Research article

Aqua Mediated Synthesis of Substituted 2-Amino-Chromenes Catalyzed by Expanded Perlite

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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 catalyzed by Expanded Perlite, as a green heterogeneous catalyst. The high reactivity and selectivity of our catalyst coupled with their ease of use and reduced environmental problems makes them attractive alternatives to homogeneous basic reagents. **Copyright © AJBCPS, all rights reserved.**

Keywords: Substituted 2-amino-2-chromenes, heterogeneous catalyst, Expanded Perlite, Water.

Introduction

2-Amino-chromenes [1] represent an important class of compounds being the main components of many naturally occurring products. They can also widely be utilised as cosmetics, pigments [2] and potential biodegradable agrochemicals [3]. These compounds have been of interest to the medicinal chemist for many years. Fused

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chromenes are biologically active compounds with a wide spectrum of activities such as antimicrobial [4], mutagenicitical [5], antiviral [6], antiproliferative [7], sex pheromonal [8], antitumoral [9] and central nervous system activities [10]. Furthermore, many bio-active compounds (e.g., antioxidants [11], enzyme inhibitors [12]) incorporate these key heterocycles. The basic structural framework of chromenes for example is a common feature of many tannins and polyphenols[13] found in tea, fruits, vegetables and red wine and these compounds have become more important as a result of their health-promoting effects.

One-pot multicomponent condensations represent as possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity [14]. Recently organic reactions in water without the use of harmful organic solvents have attracted much attention, because water is a cheap, safe and environmentally benign solvent [15].

2-Amino-chromenes are generally prepared by refluxing malononitrile, aldehyde and activated phenol in the presence of hazardous organic bases like piperidine in organic solvents like ethanol and acetonitrile [16]. A literature survey revealed the recent reports on several modified procedures using CTACl [17], TEBA [18], γ- alumina [19] and K_2CO_3 in water under microwave irradiation [20]. The use of clean solvents [21] in combination with heterogeneous and reusable catalysts [22] represents one of the more powerful green chemical technology procedures [23].

Aqua mediated reactions have received considerable attention in organic synthesis due to environmental safety reasons. Water is the cheapest, most abundant and non-toxic chemical in nature. It has unique physical and chemical properties such as a high dielectric constant and cohesive energy density compared to organic solvents. It has also special effects on reactions arising from inter- and intramolecular non-covalent interactions leading to novel salvation and assembly processes. Many organic reactions have been performed successfully in water as reaction medium, and several books and reviews have been devoted to such an application [24].

With the object of investigating the economical upgrading of Moroccan natural resources [25] for example Natural Phosphate [26] and Perlite [27], we have studied the three-component synthesis of substituted 2-amino-chromenes using expanded Perlite as new, heterogeneous and reusable catalyst and water as solvent.

Materials and Method

Chemicals and Instrumentation

All chemicals used in this study were of reagent analytical grade. For solvents were used without further purification. The crude product was purified by recrystallization or by distillation under vacum. And characterised by their ^1H NMR, ^{13}C NMR (NMR spectra were recorded on a Bruker ARX 300 spectrometer), IR spectrometry (FTIR spectra were recorded on an ATI Mattson-Genesis Series spectrophotometer using the KBr disc method) and melting point. The X-ray fluorescence analysis was performed on a dispersion wavelength spectrometer SRS 200. The particle size of the expanded Perlite was measured using Mastersizer X (Malvern Instruments). The specific surface area was determined by BET Krypton adsorption method. ESCA measurement were performed on VSW model HA 150 electron spectrometer, employing unmonochromatized AlKα (1486.6 eV) and MgKα (1253.6 eV) sources of photons, the pressure in the analytical chamber being in the low 10^{-7} Pa rang. The survey scans were recorded using fixed pass energy of 90 eV, while narrow scan spectra of the C_{1s}, O_{1s}, Si_{2p} and Al_{2p} levels were recorded using a fixed pass energy of 22 eV.

