 8 h, whereas the presence of the CTACl strongly increases the rate of the process and compound **6g** is produced in 75% yield after 6 h. The activation of reactants is most likely due to the increase of their concentration into the hydrophobic field and in fact lower yields of products **6** were observed by carrying out the same reactions in methanol, where all the compounds are soluble.

The reaction is applicable to different aromatic aldehydes even in the presence of other functionalities such as nitro, ether, chlorine, and acetal that under our reaction conditions are preserved; in addition the yields are independent of the electronic effect of substituents (Table 1).

However, with enolisable aldehydes such as cyclohexanecarbaldehyde and isobutyraldehyde the yield of the reaction decreases (53 and 41%, respectively), probably due to the possible aldol side reaction.

Table 1.



Entry	R_1	R_2	R_3	R_4	R_5	**6** Yield (%)
a	3-$NO_2C_6H_4$	CH=CH-CH=CH		H	H	92
b	4-$NO_2C_6H_4$	CH=CH-CH=CH		H	H	94
c	4-ClC_6H_4	CH=CH-CH=CH		H	H	85
d	4-$MeOC_6H_4$	CH=CH-CH=CH		H	H	90
e	3-pyridyl	CH=CH-CH=CH		H	H	91
f	4-pyridyl	CH=CH-CH=CH		H	H	93
g	4-$NO_2C_6H_4$	H	H	CH=CH-CH=CH		75
h	4-ClC_6H_4	H	H	CH=CH-CH=CH		74
i	4-$MeOC_6H_4$	H	H	CH=CH-CH=CH		
j	4-$NO_2C_6H_4$	H	OCH_2O		H	70
k	4-$NO_2C_6H_4$	H	OCH_3	OCH_3	H	60

It is worthy of note that the reaction is highly regioselective, leading to only one of the two possible isomers that can be formed; it must also be pointed out that only activated phenols afford products **6** in good yields.

In summary, the three-component conversion of aromatic aldehydes, malononitrile and phenols to 2-amino-2-chromenes has been efficiently performed in water as a 'green' solvent and by using a catalytic amount of CTACl. The easy purification of products simply by crystallisation, the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.

3. Experimental

3.1. General procedure for the preparation of 2-amino-2-chromenes 6

A mixture of the aldehyde **1** (10 mmol), malononitrile **2** (10 mmol), phenol **4** (10 mmol) and CTACl (0.1 mL) in H_2O (50 mL) was refluxed for 6 h, then cooled to rt and extracted with Et_2O. The organic phase was dried ($MgSO_4$), concentrated and the crude product was purified by crystallisation from methanol.

3.1.1. 2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*-benzo[*h*]-chromene 6a. (3.16 g, 92%): yellow solid, mp 214–216°C (lit.[7d] mp 214.5–216°C).

3.1.2. 2-Amino-3-cyano-4-(4-nitrophenyl)-4*H*-benzo[*h*]-chromene 6b. (3.23 g, 94%): yellow solid, mp 239.5–241°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz) δ=5.14 (s, 1H, H-4), 7.10 (d, 1H, *J*=8.5, H-5 or H-6), 7.30 (s, 2H, NH_2), 7.5–7.7 (m, 2H, H-8 and H-9), 7.53 (d, 2H, *J*=8.5, H-2′ and H-6′ or H-3′ and H-5′), 7.61 (d, 1H, *J*=8.5, H-6 or H-5), 7.88 (d, 1H, *J*=8.0, H-7 or H10), 8.18 (d, 2H, *J*=8.5, H-3′ and H-5′ or H-2′ and H-6′), 8.28 (d, 1H, *J*=8.0, H-10 or H-7); IR (KBr) 3477, 3350, 2191 cm^{-1}; MS (C.I.) *m/z* 372 (M^++29, 11%), 344 ($[M+H]^+$, 100) 221 (72). Anal. calcd for $C_{20}H_{13}N_3O_3$: C, 69.97, N, 12.24, H, 3.82; found: C, 70.09, N, 12.12, H, 3.99.

3.1.3. 2-Amino-3-cyano-4-(4-chlorophenyl)-4*H*-benzo[*h*]-chromene 6c. (2.83 g, 85%): yellow solid, mp 231–232.5 °C (lit.[7b] mp 232°C).

3.1.4. 2-Amino-3-cyano-4-(4-methoxyphenyl)-4*H*-benzo[*h*]-chromene 6d. (2.96 g, 90%): yellow solid, mp 183–184.5°C (lit.[13] mp 182°C).

3.1.5. 2-Amino-3-cyano-4-(3-pyridyl)-4*H*-benzo[*h*]chromene 6e. (2.72 g, 91%): yellow solid, mp 203.5–205°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz) δ=5.02 (s, 1H, H-4), 7.11 (d, 1H, *J*=8.5, H-5 or H-6), 7.24 (s, 2H, NH_2), 7.33 (dd, 1H, *J*=8.0 and 4.5, H-5′), 7.5–7.7 (m, 4H, H-6 or H-5, H-7, H-8 and H-6′), 7.89 (d, 1H, *J*=8.0, H-7 or H-10), 8.26 (d, 1H, *J*=8.0, H-10 or H-7), 8.46 (d, 1H, *J*=4.5, H-4′), 8.56 (s, 1H, H-2′); IR (KBr) 3453, 2186 cm^{-1}; MS (C.I.) *m/z* 328 (M^++29, 17%), 300 ($[M+H]^+$, 100) 221 (89). Anal. calcd for $C_{19}H_{13}N_3O$: C, 76.24, N, 14.04, H, 4.38; found: C, 76.13, N, 14.08, H, 4.51.

