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A green and convenient approach for the synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates via a one-pot, multi-component reaction in water

Adeleh Moshtaghi Zonouz [a,*], Issa Eskandari [a], Hamid Reza Khavasi [b]

[a] *Chemistry Department, Faculty of Science, Azarbaijan Shahid Madani University, Tabriz, Iran*
[b] *Shahid Beheshti University, G.C., Evin, Tehran 1983963113, Iran*

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ABSTRACT

A green and efficient one-pot, four-component synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates in water is described. The method is catalyst-free, atom-economical, and does not involve tedious work-up or purification affording the target compounds in good yields.

Green chemistry techniques continue to grow in importance. Alternative processes help to conserve resources and can reduce costs. The replacement of conventional solvents with water, which is harmless to health and is available in large quantities, is an interesting basic approach along these lines.[1–3]

Multi-component reactions (MCRs) have emerged as a powerful tool for the construction of novel and complex molecular structures due to their advantages over conventional multi-step synthesis. The major advantages of MCRs include lower costs, shorter reaction times, high atom-economy, energy saving, and the avoidance of time consuming and expensive purification processes. It is established that MCRs are generally much more environmentally friendly, and offer rapid access to large compound libraries with diverse functionalities.[4–7]

Pyranopyrazoles are fused heterocyclic compounds that exhibit bactericidal,[8] fungicidal,[9] insecticidal,[10] molluscicidal,[11,12] analgestic,[13] and anti-inflammatory activities,[14] and act as vasodilators and hypotensive,[15] hypoglycemic, and anticancer agents.[16,17] They are also potential inhibitors of human Chk1 kinase.[18] Due to their biological significance, there has been considerable interest in developing synthetic methods for the preparation of pyranopyrazole derivatives.[19–26] Four-component syntheses of pyranopyrazoles using hydrazine hydrate, ethyl acetoacetate, malononitrile, and aromatic aldehydes have been reported in the presence of catalysts such as β-cyclodextrin,[27] triethylamine,[28] cinchona alkaloid derivatives,[29] and imidazole.[30]

As part of our efforts to develop new synthetic methods in heterocyclic chemistry,[31–34] herein we report for the first time, a catalyst-free, four-component reaction of dimethyl acetylenedicarboxylate, hydrazine hydrate, malononitrile, and aromatic aldehydes for the synthesis of novel 3-methoxycarbonyl substituted pyrano[2,3-*c*]pyrazoles in water.

Initially, we carried out the MCR between dimethyl acetylenedicarboxylate, hydrazine hydrate, malononitrile, and aromatic aldehydes in water at 55–60 °C. After completion of the reaction (TLC monitoring), TLC indicated the mixture of products, so the reaction was conducted in two stages, first of all treatment of arylaldehyde and malononitrile in water at 55–60 °C gave the benzylidene malononitrile which, without isolation, was directly treated with dimethyl acetylenedicarboxylate and hydrazine hydrate. Stirring was maintained for an additional 0.5 h. The precipitated solid was filtered and purified by recrystallization from EtOH to give the pyrano[2,3-*c*]pyrazole derivatives **5a–j** in good yields (Table 1).[35] As indicated in Table 1, both electron-poor and electron-rich aldehydes were well tolerated.

The structures of the products were deduced from their elemental analysis and spectral data. In addition, the structure of **5i** was determined by an X-ray crystallographic study.[36,37]

Figure 1 shows the structure and the atomic numbering scheme used for compound **5i**.

The formation of pyranopyrazole derivatives **5a–j** can be rationalized by the following tandem reactions: (1) formation of

* Corresponding author.
E-mail address: adelehmz@yahoo.com (A. Moshtaghi Zonouz).

