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Rapid four-component reactions in water: synthesis of pyranopyrazoles

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ABSTRACT

An environmentally benign four-component reaction in aqueous medium at room temperature has been developed for the synthesis of 6-amino-5-cyano-3-methyl-4-aryl/heteroaryl-2*H*,4*H*-dihydropyrano[2,3-*c*]pyrazoles.

Green chemistry emphasizes the development of environmentally benign chemical processes and technologies.[1] Multi-component reactions (MCR) are processes in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the reactants. MCRs comply with the principles of green chemistry in terms of economy of steps as well as many of the stringent criteria of an ideal organic synthesis. These reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity coupled with minimization of time, labour, cost and waste production.[2] Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest from pharmaceutical groups.

Designing organic reactions in aqueous media is another attractive area in green chemistry.[3] Water is an abundant and environmentally benign solvent. As a reaction medium, it offers several benefits including control over exothermic reactions, salting in and salting out and variation of pH. Work up and purification can be carried out by simple phase separation techniques. Also, organic reactions in water exhibit unique reactivity and selectivity that are different from reactions in organic solvents. In particular, reactions with negative activation volume are reported to occur faster in water than in organic solvents.[4] Multi-component reactions are suggested to have a negative activation volume.[5]

Pyranopyrazoles are an important class of heterocyclic compounds. They find applications as pharmaceutical ingredients and biodegradable agrochemicals.[6–8] The first reported pyranopyrazole was synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene.[6] Various 6-amino-5-cyano-4-aryl-4*H*-pyrazolo[3,4-*b*]pyrans were synthesized by the reaction of arylidienemalononitrile with 3-methylpyrazoline-5-ones or by the condensation of 4-arylidienepyrazoline-5-one with malononitrile.[7] Sharanin et al.[8] have developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst. Shestopalov and co-workers[9] reported the synthesis of pyrazolopyran via a three-component condensation between *N*-methylpiperidone, pyrazoline-5-one and malononitrile in absolute ethanol. However, this reaction occurred only on heating or when induced by electrochemical methods under an inert atmosphere. Peng and co-workers have developed a two-component reaction involving pyran derivatives and hydrazine hydrate to obtain pyranopyrazoles in water.[10] The reaction was promoted by a combination of microwave and ultrasonic irradiation In the present work, we report an efficient and eco-friendly four-component reaction protocol in aqueous medium at room temperature for the synthesis of pyranopyrazole derivatives (Scheme 1).

This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost instantaneously, and pure product was obtained, without using any chromatographic techniques, simply by recrystallization from ethanol. The reaction between hydrazine hydrate **1**, ethyl acetoacetate **2**, benzaldehyde **3** and malononitrile **4** resulted in pyranopyrazole **5a** without need of a base. However, reactions with other aldehydes proceeded only in the presence of a catalytic amount (5–10 mol %) of a base. The reaction between **1**, **2**, 4-methylbenzaldehyde **3b** and **4** was carried out with different bases to optimize

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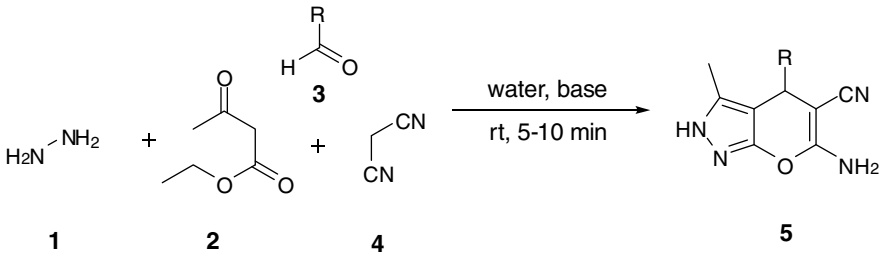


Scheme 1.

the procedure (Table 1). Reaction in the presence of piperidine produced the maximum yield (94%) of **5b** (Table 1). The above reaction was also carried out in conventional organic solvents, to investigate the effect of solvent. Water as the solvent provided the best yields compared to common organic solvents (Table 1). The use of ultra pure (milli-Q) water was better than using double distilled (DD) water. However, all the reactions were carried out in DD water only. The process was compatible with aliphatic aldehydes, substituted benzaldehydes and heterocyclic carbaldehydes as component **3** in the reaction (Table 2).[11]