Preparation and Characteristics of expanded Perlite

The unexpanded Perlite samples were obtained from Jbel Tidiennit Perlite mines locates in Nador, Morocco. The Perlite was expanded in the Laboratory of the Office of Research and Mineral Participation. Perlite is an inert glassy volcanic ryholitic rock which will expand when quickly heated to above 870°C. It expands up to 20 times its original volume.

The X-ray fluorescence analysis expanded Perlite shows that it is essentially amorphous natural alumino-silicate of white colour. The chemical composition of the expanded Perlite used in this study is summarised in table **1**.

Table 1: Chemical analysis of Expanded Perlite

Constituent	SiO_2	Al_2O_3	Fe_2O_3	P_2O_5	TiO_2	CaO	MgO	MnO	K_2O	Na_2O
Percentage (%)	75.22	13.08	01.83	00.02	00.13	01.43	00.10	00.06	04.95	03.00

However, XPS analysis of the extreme surface shows considerable enrichment in aluminium species (Si/Al= 4.65) compared to X-ray fluorescence results where atomic ratio of Si/Al =13. The only contaminant detected by XPS on the surface of expanded Perlite was carbon. The percentage and binding energy of elements presented at the expanded Perlite surface are summarised in table **2**.

Table 2: Binding energy and Percentage of elements present in the surface of Expanded Perlite.

Constituent	Si_{2p}	O_{1s}	Na_{1s}	C_{1s}	K_{2p}	Al_{2p}
Binding Energy	0102.68	0532.00	1072.48	0284.60	0293.36	0073.92
Percentage (%)	23.7	55.9	06.1	07.0	02.3	05.1

The specific surface area of expanded Perlite is 1.726 m^2/g and the particle size for this solid state ranged between 7.0 and 65.7 μm, 50% were 30.3 μm.

General Procedure

In a typical reaction a mixture of the expanded Perlite (0.5 g), benzaldehyde **1** (1 mmol), malononitrile **2** (1 mmol) and α-naphthol **4** (1 mmol) in water (5 mL) was refluxed. After completion of the reaction, the mixture was cooled to room temperature (Figure **1**).
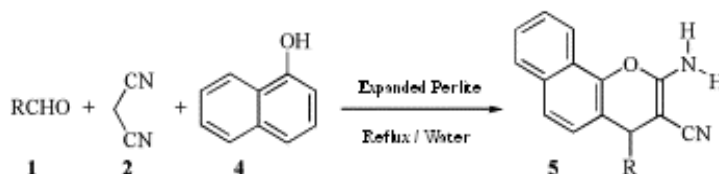

Figure 1: Synthesis of substituted 2-amino-2-chromenes catalyzed by Expanded Perlite

The solid, which separated, was filtered and then recrystallized from methanol to afford pure product, and finally identified by ^{1}H, ^{13}C NMR and IR spectrometry.

Results and Discussion

The model reaction was carried out simply by mixing benzaldehyde **1a**, malononitrile **2**, α-naphthol **4** and the heterogeneous catalyst in water and refluxing the resulting mixture. The process represents a typical cascade reaction in which the benzylidenemalononitrile **3a**, 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 (Figure **2**).
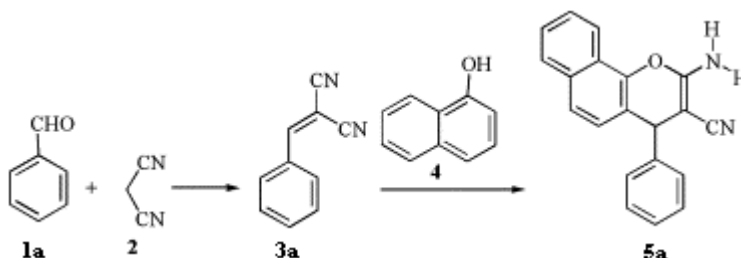

Figure 2: The two steps of the three-component reaction.

It is well known that the first step, if carried out in protic solvents like water, does not require any catalyst although it results in a net dehydration. On the contrary, the second step, presumably involving the ortho C-alkylation of α-naphthol by reaction with the electrophilic C=C double bond and the nucleophilic addition of the phenolic OH group of the CN moiety producing the final 2-amino-chromene, requires the intervention of the catalyst, as the uncatalyzed reaction afforded the final product **5a** in only 32% yield.

