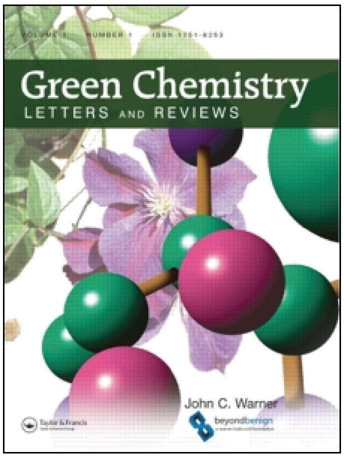

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Green, three component highly efficient synthesis of 2-amino-5,6,7,8-tetrahydro-4-*H*-chromen-3-carbonitriles in water at ambient temperature

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RESEARCH LETTER

Green, three component highly efficient synthesis of 2-amino-5,6,7,8-tetrahydro-4-*H*-chromen-3-carbonitriles in water at ambient temperature

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A three component synthesis of 2-amino-5,6,7,8-tetrahydro-4-*H*-chromen-3-carbonitriles using aldehydes, malononitrile, and dimedone in water at ambient temperature was reported.

Keywords: green synthesis; water; ambient temperature; 4*H*-chromenes

Introduction

Green chemistry is receiving considerable attention nowadays (*1*). More and more chemists are devoted to the research of green synthesis (*2*). This involves the designing of chemical processes with a view to reducing or even eliminating the use and production of hazardous materials (*3*). Recent endeavors have focused on limiting the use of organic solvents and replacing them with environmentally benign media. The use of water as a solvent for organic reactions has attracted much attention in synthetic organic chemistry in recent years, not only because water is an environmentally friendly solvent, but also because it exhibits unique reactivity and selectivity that are different from reaction in organic solvents (*4,5*). Multi-component reactions (MCRs) are now gaining much importance in synthetic organic chemistry, due to their atom economy, selectivity, simplicity in the procedure or equipment, time, and cost saving (*6–9*).

Substituted 2-amino-2-chromenes have received considerable attention due to their importance as potential agrochemicals, as well as being the main constituent of many natural products and pigments (*10–12*), which reflects the remarkable potential of such derivatives as a source of valuable drug candidates. The conventional method for their synthesis involves the reaction of an ethanolic solution of arylidenemalono-nitrile with dimedone in the presence of piperidine at reflux for six hours (*13*). However, this method suffers from long reaction times and uses large quantities of organic solvents which may be harmful to the environment. The development of an efficient green methodology for the synthesis of 2-aminochromenes is highly essential. A MCR in water at ambient temperature will overcome the disadvantage of this conventional method. In continuation to our interest for the synthesis of azines and azoles via environmentally friendly techniques (*14,15*), we report herein the synthesis of 2-amino-5,6,7,8-tetrahydro-4H-chromen-3-carbo-nitriles via three component synthesis in water at ambient temperature.

Results and discussion

When a mixture of benzaldehyde (**1**), malononitrile (**2**), and dimodon (**3**) in water (20 ml) in the presence of two drops of piperidine as a catalyst was stirred at room temperature (22°C), the corresponding 2-aminochromene derivative was obtained almost instanteously in 95% yield. The structure of the product was confirmed by comparison (TLC, mixed melting point) with an authentic sample (*13*) prepared by refluxing dimedone (**3**) with benzylidenemalononitrile in ethanol/pip. for six hours and also by spectral data. The generality of this method was examined by the use of several substituted aromatic aldehydes under the same reaction conditions. It has been found that the reaction proceeds smoothly to give 2-aminochromene derivatives in high yields and the electronic nature of the aromatic aldehyde substituent has no significant effect in the conversion (cf. Table 1).

Although, simple ^{1}HNMR did not determine the favoring enantiomer of the reaction product, molecular orbital calculations (GAMESS program) (*16*) established the (S) conformer.

A proposed mechanism to account for the formation of **6a–f** is shown in Scheme 1.

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Table 1. Synthesized 2-aminochromene derivative in H_2O/pip.

