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Aqua mediated synthesis of substituted 2-amino-4H-chromenes catalyzed by green and reusable Preyssler heteropolyacid

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Abstract—A simple, clean and environmentally benign route to the synthesis of 2-amino-4H-chromenes is described using Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, as a green and reusable catalyst in water. The products were obtained in very good yields.

2-Amino-chromenes represent an important class of compounds being the main components of many naturally occurring products. They can also widely be utilised as cosmetics, pigments[1] and potential biodegradable agrochemicals.[2] These compounds have been of interest to the medicinal chemist for many years. Fused chromenes are biologically active compounds with a wide spectrum of activities such as antimicrobial,[3] mutagenicitical,[4] antiviral,[5,6] 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 for several hours.[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 in combination with heterogeneous and reusable catalysts represents one of the more powerful green chemical technology procedures.[21]

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.[22]

Heteropolyacids, HPAs, have attracted increasing interest because of their applications, For example, as cata-

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lysts for organic reactions, corrosion resistant coatings, dopants in sol–gel matrices, membranes in selective electrodes, in gas detection apparatuses, in solid-state electrochromic devices, in liquid and solid wx electrolytic cells.[23–28]

There are two kinds of protons in the HPA crystals. One is the dissociated and hydrated proton that is combined with the HPA anion; the other is the unhydrated proton that is located on the bridge-oxygen in the HPA anion.

Since the dissociated protons have good mobility, the HPA crystals have some characteristics of a ''pseudo-liquid phase''. Hence they are superionic protonic conductors and promising solid electrolytes.

In view of the diverse therapeutic activity of chromenes and based on our previous studies on the use of water as solvent[29,30] and Preyssler type heteropolyacid as catalyst[31] for carrying out organic reactions and in continuation of our interest in the synthesis of heterocyclic compounds[32] we now report the three-component synthesis of substituted 2-amino-chromenes using Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, as readily available, green, reusable and inexpensive catalyst and water as solvent (Scheme 1).

Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, was prepared by the passage of a solution of the potassium salt in water through a column (50 cm × 1 cm) of Dowex 50 W × 8 in the H^+ form and evaporation of the elute to dryness under vacuum.

In a typical reaction[39] a mixture of the $H_{14}[NaP_5W_{30}O_{110}]$ (0.03 g), benzaldehyde (1 mmol), malononitrile (1 mmol) and α-naphthol (1 mmol) in water (5 mL) was refluxed for 3 h. After completion of the reaction, the mixture was cooled to room temperature. The solid, which separated, was filtered and then recrystallized from methanol to afford pure product.

The process represents a typical cascade reaction[33,34] in which the benzylidene malononitrile, 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 although it results in a net dehydration.[35] On the contrary, the second step, presumably involving the ortho C-alkylation of α-naphthol by reaction with the electrophilic C=C double bond[36] and the nucleophilic addition of the phenolic OH group of the CN moiety[37] producing the final 2-amino-2-chromene, requires the intervention of the catalyst, as the uncatalyzed reaction afforded the final product in only 29% yield.

A screening of three different solvents was performed in order to define the best solvent as a solvent of choice. As reported in Table 1, water was found to be the superior one affording the desired product in 91% yield.

The scope and the generality of the present method were then further demonstrated by the reaction of various aldehydes with malononitrile and α- or β-naphthol. In all cases good yields with good selectivity were obtained.

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 results are shown in Table 2.

Finally we investigated the reusability of the catalyst. The catalyst is soluble in water and could be removed easily by evaporation of the solvent. After evaporating of water the catalyst was filtered, washed with diethyl ether, dried at 130 °C for 1 h, and re-used in another reaction. The recycled catalyst was used for three consecutive reactions without observation of appreciable loss in its catalytic activities.[39]

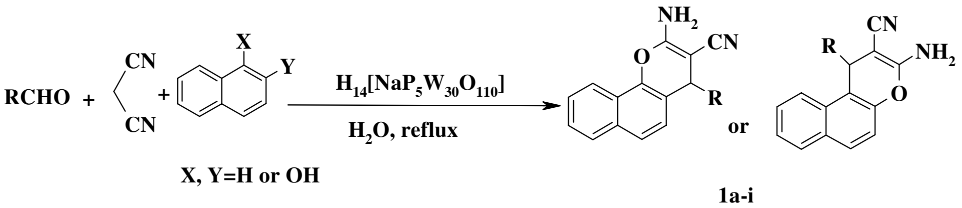
It was used three times to promote the model reaction affording the corresponding chromene in 91, 89 and 87% yields, respectively, and with the same excellent selectivity.