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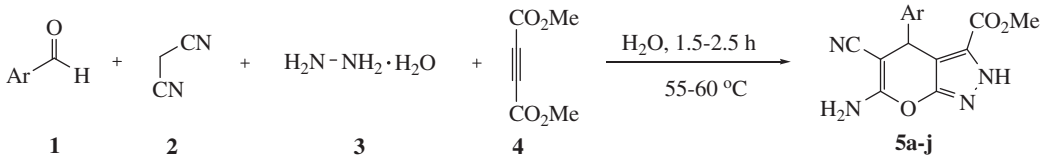
Table 1
Synthesis of 3-methyl carboxylate substituted pyrano[2,3-*c*]pyrazoles via a four-component reaction



1 **2** **3** **4** **5a-j**

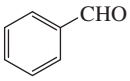
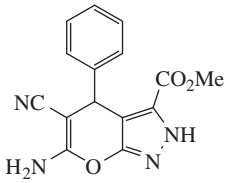
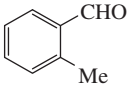
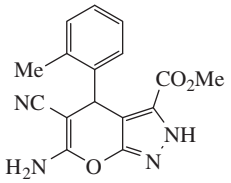
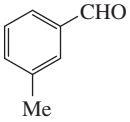
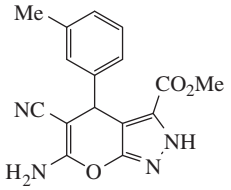
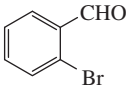
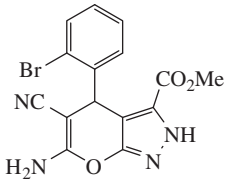
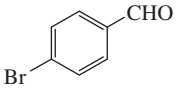
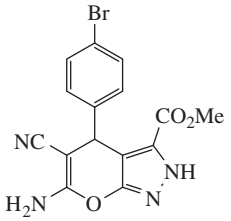
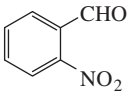
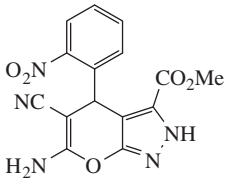
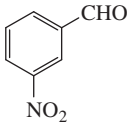
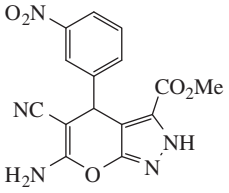
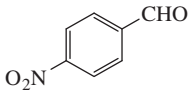
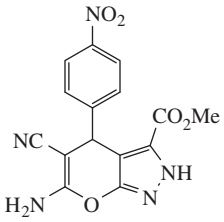
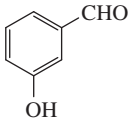
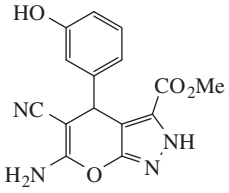
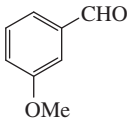
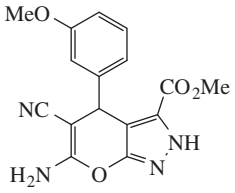
Entry	ArCHO	Product	Time (h)	Mp (°C)	Yield[a] (%)
1		 **5a**	1.5	231–232	78
2		 **5b**	2.5	239–240	75
3		 **5c**	2.5	220–222	70
4		 **5d**	2.5	242–244	73
5		 **5e**	2.5	247–248	75
6		 **5f**	2.5	230–232	64

Table 1 (*continued*)

Entry	ArCHO	Product	Time (h)	Mp (°C)	Yield[a] (%)
7		 **5g**	2.5	236–237	66
8		 **5h**	1.5	244–245	76
9		 **5i**	1.5	219–220	84
10		 **5j**	2.5	208–210	75

[a] Yield of isolated pure product after recrystallization.

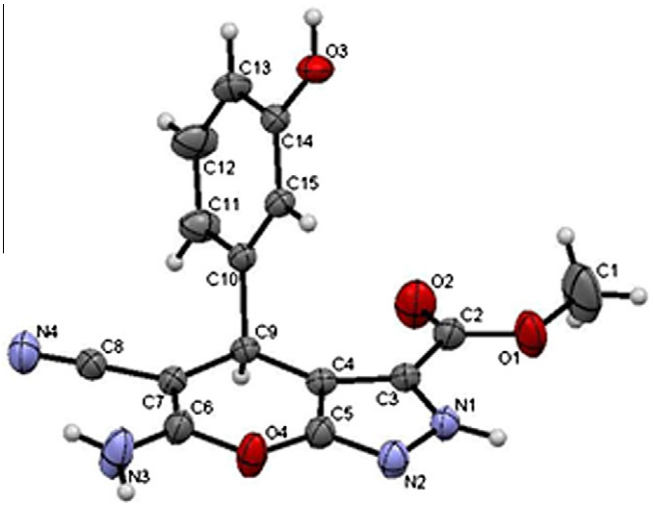
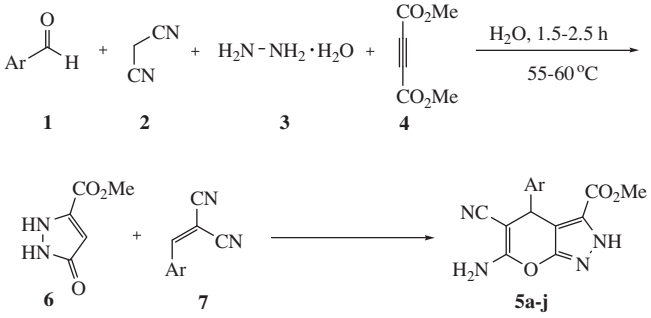


