Seyed Esmail Sadat-Ebrahimi, Shirin Katebi, Morteza Pirali-Hamedani, Setareh Moghimi, Azadeh Yahya-Meymandi, Mohammad Mahdavi, Abbas Shafiee and Alireza Foroumadi*

Three-component one-pot synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridines

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Abstract: A series of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridines has been synthesized using a simple and efficient one-pot, three-component procedure. The products were obtained in good yields in the presence of heterogeneous nanoporous acid catalyst (SBA-Pr-SO_3H).

Keywords: one-pot; pyrazolopyridines; SBA-Pr-SO_3H; three-component.

Introduction

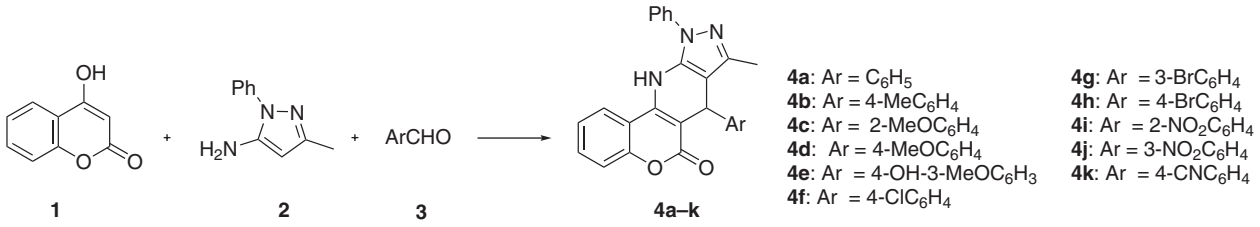
Pyrazoles and fused pyrazoles are well-recognized central units in medicine and therapeutics [1]. Among the various fused systems, pyrazolopyridines show promising biological activities as antibacterial [2], antitumor [3], antiviral [4] and anti-inflammatory [5] agents, and antagonists of corticotropin-releasing factor 1 (CRF_1) [6], chemokine receptor type 1 (CCR1) [7] and dopamine D3 receptors antagonists [8]. They are also known to be cholesterol forming [9], acetyl-CoA carboxylase (ACC) [10], HIV reverse transcriptase [11], phosphodiesterase 3/4 (PDE3/4) cyclin-dependent 1 (CDK1) [12], and B-Raf kinase inhibitors [13]. Several methods have been devised for the synthesis of substituted pyrazolopyridines [14–20]. Among them multi-component reactions (MCRs) [21–25] are of increasing importance because of their convergent, atom-economical and productive nature.

MCRs [26, 27] constitute an important pathway for one-pot construction of polycyclic compounds. This valuable feature has made the MCR chemistry a powerful procedure. Heterogeneous catalysts are often used to resolve growing concerns about environmental issues. In this context, Santa Barbara Amorphous (SBA-15) [28], in which various functional groups could be covalently bound to its mesostructured silica surface, has gained considerable attention. Sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) [29] with high acid strength could be regarded as a replacement for conventional homogenous acidic catalysts suffering from various drawbacks, mainly their toxicity and hazards to humans. Considering environmental and industrial aspects, sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) has emerged as an important catalyst in an efficient construction of complex frameworks. In continuation of our interest toward developing new pathways for the synthesis of heterocyclic compounds [30–32], herein we report the catalytic synthesis of novel compounds incorporating coumarin and pyrazolopyridine moieties.

Results and discussion

The reaction of 4-hydroxycoumarin (**1**), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2**) and benzaldehyde (**3a**) was selected as a model reaction to establish the appropriate conditions (Scheme 1). The reaction was investigated by utilizing 5 mol% SBA-Pr-SO_3H, prepared according to the literature [33], in different solvents at reflux temperature (including ethanol, water, ethanol/water and methanol). The highest yield of 83% of product **4a** was obtained for the reaction conducted in ethanol under reflux for 2 h. No improvement in the isolated yield was observed with increasing amounts of the catalyst, up to 20 mol% and no product **4a** was observed in the absence of the catalyst. Heating the mixture under reflux in acetic acid furnished product **4a** in a comparable yield, but after a long

***Corresponding author: Alireza Foroumadi,** Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran, e-mail: aforoumadi@yahoo.com; and Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, P.O. Box 1417614411, Iran
Seyed Esmail Sadat-Ebrahimi, Shirin Katebi and Azadeh Yahya-Meymandi: School of pharmacy, International Campus, Tehran University of Medical Sciences (TUMS-IC), Tehran, P.O. Box 3439123900, Iran
Morteza Pirali-Hamedani, Setareh Moghimi and Abbas Shafiee: Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, P.O. Box 141556451, Iran
Mohammad Mahdavi: Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, P.O. Box 1417614411, Iran



Scheme 1

reaction time (18 h). Additional dihydrochromeno[4,3-*b*] pyrazolo [4,3-*e*]pyridines **4b–k** were obtained in good yields under similar conditions, as shown in Scheme 1. No significant substituent effects were observed for electron-donating groups Me and OMe or electron-withdrawing groups including Cl, Br, NO_2 and CN.

Conclusion

Pyrazolo[4,3-*e*]pyridines **4a–k** were synthesized in good yields using our straightforward, one-pot and multi-component procedure.

Experimental

All chemicals were purchased from Merck and Fluka and used without further purification. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker FT-500 spectrometer in DMSO-d_6, using tetramethylsilane as an internal standard. IR spectra were recorded on a Shimadzu 470 spectrophotometer in KBr disks. Mass spectra were obtained using an Agilent Technology mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed using an Elemental Analysen system, GmbH VarioELCHNS. The synthesis of SBA-15 and SBA-Pr-SO_3H was performed as described in the literature [33].