In conclusion, $H_{14}[NaP_5W_{30}O_{110}]$ 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

Table 1. Synthesis of 3-amino-2-cyano-1-(phenyl)-1H-benzo[f]chromene in different solvents in the presence of $H_{14}[NaP_5W_{30}O_{110}]$

Entry	Solvent	Time (h)	Yield (%)[a]
1	HOAc	8	50
2	CH_3CN	6	80
3	H_2O	5	91

[a] Yields refer to isolated products.



Scheme 1.

Table 2. Synthesis of substituted 2-amino-chromenes catalyzed by $H_{14}[NaP_5W_{30}O_{110}]$

Entry	R	Phenol	Time (h)	Yield (%)[a]	Mp (°C)	
					Found	Reported[19,38]
1	C_6H_5	α-Naphthol	3	91	209	210–211
2	C_6H_5	β-Naphthol	2.75	93	280	278–280
3	$4\text{-}NO_2C_6H_4$	α-Naphthol	4.5	90	240	239.5–241
4	$4\text{-}NO_2C_6H_4$	β-Naphthol	4.25	93	188	188–189
5	$4\text{-}MeOC_6H_4$	α-Naphthol	3.25	91	191	190–191.5
6	$4\text{-}MeOC_6H_4$	β-Naphthol	3	92	182–183	182
7	$4\text{-}ClC_6H_4$	α-Naphthol	4	90	231–232	232
8	$4\text{-}ClC_6H_4$	β-Naphthol	4	91	206–208	208
9	$3\text{-}NO_2C_6H_4$	α-Naphthol	4.5	92	212	214.5–216

[a] Yields refer to isolated products.

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.