Figure 1. ORTEP structure of **5i**.

benzylidine malononitrile **7** via Knoevenagal condensation between aldehyde **1** and malononitrile **2**; (2) formation of pyrazolone **6** by reaction of hydrazine hydrate **3** and dimethyl acetylenedicarboxylate **4**; and (3) Michael addition of **6**,**7**, followed by cyclization and tautomerization (Scheme 1).



Scheme 1. Proposed reaction pathway.

In summary, a simple, efficient, eco-friendly, and catalyst-free process has been developed for the synthesis of novel pyranopyrazole derivatives in water. This green, four-component reaction, reported for the first time with dimethyl acetylenedicarboxylate, does not involve tedious work-up or purification operations, and gives rise to the target compounds in good yields.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.010.

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34. Moshtaghi, Z. A.; Eskandari, I.; Moghani, D. *Chem. Sci. Trans.* **2012**, *1*, 91.
35. *Typical procedure for the synthesis of pyranopyrazoles* ***5a–j***: A mixture of malononitrile (**2**) (0.066 g, 1 mmol) and benzaldehyde (0.1 ml, 1 mmol) in H_2O (3 ml) was stirred at 55–60 °C under an open atmosphere for 1 h. Next, hydrazine hydrate (**3**) 96% (0.05 ml, 1 mmol) and dimethyl acetylenedicarboxylate (**4**) (0.14 ml, 1.2 mmol) were added. The mixture was stirred until completion of the reaction as indicated by TLC (30 min). After cooling, the precipitated solid was filtered, washed with H_2O, and recrystallized from EtOH. Compound **5a** was obtained as white crystals. *Methyl 6-amino-5-cyano-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate* (**5a**). White crystals; mp 231–232 °C; yield: 0.232 g (78%). IR (KBr) (ν_{max}; cm^{-1}): 3386, 3325, 3266, 2953, 2202, 1723, 1654, 1613, 1469, 1396, 1077. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.59 (3H, s, OMe), 4.70 (1H, s, CH), 7.04–7.27 (5H, m, CH), 7.24 (2H, NH_2), 13.73 (1H, s, NH) ppm. ^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 37.45 (CH), 52.15 (CH_3 ester), 58.16 (C), 104.65 (C), 120.74 (CN), 127.10 (CH), 127.79 (CH), 128.67 (CH), 129.17 (C), 145.36 (C), 155.86 (C), 158.83 (C), 160.61 (C=O) ppm. Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.64; H, 3.95; N, 18.84.
36. *X-ray data for* ***5i***: CCDC 875556; $C_{15}H_{12}N_4O_4$, Mw = 312.29 g/mol, monoclinic system, space group $P2_1/c$, a = 8.7489(12), b = 20.648(3), c = 8.3466(11) Å, β = 103.748(10)°, V = 1464.6(3) Å^3, Z = 4, D_{calc} = 1.416 g cm^{-3}, μ(Mo–Kα) = 0.103 mm^{-1}, crystal dimensions = 0.33 × 0.30 × 0.25 mm. The structure was solved using SHELXS. The structure refinement and data reduction were carried out with SHELXL from the X-Step32 suite of programs. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0610, wR_2 = 0.1401 and S = 1.115 with 16504 parameters using 3964 independent reflections (θ range = 2.40–29.16 °). Hydrogen atoms were located from expected geometries and were not refined.
37. X-STEP32 Version 1.07b, X-ray structure evaluation package, 2000, Stoe&Cie, Darmstadt, Germany.