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Der Pharma Chemica, 2011, 3 (5):81-86
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ISSN 0975-413X
CODEN (USA): PCHHAX

A simple and clean method for four-component synthesis of pyrano[2,3-c]pyrazole derivatives

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ABSTRACT

A new convenient method for the synthesis of 6-amino-2H,4H-pyrano[2,3-c] pyrazole-5-carbonitriles, namely, four component condensation of aromatic aldehydes, activated methylene reagent, ethyl acetoacetate, and hydrazine hydrate in water medium.

Key words: Green chemistry, Multi-component reactions, Pyranopyrazoles, Pharmaceutical ingredients.

INTRODUCTION

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 [2-5]. 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 [6-9]. 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 [10-12]. Multi-component reactions are suggested to have a negative activation volume [13,14].

Pyranopyrazoles are an important class of heterocyclic compounds, they find applications as pharmaceutical ingredients and biodegradable agrochemicals [15-17]. The first reported pyranopyrazole was synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene [15]. 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. Sharanin *et al* [18] have developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst. Shestopalov and co-workers [19,20] 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 [21].

MATERIALS AND METHODS

General:

Melting points were recorded on an Electrothermal digital melting Point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FTIR 500 spectrophotometer using KBr optics. ¹H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer using DMSO-*d*₆ or CDCl₃ as solvent and TMS as internal standard. CHN analyses were carried out on a Carlo-Erba EA1110 CNNO-S analyzer.

General procedure for the preparation of 6-Amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles or carboxylate (1a-d).

To a stirred aqueous mixture of hydrazine hydrate 96% (2 mmol) and ethyl acetoacetate (2 mmol), aldehyde (2 mmol), malononitrile or ethyl cyanoacetate (2 mmol) and triethylamine (1 ml) were added successively at room temperature under an open atmosphere with vigorous stirring for 20 min. The precipitated solid was filtered, washed with water and then with a mixture of ethyl acetate/ hexane (20:80). The product obtained was purified by recrystallization from ethanol.

6-Amino-4-(9-anthracenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (1a).

Orange solid; m.p.277 °C., yield (85%); IR (KBr): $\bar{\nu}$ = 3354, 3311 (NH₂), 2923, 2905, 2851 (CH stretching), 2205 (CN) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz): δ = 1.85 (s, 3H, CH₃), 5.61 (s, 1H, pyran CH), 6.72–9.29 (m, 11H, Ar-H+NH₂), 12.23 (s, 1H, NH) ppm; MS(m/z): 352(M⁺,85%); Anal. Calcd for C₂₂H₁₆N₄O: C,74.98; H, 4.58; N, 15.90; O, 4.54. Found: C, 74.32; H, 4.51; N, 15.66; O, 4.75.

6-Amino-4-(2-furyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (1b).

Orange solid; m.p.261 °C., yield (78%); IR (KBr): $\bar{\nu}$ = 3395, 3364 (NH₂), 2963, 2951, 2882 (CH stretching), 2213 (CN) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz): δ = 1.91 (s, 3H, CH₃), 4.88 (s, 1H, pyran CH), 6.95–8.48 (m, 5H, Ar- H+NH₂), 11.82 (s, 1H, NH); MS(m/z): 242 (M⁺ 11 ,92%); Anal. Calcd for C₁₂H₁₀N₄O₂: C, 59.50; H, 4.16; N, 23.13; O, 13.21, Found: C, 59.69; H, 4.31; N, 23.28; O,13.62.

Ethyl 6-amino-4-(9-anthracenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate (1c).

Orange solid; m.p.293 °C., yield (75%); IR (KBr): $\bar{\nu}$ = 3362, 3319 (NH₂), 2965, 2912, 2863 (CH stretching), 1685 (COOCH₂CH₃) cm⁻¹; ¹H NMR (DMSO-*d*₆, 300 MHz): δ =1.64 (s, 3H, CH₃), 1.75 (t, 3H, CH₃), 4.31 (q, 2H, CH₂), 5.11 (s, 1H, pyran CH), 6.33– 8.65(m, 11H, Ar-

H+NH₂), 10.95 (s, 1H, NH) ; MS(m/z): 399(M⁺, 51%); Anal. Calcd for C₂₄H₂₁N₃O₃: C, 72.16; H, 5.30; N, 10.52; O, 12.02. Found: C, 71.66; H, 5.31; N, 10.35; O, 12.15.

Ethyl 6-amino-4-(2-furyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate (1d).