Compound	Ar (1)	Time/minute	Yield (%)	Mp (°C)	
				Found	Reported
6a	C_6H_5	30	95	225–226	226–228 (17)
6b	4–Cl–C_6H_4	45	93	206–208	207–209 (17)
6c	4–NO_2–C_6H_4	45	92	210–211	208–211 (18)
6d	4–CH_3–C_6H_4	45	94	213–214	214–216 (18)
6e	4–OMe–C_6H_4	40	94	201–202	198–200 (17)
6f	4–OH–C_6H_4	60	91	205–207	206–208 (19)

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were measured with a Shimadzu Model 470 spectrophotometer. The NMR spectra were recorded on a Bruker AM 400 spectrometer with DMSO-d6 as solvent and TMS as internal reference, chemical shifts are expressed as δ ppm. Mass spectra were measured on a GCMS-QP 1000 EX mass spectrometer. Analytical-TLC was performed with silica gel plates using silica gel 60 PF_{254} (Merck). Chemicals were purchased from Merck Chemicals.

General procedure

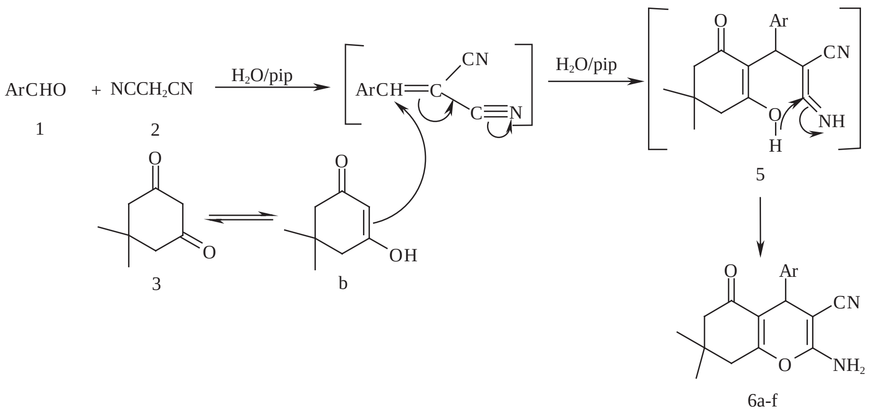
To a suspension of equimolar (0.01) mixture of each of aromatic aldehyde, malononitrile, and dimedone in water (20 ml) two drops of piperidine were added. The reaction mixture was stirred at room temperature (22°C) in which, after 10 minutes, the reactants were dissolved and a precipitate started to be formed. After completion of the reaction, the precipitate formed was collected by filtration and re-crystallized from ethanol. All the synthesized compounds have been described previously and our spectral data (IR, ^1H, and ^{13}C NMR) are substantially identical with those found in literature.

Compound 6e

Mp: 201–202°C. IR (KBr): 3395, 3327, 2200, 1688 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.93 (s, 3H), 1.07 (s, 3H), 2.06 (*d*, $J = 16$ Hz, 1H), 2.22 (*d*, $J = 16$ Hz, 1H), 2.44 (*d*, $J = 17.7$ Hz, 1H), 2.55 (*d*, $J = 17.7$ Hz, 1H), 3.73 (s, 3H, OCH_3), 5.01 (s, 1H), 6.15 (s, 2H, NH_2), 6.93 (*d*, $J = 8.5$ Hz, 2H, CH–aromatic), 7.13 (*d*, $J = 8.5$ Hz, 2H, CH–aromatic).

Conclusion

We have developed an easy, high yielding, convenient, and green method for the synthesis of 2-amino-5,6,7,8-tetrahydro-4-*H*-chromen-3-carbonitriles from the reaction of aromatic aldehydes, malononitrile, and dimedone in water at ambient temperature. The process proved to be a simple, environmentally friendly technique of high yields, and a pronounced rate of acceleration was achieved in performing the reaction in water.



Scheme 1. Mechanism to account for the formation of **6a-f**.

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