A screening of three different solvents using expanded Perlite was performed in order to define the best solvent as a solvent of choice. As reported in Table **3**, water was found to be the superior one affording the desired product **5a** in 92% yield.

Table 3: Synthesis of product **5a** catalyzed by Expanded Perlite

Entry	Solvent	Time (h)	Yield (%)
1	HOAc	8	46
2	CH$_3$CN	5	78
3	H$_2$O	4	92

The scope and the generality of the present method were then further demonstrated by the reaction of various aldehydes with malononitrile and α-naphthol. In all cases good yields with good selectivity were obtained. The results are shown in Table **4**.

Table 4: Synthesis of substituted 2-amino-chromenes catalyzed by expanded Perlite.

Product	R	Time (h)	Yield (%)	Mp (°C)
5a	C$_6$H$_5$	4h	92	207-210
5b	4-MeOC$_6$H$_4$	4h20min	94	190-192
5c	4-ClC$_6$H$_4$	4h45min	90	232-234
5d	3-NO$_2$C$_6$H$_4$	5h	93	213-215

2-Amino-3-cyano-4-phenyl-4H-benzo[h]chromene (5a): Yellow solid, mp = 207-210°C. ^{1}H NMR (CDCl3, 300 MHz) δ en ppm : 4.79 (2H, s, NH2). 4.86 (1H, s, H-4). 7.02 (1H, d, J$_{HH}$ = 8.4 Hz, H-5). 7.12 -7.38 (5H, m, H-2', 3', 4', 5', 6'). 7.44 -7.6 (3H, m, H-6, 8, 9). 7.8 (1H, d, J$_{HH}$ = 7.8 Hz, H-7). 8.17 (1H, d, J$_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR

(CDCl3, 75 MHz) δ en ppm : 41.47 (s, C-4). 61.34 (s, C-3). 117.26 (s, CN). 119.75 (s, C-4a). 120.77 (s, C-10). 123.23 (s, C-10a). 124.62 (s, C-6), 126.22 (s, C-5). 126.66 (s, C-8). 126.74 (s, C-9). 127.36 (s, C-4'). 127.74 (s, C-7). 128.84 (s, C-3', 5'). 129.19 (s, C-2', 6'), 133.3 (C-6a). 142.4 (C-1'). 144.41(C-10b). 159.02 (C-2). FTIR (KBr) cm^{-1}: 3436 (CH), 3317 (NH2), 2183 (CN), 1655 (NH2). MS (EI) m/z (%) : 298 (M$^+$), 221,(100).

2-Amino-3-cyano-4-(4-methoxylphenyl)-4Hbenzo[h]chromene (5b): Yellow solid, mp = 190-192°C. ^{1}H NMR (CDCl3, 300 MHz) δ en ppm : 3.5 (3H, s, C6H4OC*H*3). 4.81 (2H, s, N*H*2). 4.88 (1H, s, *H*-4). 7.03 (1H, d, J_{HH} = 8.4 Hz, *H*-5). 7.23-7.35 (4H, m, *H*-2', 3', 5', 6'). 7.5 -7.59 (3H, m, *H*-6, 8, 9). 7,8 (1H, d, J_{HH} = 8.1 Hz, *H*-7). 8.19 (1H, d, J_{HH} = 7.8 Hz, *H*-10). ^{13}C NMR (CDCl3, 75 MHz) δ en ppm : 41.79 (s, C-4). 55.3 (s, C6H4OC*H*3). 61.65 (s, C-3). 117.58 (s, CN). 120 (s, C-4a). 121.1 (s, C-10). 123.55 (s, C-10a). 124.95 (s, C-6), 126.55 (s, C-5). 126.99 (s, C-8). 127.07 (s, C-9). 127.69 (s, C-7). 128.43 (s, C-3', 5'). 128.17 (s, C-2', 6'). 129.52 (s, C-1'). 133.62 (C-6a). 144.74 (C-10b). 154 (s, C-4'). 159,35 (C-2). FTIR (KBr) cm^{-1}: 3416 (CH), 3316 (NH2), 2183 (CN), 1633 (NH2). MS (EI) m/z (%) : 328 (M$^+$); 221 (100).

