Four-component catalyst-free reaction in water: Combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile derivatives†

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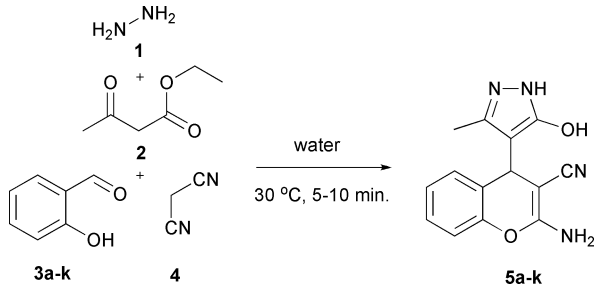
A catalyst-free combinatorial library of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile derivatives has been developed by a four-component reaction between hydrazine hydrate (1), ethyl acetoacetate (2), 2-hydroxybenzaldehydes (3) and malononitrile (4) in water at ambient temperature.

The challenging task of achieving 'efficiency' in all aspects of chemical production, advocated by green chemistry can be realized by innovative research which comprehensively addresses the issues of atom economy, economy of steps and avoidance of auxiliary chemicals.[1] Developing a simple, eco-friendly reaction protocol for the synthesis of compound libraries of medicinal scaffolds is as an attractive area of research in both academic and pharmaceutical R&D.[2] Multi-component reaction (MCR) protocols in water will be one of the most suitable strategies, which will meet the requirements of green chemistry as well as for developing libraries of medicinal scaffolds.[3]

The chromene framework,[4] particularly 4-aryl/alkyl-2-aminochromenes, is an important medicinal scaffold. Several compounds having this framework show pro-apoptotic activity against cancer cells as a single agent or in combination with chemo radiotherapy,[5] as well as anticoagulant, spasmolytic, diuretic, insecticidal, and antianaphylactin activity.[6] Some of them can also be employed as cosmetics and pigments,[4] and utilized as potential biodegradable agrochemicals.[7]

Pyrazolones are important ingredients in many pharmaceutical preparations, such as analgesics, antipyretics *etc.* Heterocycle substituted pyrazolones are reported to possess kinase inhibitory properties, particularly of enzymes which catalyze the phosphorylation of serine and threonine in proteins. Therefore, an inhibitor of these protein kinases can be developed as a drug candidate for treating diseases related to these enzymes, such as rheumatoid arthritis, psoriasis, septic shock, bone loss, cancers and other proliferative diseases.[8]

A molecular skeleton which integrates chromene as well as pyrozolone moieties might possess properties of both and enhance the activity. To the best of our knowledge only one compound possessing such molecular skeleton has been reported in the literature.[9] The reported procedure focuses on the synthesis of 4-substituted-2-amino-4*H*-chromene framework involving a three-component electrochemical reaction in organic solvent and pyrazolone has been used as one of the substituents. We are actively engaged in developing multi-component reaction protocols in water.[3,10] Herein, we report for the first time a catalyst-free four-component reaction for a combinatorial synthesis of novel highly functionalised 4-pyrazolyl-4*H*-chromene frameworks in water at ambient temperature (Scheme 1).



Scheme 1 Catalyst-free four-component synthesis of 4-pyrazolyl-4*H*-chromenes (**5a–k**).

A four-component reaction between hydrazine hydrate **1**, ethyl acetoacetate **2**, 2-hydroxybenzaldehyde **3** and malononitrile **4** in water at ambient temperature resulted in novel pyrazolyl-4*H*-chromene derivatives **5** in good to excellent yields. The reaction is compatible with several 2-hydroxybenzaldehyde derivatives (Table 1). The product is separated from the reaction mixture and isolated by filtration, and was pure on TLC. Conventional chromatographic purification or recrystallisation was not required. However, the product was washed with water and then a small amount of an ethyl acetate/hexane mixture (1:1). Formation of the product is suggested to involve the tandem reactions of: (i) reaction between **1** and **2** resulting in instantaneous formation of pyrazolone **6**, (ii) Knoevenagel condensation between 2-hydroxybenzaldehyde and malononitrile forming 2-imino-2*H*-chromene-3-carbonitrile **7** intermediate by 6-*exo-dig* cyclization of the hydroxyl group with the cyano group, and (iii) Michael addition of **6** to **7** and subsequent rearrangement. The reaction is completed within 5–10 minutes (Scheme 2). The pyrazolone moiety is present as a hydroxyl tautomer in the product. A reaction between 2-hydroxybenzaldehyde with malononitrile to form the 2-imino-2*H*-chromene-3-carbonitrile intermediate in water and its reaction with Michael donors have been reported.[11]

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, including spectroscopic data for all the new compounds along with NMR spectra. See DOI: 10.1039/b913838b

