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ORIGINAL ARTICLE

DABCO catalyzed rapid one-pot synthesis of 1,4-dihydropyrano [2,3-*c*] pyrazole derivatives in aqueous media

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KEYWORDS

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Ethylacetoacetate

Abstract A simple and efficient protocol is developed for the synthesis of dihydropyrano[2,3-*c*] pyrazole derivatives by a one pot, four component reaction of ethylacetoacetate, hydrazine hydrate, malanonitrile and various aldehydes in the presence of a catalytic amount of DABCO in aqueous medium. This method provides several advantages such as high yield, shorter reaction time, mild reaction condition, operational simplicity, easy work-up procedure with environment friendly nature and purification of products by non-chromatographic methods has been developed.

1. Introduction

The multi-component reactions (MCRs) have emerged as a great tool for synthetic transformations due to their operational simplicity, less hazardous and minimum side products with higher yields of desired products. They have advantages over multi step reactions in comparison with experimental procedures such as the yield of the desired products, time of the reactions, isolation of any intermediate compound, which saves time, energy and raw materials required for the reaction, making the protocol economically attractive and environmentally friendly [1]. In recent years, pyranopyrazoles have attracted great importance due to their biological and pharmaceutical activities [2]. In addition to their known bactericidal, fungicidal and herbicidal activities they exhibit analgesic, anti-inflammatory activity and also act as vasodilators, hypotensive and hypoglycemic agents [3–5].

Substituted pyranopyrazoles were firstly synthesized in 1973 by a reaction between 3-methyl-5-pyrazolone and tetracyanoethylene [6]. The 2-amino-4-substituted pyrano[2,3-*c*] pyrazole-3-carbonitriles were obtained in 1974 by the addition of malanonitrile to arylidene-3-methyl-2-pyrazolin-5-one [7]. Later on a number of synthetic methods were developed for the synthesis of pyrano pyrazoles, using arylidenemalanonitrile and 3-methyl-5-pyrazolone [8] or 4-arylidine-3-methyl-5-pyrazolone and malanonitrile [9], and also by the three component condensation of aromatic aldehydes, malanonitriles and

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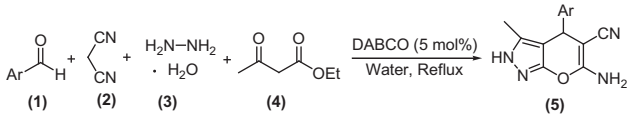
3-methyl-5-pyrazolone [10]. Pyranopyrazoles are also synthesized by the condensation of two components [11]. Recently these compounds are synthesized by the condensation of four component reaction catalyzed by piperidine [12], triethylamine [13], L-proline or KF-alumina [14], trichloroacetic acid [15], iodine [16], γ-alumina [17], ionic liquid [18], amberlyst A21 [19], nanosized magnesium oxide [20], Fe_3O_4 nanoparticles [21] per-6-ABCD [22], silicotungstic acid [23], and isonicotinic acid [24]. Some of the reported methods suffer from one or more limitations such as prolonged reaction time, use of organic solvents, and harsh reaction conditions. Thus, the development of new environmentally friendly and more effective procedure for the synthesis of pyranopyrazoles and carrying out organic reactions in water is of significant interest. Water, due to its features such as ecological friendly, safe, non-toxic, non-flammable, clean, green, inexpensive as well as readily available has been recommended to be used as a solvent in organic syntheses [25].

In recent years, 1,4-diazabicyclo[2.2.2]octane (DABCO) has received considerable attention as an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic catalyst for various organic transformations [26] such as for Baylis–Hillman reaction [27], for Heck reaction [28] and the selective cleavage of esters [29]. Furthermore, DABCO was used as catalyst for the synthesis of naphtopyran [30], benzopyrans [31], 3-cyanopyrimidones [32], dihydropyranochromenes [33], and imidazoles [34]. In the present work we wish to report DABCO as an efficient catalyst to promote rapid one-pot multicomponent reaction between aromatic aldehydes, malanonitrile, ethyl acetoacetate and hydrazine hydrate in aqueous media (Scheme 1).