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References and notes

1. Ellis, G. P. In *The Chemistry of Heterocyclic Compounds Chromenes, Chromanes and Chromones*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, 1977; pp 11–139, Chapter II.
2. Hafez, E. A.; Elnagdi, M. H.; Elagemey, A. G. A.; El-Taweel, F. M. A. A. *Heterocycles* **1987**, *26*, 903.
3. Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715.
4. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *47*, 395.
5. Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787.
6. Martinez, A. G.; Marco, L. *J. Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165.
7. Dell, C. P.; Smith, C. W. European Patent Appl. EP537949 *Chem. Abstr.* **1993**, *119*, 139102d.
8. Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, *51*, 2001.
9. Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750.
10. Eiden, F.; Denk, F. *Arch. Pharm. Weinheim Ger. (Arch. Pharm.)* **1991**, *324*, 353.
11. Kazuo, M.; Kazuya, O.; Hironobu, H. *J. Org. Chem.* **1989**, *54*, 557.
12. Ishikawa, T. *Heterocycles* **2000**, *53*, 453.
13. (a) Jankun, J.; Selman, S. H.; Swiercz, R.; Skrzypczak-Jankun, E. *Nature* **1997**, *387*, 56; (b) Covington, A. D. *Chem. Soc. Rev.* **1997**, 111; (c) van Rensburg, H.; van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron Lett.* **1997**, *38*, 3089.
14. Hudlicky, T. *Chem. Rev.* **1996**, *3*, 96.
15. (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, 1998; (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (c) Cornils, B.; Herrmann, W. A. *Aqueous-phase Organometallic Chemistry-Concepts and Applications*; Wiley-VCH: Weinheim, 1998.
16. Elagamay, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem. B* **1990**, *29*, 885.
17. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395.
18. Shi, D. Q.; Zhang, S.; Zhuang, Q. Y.; Tu, S. J.; Hu, H. W. *Youji Huaxue* **2003**, *23*, 809.
19. Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. *Tetrahedron Lett.* **2004**, *45*, 2297.
20. Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295.
21. (a) Clark, J. H. In *Chemistry of Waste Minimisation*; Chapman and Hall: London, 1995; (b) Clark, J. H.; Macquarrie, D. *J. Chem. Soc. Rev.* **1996**, 303; (c) Sheldon, R. A. *Chem. Ind. (London)* **1997**, 12.
22. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159; (b) Kobayashi, S. *Synlett* **1994**, 689; (c) Okuhara, T. *Chem. Rev.* **2002**, *102*, 3641.
23. Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113.
24. Lomakina, S. V.; Shatova, T. S.; Kazansky, L. P. *Corros. Sci.* **1994**, *36*, 1645.
25. Tasumisago, M.; Honjo, H.; Sakai, Y.; Minami, T. *Solid State Ionics* **1994**, *74*, 105.
26. Sheu, C.; Shih, J. S. *Anal. Chim. Acta* **1996**, *324*, 125.
27. Babinec, S. J. *Proc. Electrochem. Soc.* **1994**, *94*, 30.
28. Giordano, N.; Staiti, P.; Arico, A. S.; Passalacqua, E.; Abate, L.; Hocevar, S. *Electrochimica Acta* **1997**, *42*, 1645.
29. Heravi, M. M.; Taheri, Sh.; Bakhtiari, Kh.; Oskooie, H. A. *Catal. Commun.* **2007**, *8*, 211.
30. Heravi, M. M.; Derikvand, F.; Haghighi, M.; Bakhtiari, Kh. *Lett. Org. Chem.* **2006**, *3*, 297.
31. (a) Heravi, M. M.; Zadsirjan, V.; Bakhtiari, Kh.; Bamoharram, F. F. *Catal. Commun.* **2007**, *8*, 315; (b) Heravi, M. M.; Zadsirjan, V.; Bakhtiari, Kh.; Bamoharram, F. F. *Synlett* **2006**, 1768; (c) Bamoharram, F. F.; Roshani, M.; Alizadeh, M. H.; Razavi, H.; Moghayadi, M. *J. Braz. Chem. Soc.* **2006**, *17*, 505; (d) Heravi, M. M.; Behbahani, F. K.; Bamoharram, F. F. *J. Mol. Catal. A.* **2006**, *253*, 16.
32. (a) Heravi, M. M.; Rahimzadeh, M.; Bakavoli, M.; Ghassemzadeh, M. *Tetrahedron Lett.* **2004**, *45*, 5747; (b) Heravi, M. M.; Rahimzadeh, M.; Bakavoli, M.; Ghassemzadeh, M. *Tetrahedron Lett.* **2005**, *46*, 1607; (c) Heravi, M. M.; Tajbakhsh, M.; Ahmadi, A. N.; Mohajerani, B. *Monatsh. Chem.* **2006**, *137*, 175; (d) Heravi, M. M.; Bakhtiari, Kh.; Oskooie, H. A.; Taheri, Sh. *J. Mol. Catal. A: Chem.* **2007**, *263*, 279.
33. Domling, A.; Herdtweck, E.; Ugi, I. *Acta Chem. Scand* **1998**, *52*, 107.
34. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937; (b) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

35. Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. *Green Chem.* **2000**, *2*, 101.
36. Abdel-Latif, F. F. *Indian J. Chem. B* **1990**, *29*, 664.
37. Martin, N.; Seoane, C.; Carlos, J.; Soto, J. L. *Tetrahedron* **1988**, *44*, 5861.
38. Jin, T.-Sh.; Xiao, J.-Ch.; Wang, S.-J.; Li, T.-Sh. *Ultrason. Sonochem.* **2004**, *11*, 393.
39. Preparation of 2-amino-4H-chromenes: General procedure. A mixture of an appropriate benzaldehyde (1 mmol), malononitrile (1 mmol), α- or β-naphthol (1 mmol) and $H_{14}[NaP_5W_{30}O_{110}]$ (0.03 g), in water (5 mL) were refluxed for 3 h; After completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature. The precipitate was collected by filtration and recrystallized from MeOH. In order to show generality of the procedure, the reaction was repeated with other benzaldehyde derivatives. The results are summarized in Table 1.Recyclibility of the catalyst: After evaporating of water the catalyst was filtered, washed with diethyl ether, dried at 130 °C for 1 h, and re-used in another reaction.