All the synthesized compounds were characterized by IR, NMR, elemental analysis and LCMS. The structure of **5q**[12] was established by X-ray crystallography and was found to be the 2H isomer which is consistent with an earlier report[13] (Fig. 1). The formation of the product is proposed to involve the following tandem reactions: pyrazolone **6** formation by reaction between **1** and **2**, Knoevenagal condensation between **3** and **4** (**7**), Michael addition of **6** to **7**, followed by cyclization and tautomerization, (Scheme 2). To investigate the role of water in the reaction, a two-component reaction between ethyl acetoacetate and hydrazine hydrate was carried out in water and organic solvents. It was observed that pyrazolone **6** formation was instantaneous in water, whilst the same reaction occurred slowly in organic solvents. A similar rapid reaction between a 1,3-diketone and hydrazine in water in the presence of polystyrenesulfonic acid (PSSA) catalyst to yield pyrazoles was reported by Polshettiwar and Varma.[14] The lower yield of pyranopyrazole **5** and slow reaction rate in organic solvents may be ascribed to the slower rate of the formation of pyrazolone **6** with concomitant competitive reactions.

The aqueous medium, four-component reaction protocol developed in the present study offers a fast and eco-friendly method for the synthesis of pyranopyrazoles. The protocol also offers flexibility in tuning the molecular complexity and diversity in a single step.

Table 1
Effect of base and solvent

Entry	Base	Solvent	Time (min)	Yield
1	Et_3N	Water	30	38
2	Et_2NH	Water	30	58
3	Pyrrolidine	Water	30	53
4	Piperidine	Water	5	94
5	Morpholine	Water	30	62
6	Piperazine	Water	30	63
7	K_2CO_3	Water	60	71
8	Piperidine	Brine	60	22
9	Piperidine	DD Water[a]	5	91
10	Piperidine	Milli-Q Water	5	96
11	Piperidine	EtOH	90	66
12	Piperidine	DMSO	120	—
13	Piperidine	DMF	120	—
14	Piperidine	MeCN	60	35
15	Piperidine	THF	120	Trace
16	Piperidine	$CHCl_3$	120	43
17	Piperidine	CH_2Cl_2	60	31
18	Piperidine	$ClCH_2CH_2Cl_2$	90	37
19	Piperidine	Toluene	15	71

[a] Double distilled water.

Table 2
Four-component synthesis of pyranopyrazoles **5**

Entry	Aldehyde	Yield
5a	C_6H_5	83, 80[a]
5b	4′-Me–C_6H_4	94
5c	4′-MeO–C_6H_4	85
5d	4′-O_2N–C_6H_4	79
5e	4′-Cl–C_6H_4	89
5f	4′-HO–C_6H_4	86
5g	4′-F–C_6H_4	76
5h	2′-MeO–C_6H_4	80
5i	3′-MeO–C_6H_4	87
5j	3′-O_2N–C_6H_4	66
5k	3′-MeO,4′–MeO–C_6H_3	74
5l	3′-MeO,5′–MeO–C_6H_3	76
5m	2′-Cl,3′–Cl–C_6H_3	81
5n	2′-Cl,4′–Cl–C_6H_3	78
5o	3′-MeO,4′-MeO, 5′-MeO–C_6H_2	74
5p	3′-Pyridinyl	76
5q	4′-Pyridinyl	83
5r	2′-Furanyl	67
5s	2′-Thiophenyl	89
5t	Isopropyl	74

[a] Without catalyst.

