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Basic alumina catalysed synthesis of substituted 2-amino-2-chromenes via three-component reaction

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Abstract—Substituted 2-amino-2-chromenes were obtained in excellent yield and selectivity simply by mixing malononitrile, α-naphthol and aromatic aldehydes in water in the presence of basic alumina as heterogeneous and reusable catalyst.

The use of clean solvents in combination with heterogeneous and reusable catalysts represents one of the more powerful green chemical technology procedures.[1] The environmental acceptability of the process is improved if the multicomponent strategy is applied. Indeed, it is well known that the multicomponent reactions (MCR), consisting of two or more synthetic steps, which are carried out without isolation of any intermediate, allow to reduce time, save money, energy and raw materials.[2]

In addition the use of green solvents like water shows both economical and synthetic advantages: not only the chemical processes needed to produce organic solvents will be reduced, the atmospheric pollution by escaping VOC will be decreased and the waste treatment will be reduced, but also dramatic rate enhancements can be achieved in many organic reactions, that is Claisen rearrangement, aldol condensation, Diels–Alder cycloaddition.[3]

Alumina is a particularly interesting metal oxide as it is widely used industrially as filler, adsorbent, drying agent, catalyst, catalyst support and reagent. γ-Alumina is the transition alumina most commonly utilised to carry out surface organic chemistry.[4] In contrast to clays and zeolites, this material does not contain accessible channels or cavities and shows large surface area and highly porous exteriors available to substrates.

2-Amino-chromenes represent an important class of compounds being the main components of many natural occurring products, and are widely employed as cosmetics, pigments[5] and potential biodegradable agrochemicals.[6] These compounds are generally prepared by reacting malononitrile, an aldehyde and an activated phenol in the presence of organic bases like piperidine (frequently utilised in stoichiometric amounts)[7] in an organic solvent (i.e., acetonitrile, ethanol). More recently a green methodology based on the use of cetyltrimethylammonium chloride in water has been reported.[8] Nevertheless the use of efficient catalysts easily removable and reusable is desirable, according to the requirements of the modern large-scale organic synthesis.[9]

In continuation of our investigations on the use of heterogeneous catalysts for fine chemicals preparation,[10] we have studied the three-component synthesis of substituted 2-amino-chromenes using γ-alumina as cheap, heterogeneous and reusable catalyst and water as solvent.

The model reaction was carried out simply by mixing benzaldehyde **1**, malononitrile **2**, α-naphthol **4** and the heterogeneous catalyst in water and refluxing the resulting mixture for 2 h. The process represents a typical cascade reaction[2b,11] in which the benzylidenemalononitrile **3**, containing the electron-poor C–C double bond, is fast and quantitatively produced by Knoevenagel addition of malononitrile to the aromatic aldehyde and subsequent water elimination (Scheme 1).

It is well known that the first step, if carried out in protic solvents like water, does not require any catalyst

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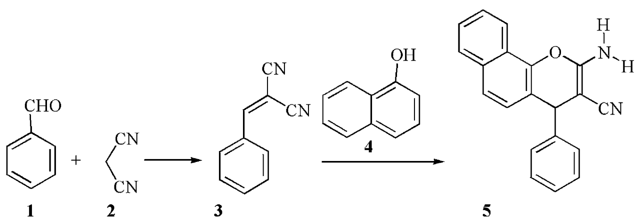


Scheme 1. The two steps of the three-component reaction.

although it results in a net dehydration.[12] On the contrary the second step, presumably involving the *ortho* C-alkylation of α-naphthol by reaction with the electrophilic C=C double bond[13] and the nucleophilic addition of the phenolic OH group the CN moiety[14] producing the final 2-amino-2-chromene **5**, requires the intervention of the catalyst, as the uncatalysed reaction afforded the final product in only 29% yield.

A screening of four different heterogeneous catalysts, namely two metal oxides and two clays, was performed in order to find out the best solid promoter. As reported in Table 1, basic alumina was found to be the superior one affording the desired product in 84% yield.