Orange solid; m.p. 251 °C., yield (81%); IR (KBr): $\bar{\nu}$ = 3361, 3325 (NH₂), 2918, 2931, 2898 (CH stretching), 1706 (COOCH₂CH₃) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.45 (s, 3H, CH₃), 1.61 (t, 3H, CH₃), 4.22 (q, 2H, CH₂), 5.11 (s, 1H, pyran CH), 6.39–8.95 (m, 5H, Ar-H+NH₂), 10.86 (s, 1H, NH) ; MS(m/z): 289 (M⁺, 11%); Anal. Calcd for C₁₄H₁₅N₃O₄: C, 58.13; H, 5.23; N, 14.53; O, 22.12. Found: C, 57.62; H, 5.35; N, 15.06; O, 22.86.

General procedure for the preparation of 6-amino-4-aryl-3-oxo-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile or carboxylate (2a-d).

To a stirred aqueous mixture of hydrazine hydrate 96% (2 mmol) and diethyl malonate (2 mmol), aldehyde (2 mmol), malononitrile or ethyl cyanoacetate (2 mmol) and triethyl amine (1ml) were added successively at room temperature under an open atmosphere with vigorous stirring for 25 min. The precipitated solid was filtered, washed with water and then with a mixture of ethyl acetate/ hexane (20:80). The product obtained was purified by recrystallization from ethanol.

6-Amino-4-(9-anthracenyl)-3-oxo-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2a).

Orange solid; m.p. 253 °C., yield (83%); IR (KBr): $\bar{\nu}$ = 3361, 3323 (NH₂), 2934, 2941, 2869 (CH stretching), 2219 (CN), 1668 (CO-pyrazolone) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 4.90 (s, 1H, pyran CH), 7.21–8.69 (m, 11H, Ar-H+NH₂), 11.41 (s, 1H, NH) ; MS(m/z): 352 (M⁺, 15%); Anal. Calcd for C₂₁H₁₂N₄O₂: C, 71.58; H, 3.43; N, 15.90; O, 9.08. Found: C, 72.25; H, 3.51; N, 15.10; O, 9.23.

6-Amino-4-(2-furyl)-3-oxo-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (2b).

Orange solid; m.p. 275 °C., yield (85%); IR (KBr): $\bar{\nu}$ = 3362, 3340 (NH₂), 2972, 2916, 2875 (CH stretching), 2215 (CN), 1675 (CO-pyrazolone) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 5.12 (s, 1H, pyran CH), 7.16–9.01 (m, 5H, Ar-H+NH₂), 11.82 (s, 1H, NH) ; MS(m/z): 242(M⁺, 64%); Anal. Calcd for C₁₁H₆N₄O₃: C, 54.55; H, 2.50; N, 23.13; O, 19.82. Found: C, 55.32; H, 2.53; N, 22.49; O, 20.68.

Ethyl 6-amino-4-(9-anthracenyl)-3-oxo-2,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate (2c).

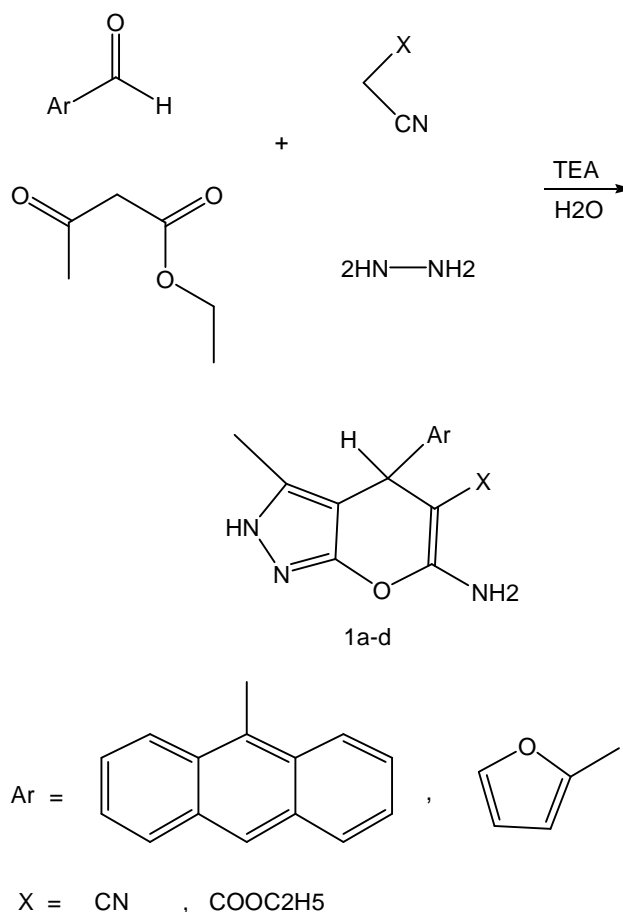
Orange solid; m.p. 253 °C., yield (73%); IR (KBr): $\bar{\nu}$ = 3341, 3310 (NH₂), 3009, 2916, 2874 (CH stretching), 1702 (COOCH₂CH₃), 1683 (CO-pyrazolone) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.68 (t, 3H, CH₃), 3.92 (s, 1H, pyran CH), 4.19 (q, 2H, CH₂), 6.41–8.65 (m, 11H, Ar-H+NH₂), 11.35 (s, 1H, NH) ; MS(m/z): 399(M⁺, 85%); Anal. Calcd for C₂₃H₁₇N₃O₄: C, 69.17; H, 4.29; N, 10.52; O, 16.02. Found: C, 68.12; H, 4.59; N, 10.89; O, 16.35.