2. Experimental

2.1. General

All chemicals were purchased from sd fine & Qualigens and used without further purification. All yields were referred to isolate products after purification. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on KBr disks on a FT IR Jasco – 4100 type A and the values are expressed as ν_{max} cm^{-1}, ^1H NMR and ^{13}C NMR spectra were recorded on Bruker avance II 400 NMR spectrophotometer using tetramethylsilane (TMS) as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in hertz. All products are known compounds and were characterized by comparison of their spectral and physical data with literature values. The progress of the reaction was monitored by TLC using aluminium plates with silica gel 60 F_{254} (Merck).



Scheme 1 Synthesis of pyrano[2,3-*c*]pyrazoles.

2.2. General procedure

The aromatic aldehyde (2 mmol), malanonitrile (2 mmol), ethylacetoacetate (2 mmol), hydrazine hydrate (2 mmol), and DABCO (5 mol%) were added successively in 20 ml of water and refluxed for the appropriate time (Table 3). The progress of the reaction was monitored by TLC (ethyl acetate: n-hexane = 2:8). After completion of reaction, the reaction mixture was diluted with cold water. The solid crude products, which separated out, were filtered, washed with water and dried. The crude product was purified by recrystallization with ethanol to afford pure product 5.

2.3. Selected spectroscopic data

2.3.1. 6-Amino-4-phenyl-3-methyl-2,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (5b)

White solid, mp 246–248 °C, IR (KBr): (ν_{max}) = 3370, 3171, 2192, 1652, 1599, 1402, 1043 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.77 (s, 3H, CH_3), 4.54 (s, 1H, C-4), 6.73 (s, 2H, NH_2), 7.17 (m, 3H, Ar-H), 7.29 (d, 2H, *J* = 7.2 Hz, Ar-H), 12.00 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6 100 MHz) δ = 9.70, 36.23, 57.14, 78.57, 78.90, 79.23, 97.97, 120.74, 126.66, 127.42, 128.35, 135.50, 144.38, 154.71, 160.81 ppm; $C_{14}H_{12}N_4O$ MS (ESI+): *m*/*z* 253.13 $(M+H)^+$.

2.3.2. 6-Amino-4-(3-nitrophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5c)

White solid, mp 240–242 °C, IR (KBr): (ν_{max}) = 3409, 3227, 2189, 1645, 1599, 1490, 1403, 1051, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.79 (s, 3H, CH_3), 4.64 (s, 1H, C-4), 6.95 (s, 2H, NH_2), 7.20 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.37 (d, 2H, *J* = 8.4 Hz, Ar-H), 12.15 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 9.71, 35.54, 56.72, 97.16, 120.65, 128.43, 129.33, 131.22, 135.67, 143.44, 154.68, 160.88 ppm; $C_{14}H_{11}N_5O_3$ MS (ESI+): *m*/*z* 298.11 $(M+H)^+$.

2.3.3. 6-Amino-4-(4-nitrophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5e)

White solid, mp 250–252 °C; IR (KBr): (ν_{max}) = 3537, 3223, 2195, 1652, 1597, 1514, 1402, 1354, 856 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 4.79 (s, 1H, C-4), 6.97 (s, 2H, NH_2), 7.45 (d, 2H, *J* = 6.9 Hz, Ar-H), 8.18 (d, 2H, *J* = 6.9 Hz, Ar-H), 12.14 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 9.70, 35.84, 55.85, 96.53, 120.47, 123.87, 128.81, 135.85, 146.34, 152.07, 154.63, 161.11 ppm; $C_{14}H_{11}N_5O_3$ MS (ESI+): *m*/*z* 298.12 $(M+H)^+$.

2.3.4. 6-Amino-4-(3,4,5-trimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5t)

White solid, mp 210–212 °C; IR (KBr): (ν_{max}) = 3420, 3218, 2193, 1651, 1598, 1493, 1210, 1190 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6,): δ = 1.88 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.73 (s, 6H, 2 × OCH_3), 4.57 (s, 1H, C-4), 6.46 (s, 2H, NH_2), 6.84 (s, 2H, Ar-H), 12.08 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 9.91, 36.52, 55.69, 56.90, 59.86, 78.53, 78.87, 79.19, 97.20, 104.44, 120.82, 135.63, 136.05, 139.99, 152.73, 154.68, 160.90 ppm; $C_{17}H_{18}N_4O_4$ MS (ESI+): *m*/*z* 343.11 $(M+H)^+$.