3.1.6. 2-Amino-3-cyano-4-(4-pyridyl)-4*H*-benzo[*h*]chromene 6f. (2.78 g, 93%): yellow solid, mp 199.5–200°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz) δ=4.97 (s, 1H, H-4), 7.11 (d, 1H, *J*=8.5, H-5 or H-6), 7.27 (m, 4H, H-2′, H-6′ and NH_2), 7.5–7.7 (m, 2H, H-8 and H-9), 7.63 (d, 1H, *J*=8.5, H-6 or H-5), 7.90 (d, 1H, *J*=8.0, H-7 or H-10), 8.25 (d, 1H, *J*=8.0, H-10 or H-7), 8.51 (d, 2H, *J*=4.5, H-3′ and H-5′); IR (KBr) 3354, 3308 and 2195 cm^{-1}; MS (C.I.) *m/z* 328 (M^++29, 18%), 300 ($[M+H]^+$, 100) 221 (56). Anal. calcd for $C_{19}H_{13}N_3O$: C, 76.24, N, 14.04, H, 4.38; found: C, 76.18, N, 14.00, H, 4.46.

3.1.7. 3-Amino-2-cyano-1-(4-nitrophenyl)-1*H*-benzo[*f*]-chromene 6g. (2.58 g, 75%): pale yellow solid, mp 188–189°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz): δ 5.56 (s, 1H, H-4), 7.16 (s, 2H, NH_2), 7.37 (d, 1H, J=9.0 Hz, H-9 or H-10), 7.4–7.5 (m, 2H, H-6 and H-7), 7.47 (d, 2H, *J*=8.5 Hz, H-2′ and H-6′), 7.7-8.0 (m, 2H, H-5 and H-8), 7.98 (d, 1H, *J*=9.0 Hz, H-10 or H-9), 8.15 (d, 2H, *J*=8.5 Hz, H-3′ and H-5′); IR (KBr) 3429, 3331 and 2190 cm^{-1}; MS (C.I.) *m/z* 344 ($[M+H]^+$, 41%), 221 (100). Anal. calcd for $C_{20}H_{13}N_3O_3$: C, 69.97, N, 12.24, H, 3.82; found: C, 70.10, N, 12.08, H, 3.88.

3.1.8. 3-Amino-2-cyano-1-(4-chlorophenyl)-1*H*-benzo[*f*]-chromene 6h. (2.46 g, 74%): yellow solid, mp 207–208.5°C (lit.[7b] mp 208°C).

3.1.9. 3-Amino-2-cyano-1-(4-methoxyphenyl)-1*H*-benzo[*f*]-chromene 6i. (2.46g, 75%): yellow solid, mp 190-191.5°C (lit.[13] mp 192°C).

3.1.10. 2-Amino-3-cyano-4-(4-nitrophenyl)-6,7-methylendioxy-4*H*-chromene 6j. (2.36 g, 70%): yellow solid, mp 162–165°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz): δ 4.86 (s, 1H, H-4), 5.96 (s, 1H, 1/2 CH_2), 6.01 (s, 1H, 1/2 CH_2), 6.57 (s, 1H, H-5 or H-8), 6.71 (s, 1H, H-8 or H-5), 7.00 (s, 2H, NH_2), 7.47 (d, 2H, *J*=8.5 Hz, H-3′ and H-5′), 8.26 (d, 2H, *J*=8.5 Hz, H-2′ and H-6′); IR (KBr) 3426, 3331 and 2193 cm^{-1}; MS (C.I.) *m/z* 337 (M^+, 43%), 215 (100). Anal. calcd for $C_{17}H_{11}N_3O_5$: C, 60.54, N, 12.46, H, 3.29; found: C, 60.42, N, 12.31, H, 3.45.

3.1.11. 2-Amino-3-cyano-4-(4-nitrophenyl)-6,7-dimethoxy-4*H*-chromene 6k. (2.12 g, 60%): yellow solid, mp 193–194°C (MeOH); ^{1}H NMR (DMSO d_6, 300 MHz) δ=3.59 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.87 (s, 1H, H-4), 6.57 (s, 1H, H-5 or H-8), 6.65 (s, 1H, H-8 or H-5), 6.97 (s, 2H, NH_2), 7.46 (d, 2H, *J*=9.0, H-2′ and H-6′), 8.20 (d, 2H, *J*=9.0, H-3′ and H-5′); IR (KBr) 3427, 2189 cm^1; MS (C.I.) *m/z* 382 (M^++29, 18%), 354 ($[M+H]^+$, 100) 231 (28). Anal. calcd for $C_{18}H_{15}N_3O_5$: C, 61.19, N, 11.89, H, 4.28; found: C, 61.13, N, 12.01, H, 4.21.

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