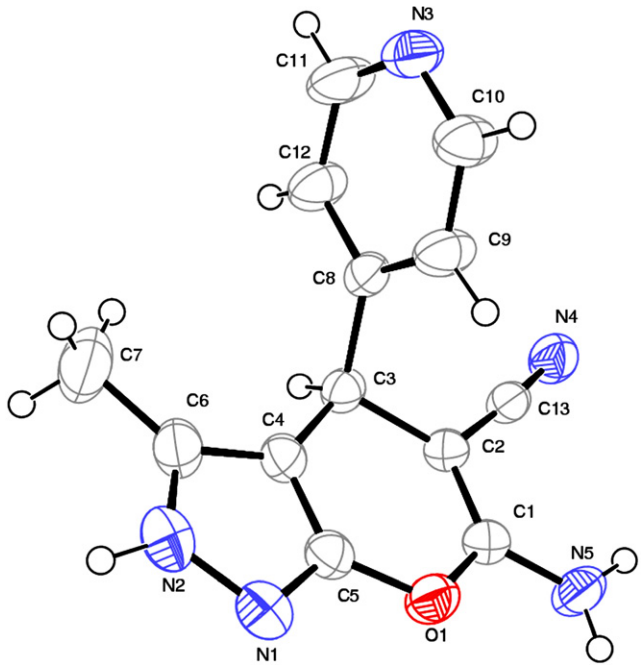
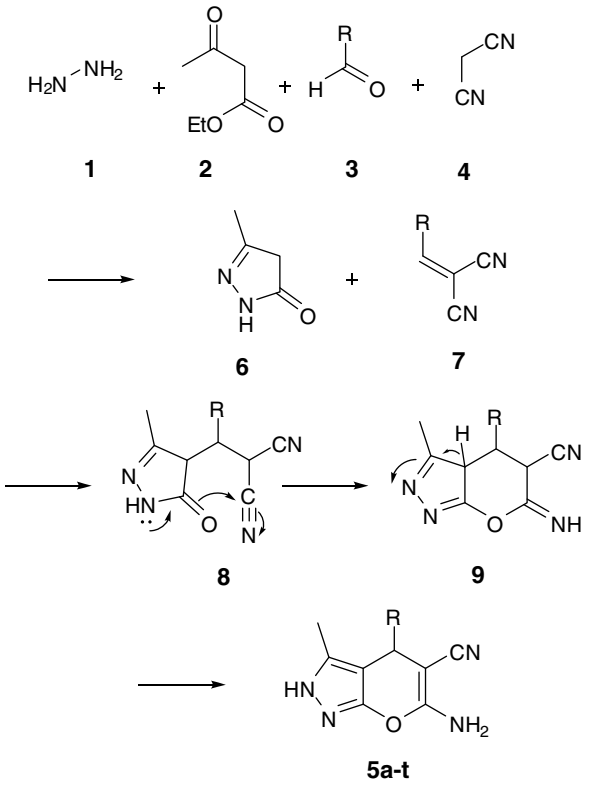


Figure 1. ORTEP diagram of the single-crystal X-ray structure of pyranopyrazole **5q**.



Scheme 2.

Acknowledgement

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11. *General procedure for Pyranopyrazoles*: To a stirred aqueous mixture of hydrazine hydrate 96% **1** (0.107 g, 2 mmol) and ethyl acetoacetate **2** (0.260 g, 2 mmol), aldehyde **3** (2 mmol), malononitrile **4** (0.132 g, 2 mmol) and piperidine (5 mol %) were added successively at room temperature under an open atmosphere with vigorous stirring for 5–10 min. The precipitated solid was filtered, washed with water and then with a mixture of ethyl acetate/hexane (20:80). The product obtained was pure by TLC and ^{1}H NMR spectroscopy. However, the products were further purified by recrystallization from ethanol.
Compound **5q**: White solid, mp 218–221 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 12.16 (s, 1H), 8.45 (s, 2H), 7.14 (s, 2H), 6.99 (s, 2H), 4.60 (s, 1H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 161.7, 155.2, 153.3, 150.4, 136.3, 123.2, 121.0, 96.7, 56.1, 36.0, 10.2. IR (KBr): 3414, 3325, 3057, 2172, 1662, 1612, 1581, 1493, 1429, 1146, 1086, 1045, 796, 683, 617 cm^{-1}. LC–MS *m*/*z* (ESI) found: 254.0; calcd for $C_{13}H_{12}N_5O$: $(M+1)^+$: 254.1. Anal. Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.655. Found: C, 61.89; H, 4.52; N, 27.99.
12. Crystallographic data for **5q** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 664522. Copy of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 (0) 1223 33603 or e-mail: deposit@ccdc.cam.ac.uk).
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