Ethyl 6-amino-4-(2-furyl)-3-oxo-2,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate (2d).

Orange solid; m.p. 265 °C., yield (77%); IR (KBr): $\bar{\nu}$ = 3395, 3367 (NH₂), 2958, 2915, 2875 (CH stretching), 1710 (COOCH₂CH₃), 1669 (CO-pyrazolone) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.76 (t, 3H, CH₃), 4.34 (q, 2H, CH₂), 4.96 (s, 1H, pyran CH), 6.45–9.63 (m, 5H, Ar-H+NH₂), 12.06 (s, 1H, NH) ; MS(m/z): 289(M⁺, 6%); Anal. Calcd for C₁₃H₁₁N₃O₅: C, 53.98; H, 3.83; N, 14.53; O, 27.66. Found: C, 54.67; H, 3.66; N, 14.09; O, 26.87.

RESULTS AND DISCUSSION

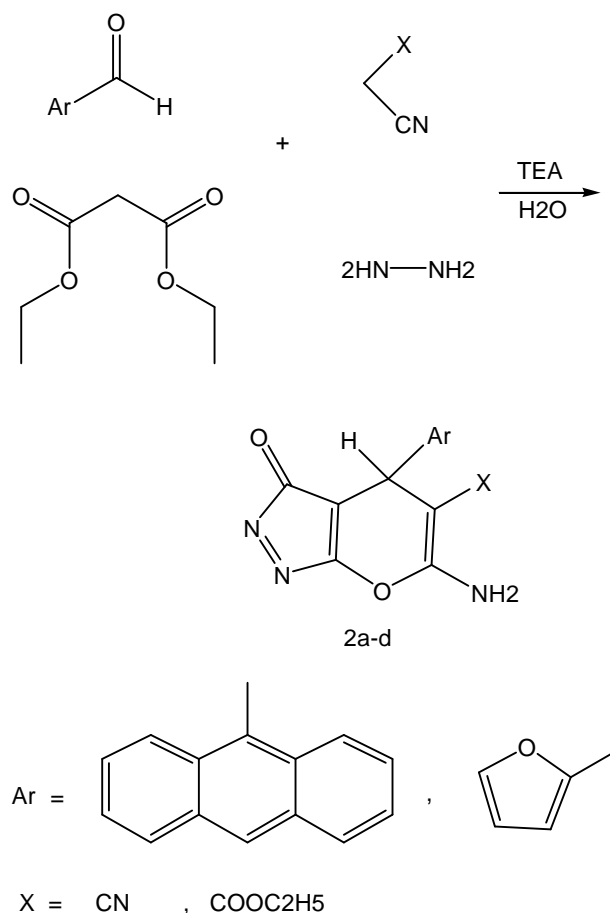
Although polyheterocycles can be obtained from well-chosen starting materials, a Knoevenagel-based reaction was recently reported for the simultaneous construction of two different fused heterocycles from acyclic precursors. In fact, a four component Knoevenagel–Michael addition–cyclization sequence has been studied for the synthesis of dihydropyranopyrazole derivatives from hydrazine hydrate, a malonitrile, a β -ketoester, and an aldehyde^{22,23}.



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, ethyl acetoacetate, aldehyde and malononitrile or ethyl cyanoacetate resulted in pyranopyrazoles (**1a-d**) in the presence of a catalytic amount triethyl amine in water medium, Scheme 1.

Interestingly enough, a closely related protocol was successfully proposed for the synthesis of 6-amino-4-aryl-3-oxo-2,4-dihydropyranopyrazole derivatives (**2a-d**) by using diethyl malonate as an alternative of ethyl acetoacetate, Scheme 2.



Scheme 2

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