2-Amino-3-cyano-4-(4-chlorphenyl)-4Hbenzo[h]chromene (5c): Yellow solid, mp = 232-234°C. ^{1}H NMR (CDCl3, 300 MHz) δ en ppm : 4.81 (2H, s, N*H*2). 4.87 (1H, s, *H*-4). 6.99 (1H, d, J_{HH} = 8.52 Hz, *H*-5).7.18 (2H, d, J_{HH} = 8.4 Hz, *H*-2', 6'). 7.31 (2H, d, J_{HH} = 8.4 Hz, 3', 5'). 7.52-7.62 (3H, m, *H*-6, 8, 9). 7.81 (1H, d, J_{HH} = 7.35 Hz, *H*-7). 8.19 (1H, d, J_{HH} = 7.92 Hz, *H*-10). ^{13}C NMR (CDCl3, 75 MHz) δ en ppm : 40.93 (s, C-4). 60.96 (s, C-3). 116.66 (s, CN). 119.52 (s, C-4a). 120.78 (s, C-10). 123.21 (s, C-10a). 124.82 (s, C-6). 125.97 (s, C-5). 126.82 (s, C-8). 126.94 (s, C-9). 127.80 (C-7). 129.05 (s, C-3',5'). 129.48 (s, C-2', 6'). 133.27 (s, C-4'), 133.38 (s, C-6a). 142.93 (s, C-1'). 143.30 (s, C-10b). 159 (s, C-2). FTIR (KBr) cm^{-1}: 3433 (CH), 3316 (NH2), 2183 (CN), 1650 (NH2). MS (EI) m/z (%): 332 (M$^+$), 221 (100).

2-Amino-3-cyano-4-(3-nitrophenyl)-4Hbenzo[h]chromene (5d): Yellow solid, mp = 213-215°C. ^{1}H NMR (CDCl3 , 300 MHz) δ en ppm : 4.97 (2H, s, N*H*2). 5.03 (1H, s, *H*-4). 6.96 (1H, d, J_{HH} = 8.4 Hz, *H*-5).7.49-7.66 (5H, m, *H*-6, 8, 9, 4', 5'). 7.82 (1H, d, J_{HH} = 7.5 Hz, *H*-7). 8.11 (2H, m, *H*-2', 6'). 8.21 (1H, d, J_{HH} = 7.8 Hz, *H*-10). ^{13}C NMR (CDCl3, 75 MHz) δ en ppm : 41.67 (s, C-4). 61.2 (s, C-3). 116.00 (s, CN). 119.63 (s, C-4a). 121.19 (s, C-10). 122.94 (s, C-9). 123.36 (s, C-6). 123.74 (s, C-10a). 125.47 (s, C-2'). 125.86 (s, C-4'). 127.36 (s, C-7). 127.54 (s, C-5).128.15 (s, C-8). 130.21 (s, C-6'). 133.85 (C-6a). 134.61 (s, C-5'). 144 (C-1'). 146.88 (s, C-3'). 149.05 (s, C-10b). 159.73 (C-2). FTIR (KBr) cm^{-1}: 3457 (CH), 3350 (NH2), 2180 (CN), 1614 (NH2). MS (EI) m/z (%): 343 (M$^+$), 221 (100).

It is noteworthy to mention that, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in high yields in relatively short reaction times. The use of the expanded Perlite is particularly interesting since its regenerated by calcinations at 800°C during 15 min, and after five successive recoveries, product **5a** was obtained with same yield.

Conclusion

In conclusion, the expanded Perlite can serve as an efficient catalyst for the synthesis of 2-amino-4H-chromenes as biologically and pharmacologically active compounds. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and work-up procedure which makes it a useful and attractive process for the synthesis of these compounds. Most importantly, water has been chosen as a green solvent for these reactions.

Acknowledgement

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