Table 1 Catalyst-free synthesis of 4-pyrazolyl-4*H*-chromene in water

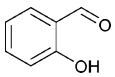
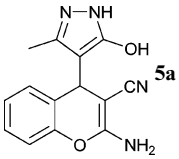
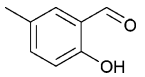
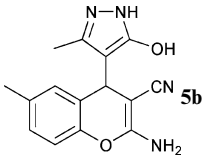
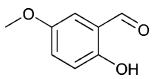
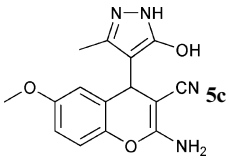
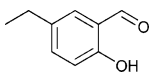
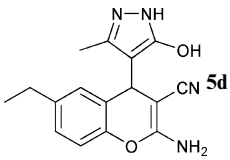
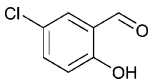
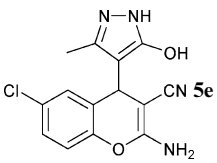
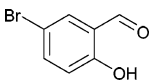
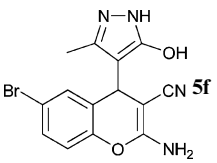
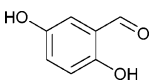
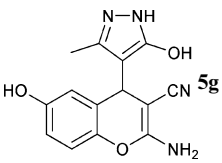
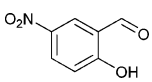
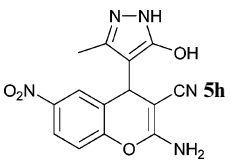
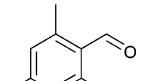
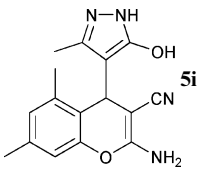
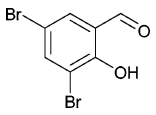
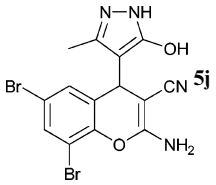
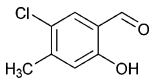
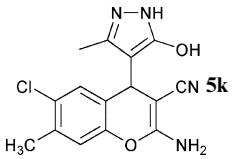
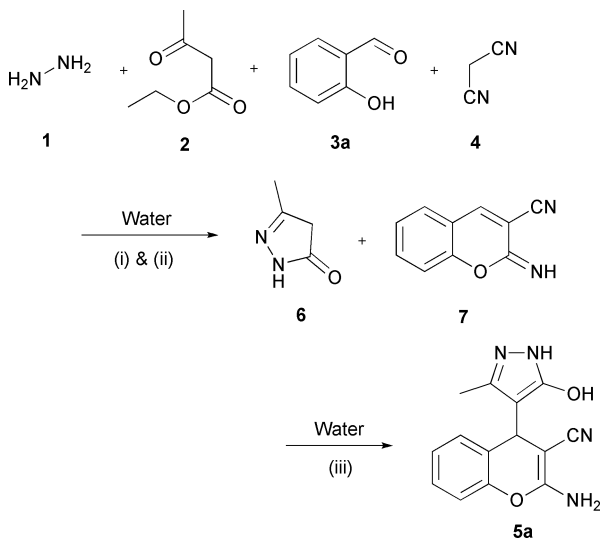
Entry	Salicyaldehyde **3**	4-Pyrazoyl-4*H*-chromenes **5**	Yield (%)[a]
1		 **5a**	87
2		 **5b**	81
3		 **5c**	78
4		 **5d**	83
5		 **5e**	90
6		 **5f**	92
7		 **5g**	79
8		 **5h**	86
9		 **5i**	76

Table 1 *(Contd.)*

Entry	Salicyaldehyde **3**	4-Pyrazoyl-4*H*-chromenes **5**	Yield (%)[a]
10		 **5j**	74
11		 **5k**	79

[a] Isolated pure product.



Scheme 2 Proposed reaction pathway.

The four-component catalyst-free reaction protocol developed in water results in a potential medicinal scaffold. This reaction protocol conforms to several green chemistry principles coupled with the potential for developing combinatorial libraries. Green aspects of this reaction include: (i) highly atom economic – ethanol and water are the byproducts, (ii) being a multi-component reaction it is step economic, (iii) water is being used as the reaction medium, therefore use of conventional volatile organic solvents is avoided and (iv) avoidance of catalyst.

Experimental

General procedure

To a stirred aqueous mixture of hydrazine hydrate 98% **1** (0.107 g, 2 mmol) and ethyl acetoacetate **2** (0.260 g, 2 mmol), 2-hydroxy benzaldehyde **3** (2 mmol), malononitrile **4** (0.132 g, 2 mmol) were added successively at ambient temperature under an open atmosphere with vigorous stirring for 5–10 min. The precipitated solid was filtered, washed with water and then with 5 mL of ethyl

acetate/hexane mixture (1:1). The product obtained was pure by TLC and spectral techniques.

Acknowledgements

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