General synthesis of compounds 4a–k

A mixture of 4-hydroxycoumarin (1 mmol), an aldehyde (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol) and 5 mol% SBA-SO_3H in ethanol (5 mL) was stirred and heated under reflux. Upon completion, which was indicated by TLC analysis, the mixture was filtered off and the filtrate was cooled to room temperature. The precipitate of **4a–k** was collected and purified by silica gel chromatography eluting with petroleum ether/ethyl acetate (8:2). The catalyst was washed with water and acetone. After drying under a reduced pressure, the catalyst could be reused several times without the loss of activity.

8-Methyl-7,10-diphenyl-10,11-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one (4a) The product was obtained within 2 h in 83% yield as a pale yellow solid; mp 221–222°C; IR: 3400, 1698, 1631, 1535, 1455, 1024, 748, 701 cm^{-1}; ^{1}H NMR: δ 1.93 (s, 3H), 5.19 (s, 1H), 7.15 (t, 1H, *J* = 7.3 Hz), 7.25–7.30 (m, 4H), 7.35 (d, 1H, *J* = 8.0 Hz), 7.38–7.43 (m, 2H), 7.57 (t, 2H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.3 Hz), 7.68 (d, 2H, *J* = 7.0 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 9.95 (s, NH); ^{13}C NMR: δ 11.9, 37.3, 101.4, 103.9, 113.9, 116.4, 122.5, 123.6, 123.7, 126.2, 126.6, 127.8, 128.0, 129.3, 131.7, 136.0, 138.7, 143.8, 145.8, 146.0, 152.0, 160.4; MS: *m/z* 405 ([M]$^+$, 26), 328 (100), 284 (60), 77 (41%). Anal. Calcd for $C_{26}H_{19}N_3O_2$: C, 77.02; H, 4.72; N, 10.36. Found: C, 76.94; H, 4.59; N, 10.48.

8-Methyl-10-phenyl-7-(*p*-tolyl)-10,11-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one (4b) The product was obtained within 1.5 h in 80% yield as a pale yellow solid; mp 154–156°C; IR: 3348, 1690, 1627, 1551, 1440, 1011, 819 cm^{-1}; ^{1}H NMR: δ 1.93 (s, 3H), 3.69 (s, 3H), 5.13 (s, 1H), 6.82 (d, 2H, *J* = 8.5 Hz), 7.18 (d, 2H, *J* = 8.5 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.38–7.42 (m, 2H), 7.57 (t, 2H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 7.67 (d, 2H, *J* = 7.5 Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 9.94 (s, NH); ^{13}C NMR: δ 11.9, 20.9, 36.4, 101.4, 104.6, 113.7, 114.0, 116.4, 122.8, 123.1, 123.7, 126.2, 128.8, 129.6, 131.3, 136.0, 138.3, 138.7, 143.5, 145.6, 151.3, 157.6, 160.0. Anal. Calcd for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.21; H, 4.96; N, 10.06.

7-(2-Methoxyphenyl)-8-methyl-10-phenyl-10,11-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one (4c) The product was obtained within 2.5 h in 81% yield as a pale yellow solid; mp 202°C; IR: 3236, 1681, 1631, 1536, 1458, 1027, 755, 698 cm^{-1}; ^{1}H NMR: δ 1.93 (s, 3H), 3.78 (s, 3H), 5.50 (s, 1H), 6.82 (t, 1H, *J* = 7.5 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 7.10–7.15 (m, 2H), 7.33 (d, 1H, *J* = 8.5 Hz), 7.36–7.41 (m, 2H), 7.56 (t, 2H, *J* = 7.5 Hz), 7.61 (t, 1H, *J* = 7.5 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 8.04 (d, 1H, *J* = 8.5 Hz), 9.83 (s, NH); ^{13}C NMR: δ 11.7, 31.4, 55.5, 95.4, 101.1, 103.7, 111.3, 114.0, 116.3, 120.4, 122.3, 123.4, 123.5, 126.4, 127.4, 129.2, 129.3, 131.5, 134.2, 136.2, 138.8, 144.6, 145.6, 152.0, 159.8. Anal. Calcd for $C_{27}H_{21}N_3O_3$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.50; H, 4.92; N, 9.71.

7-(4-Methoxyphenyl)-8-methyl-10-phenyl-10,11-dihydrochromeno [4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one (4d) The product was obtained within 2 h in 79% yield as a pale yellow solid; mp 196–198°C; IR: 3244, 1711, 1628, 1539, 1457, 1027, 841, 758, 689 cm^{-1}; ^{1}H NMR: δ 1.94 (s, 3H), 3.69 (s, 3H), 5.14 (s, 1H), 6.82 (d, 2H, *J* = 7.5 Hz), 7.19 (d, 2H, *J* = 7.5 Hz), 7.34 (d, 1H, *J* = 8.5 Hz), 7.41 (t, 2H, *J* = 7.5 Hz), 7.55–7.62 (m, 3H), 7.68 (d, 2H, *J* = 8.5 Hz), 8.05 (d, 1H, *J* = 7.5 Hz), 9.89 (s, NH); ^{13}C NMR: δ 11.9, 36.4, 54.9, 101.7, 104.1, 113.4, 113.9, 116.4, 122.5, 123.5, 123.6, 126.5, 128.8, 129.3, 131.6, 135.9, 138.3, 138.7, 143.5, 145.8, 151.9, 157.6, 160.4; MS: *m/z* 435 ([M]$^+$, 25), 328 (100), 107 (51), 251 (41), 77 (32%). Anal. Calcd for $C_{27}H_{21}N_3O_3$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.56; H, 4.92; N, 9.54.

7-(4-Hydroxy-3-methoxyphenyl)-8-methyl-10-phenyl-10,11-dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one (4e) The product was obtained within 2 h in 82% yield as a pale yellow solid;