As it is reported, γ-alumina is basic and when contacted with water it yields a basic solution,[15] we suspected that the activation of reagents in the second step could be promoted by the basic water solution. To this end we carried out the same reaction in the basic water obtained after filtration of a stirred suspension of γ-alumina and we recovered compound **5** in only 25% yield, confirming the important role of the catalyst surface in the activation of the reagents.

Then we faced the problem of catalyst recycling. The γ-alumina, recovered by Büchner filtration and washed with methanol, has been reused four times to promote the model reaction affording the corresponding chromene in 85%, 87%, 84% and 83% yield, respectively, and with the same excellent selectivity.

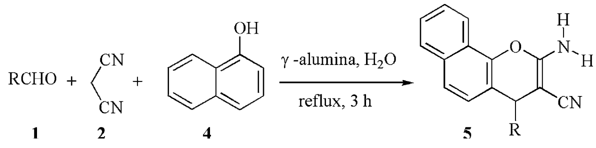
The standardised methodology was applied to a variety of aromatic aldehydes even in the presence of other functionalities such as nitro, ether and chlorine that under our reaction conditions were preserved (see Table 2).[16]

In all cases good yield and selectivity were obtained; it is worthy to note that the purification procedure was extremely simple as after removal of the catalyst by filtration and washing with methanol, the solvents were distilled off and the products purified by crystallisation from methanol. In addition, the reaction shows high regioselectivity affording only one of the two possible isomers that can be formed.

Table 1. Compound **5** synthesis catalysed by different solid catalysts

Entry	Catalyst	Yield (%)	
		3	**5**
a	γ-Alumina (Carlo Erba)	13	84
b	Silica gel (Merck)	35	61
c	Montmorillonite KSF (Fluka)	48	50
d	Hydrotalcite Pural MG 30 (Sasol)	72	24

Table 2. Synthesis of substituted 2-amino-chromenes **5**



Entry	R	**5** Yield (%)	**5** Selectivity (%)
a[17]	C_6H_5	96	98
b[18]	2-$NO_2C_6H_4$	94	97
c[7c]	3-$NO_2C_6H_4$	95	97
d[8]	4-$NO_2C_6H_4$	97	98
e[8]	3-pyridyl	98	99
f[8]	4-pyridyl	89	91[a]
g[7a]	4-OHC_6H_4	87	89[a]
h[7a]	4-ClC_6H_4	84	87[a]
i[17]	4-$OCH_3C_6H_4$	83	85[a]

[a] The sole by-product is the corresponding benzylidenemalononitrile.

However, with enolizable aldehydes the yield and selectivity of the reaction notably decrease (i.e., 41% and 53% , respectively, with isobutyraldehyde), probably due to the possible aldol condensation side reaction.

In summary, we have reported a new and effective methodology for the eco-compatible preparation of 2-amino-2-chromenes via three-component reaction. The easy purification of products simply by crystallisation, the use of water as solvent and of γ-alumina as heterogeneous and reusable catalyst suggest good prospect for the industrial applicability of this process; the sole drawback being represented by the fact that only α-naphthol can be utilised as activated phenol.

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16. Sample procedure (Table 2, entry d): γ-Alumina (0.50 g), *p*-nitrobenzaldehyde (0.010 mol, 1.51 g), malononitrile (0.010 mol, 0.66 g, 0.63 mL) and α-naphthol (0.010 mol, 1.44 g) in water (10 mL) were refluxed for 3 h; the catalyst was removed by filtration and washed with methanol (20 mL); the solvents were distilled off and the crude was purified by crystallisation from methanol affording 3-amino-2-cyano-1-(4-nitrophenyl)-1*H*-benzo[*f*]chromene **5d** (3.33 g, 97%): pale yellow solid, mp 188–189 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): 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).
All products **5a**–**i** were characterised (IR, ^{1}H NMR and MS) and their mps compared with literature reported ones.
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