ISSN: 0974 - 7516 Volume 10 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 10(1), 2014 [1-4]

Catalyst-free, one-pot three-component approach for regioselective synthesis of several substituted pyrazolo[3,4-b]pyridin-6(7*H*)-ones

Azam Monfared[1], Manouchehr Mamaghani[2], Abbas Azimi Roshan[1,2], Hamzeh Kiyani*[3]

[1]Department of Chemistry, University of Payam Noor (PNU), Tehran, (I.R.IRAN)

[2]Department of Chemistry, University of Guilan, P.O.Box 1914, Rasht, (I.R.IRAN)

[3]School of Chemistry, Damghan University, 36715-364, Damghan, (I.R.IRAN)

E-mail: m-chem41@guilan.ac.ir; hkiyani@du.ac.ir

ABSTRACT

A series of 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridine-6(7*H*)-ones were synthesized *via* catalyst-free, one-pot three-component reaction of 5-amino-3-methyl-1*H*-pyrazole, Meldrum's acid, and various aldehydes in refluxing ethanol. This protocol has merits of higher yields, easy-work-up, and environmentally friendly approach.

KEYWORDS

Three-component;
Meldrum's acid;
Catalyst-free;
Pyrazolo [3,4-b] pyridin-6(7*H*)-one;
5-Amino-3-methylpyrazole.

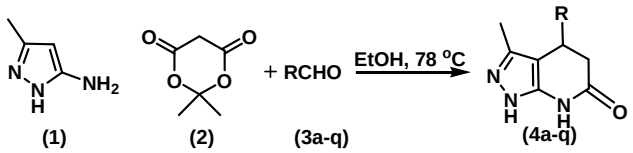
INTRODUCTION

After the discovery of multi-component reactions (MCRs) in 1850 by Strecker, the concept has stimulated considerable interest in organic chemistry because it affords useful products in a one-pot reaction, which use of more than two starting materials[1]. Also MCRs in which, three or more reactants are brought together in a highly convergent approach to quickly construct molecular structure and complexity, high atom economy and environmentally benign procedures, have occupied a prominent and advantageous position in pharmaceutical and modern synthetic organic chemistry[2] owing to their appreciated features such as convergence, efficiency, facile completing, and usually high yield of products[2c]. On the other hand, pyrazole and its derivatives are key substructures in a large variety of compounds and pyrazole-containing compounds have received considerable attention owing to their diverse biological activities and pharmacological properties[3-6], some pyrazoles have been implemented as antileukemic[7], antitumor[8] and anti-proliferative[9] agents. In addition combination of the pyrazole moiety with various heterocyclic ring systems have been resulted in interesting biological and pharmacological properties[10-12]. In particular pyrazolopyridine scaffolds have attracted many interests in recent years as possible antiviral agent[13,14], potent p38 kinase inhibitors[15], human immunodeficiency virus (HIV) reverse transcriptase[16], and inhibitors of cGMP degradation[17]. A number of derivatives show evidence of potential antimalarial properties[18]. Others illustrate intense fluorescence in the blue green region and have been considered for applications as fluorescence standards and luminophores in OLEDs[19], herbicidal activity[20], and also used as vasodilators[21] or evaluated for CCR1 antagonists and active inhibitors in the enzymatic and cellular assays[22-23]. Therefore, widespread studies have been devoted to the synthesis and valuation of activities of pyrazolopyridines[24]. However, most of these methods

suffer from multi-step reactions, use of more expensive reagents, harsh reaction conditions, long reaction times, low yields and low regioselectivity of products, therefore, development of an efficient and versatile method is still necessary for the synthesis of pyrazolopyridines[25].

RESULTSAND DISCUSSION

In this report we have devised an efficient one-pot, three-component reaction for the synthesis of several derivatives of pyrazolo[3,4-b]pyridin-6(7*H*)-ones **(4a-q)** from 5-amino-3-methyl-1*H*-pyrazole **(1)**, 6,6-dimethyl-1,3,5-trioxane-2,4-dione (Meldrum's acid) **(2)**, and aldehydes **(3a-q)** under heating in refluxing EtOH (Scheme 1).



(1) (2) (3a-q) (4a-q)

Scheme 1 : Synthesis of 4-aryl and alkyl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]-pyridin-6(7*H*)-ones (4a-q)

Equimolar amounts of precursors **(1)**, **(2)** and **(3)** were reacted in refluxing EtOH to produce the desired pyrazolo[3,4-b]pyridin-6(7*H*)-one derivatives **(4a-q)** in short reaction periods with high to excellent yields. The results are summarized in TABLE 1.

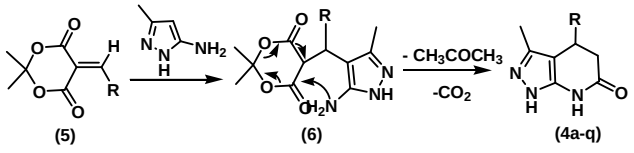
As can be seen in TABLE 1, both substituted benzaldehydes containing electron-releasing and electron-withdrawing substituent gave the corresponding products in high yields and short reaction time (TABLE 1, entries 1-12). Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation offers a significant advantage. Because of the desired products are insoluble in EtOH, therefore, the products can be directly separated from the mixture of reaction by simple filtration. Also, this protocol can be applied to electron-rich heterocyclic aromatic aldehydes (TABLE 1, entries 14-15), and electron-efficient hetero-aryl aldehydes (TABLE 1, entries 16-17), as well as alkyl aldehydes (TABLE 1, entry 13). All of compounds were characterized by spectroscopic methods (IR, ^{1}H NMR and ^{13}C NMR) and elemental analyses.

Mechanistically the formation of the products **(4a-q)** can be visualized by initial Knoevenagel condensation of aldehydes **(3)** and 6,6-dimethyl-1,3,5-trioxane-2,4-dione resulting in arylidene **(5)**, followed by a Michael type nucleophilic addition of C-4 of the pyrazole ring to the enone intermediate **(5)**, and subsequent cyclodehydration to furnish the desired compounds (Scheme 2).

TABLE 1 : Catalyst-free one-pot three-component synthesis of 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]-pyridin-6(7*H*)-one derivatives (4a-q)

Entry	Ar / Product[a]	Time /min	Yield (%)[b]	Mp (Lit. Mp °C)[c]
1	3-NO_2-C_6H_4 / 4a	80	92	266 (265-267)
2	4-$Me_2N$$C_6H_4$ / 4b	90	91	348 (347-349)
3	4-$NO_2C_6H_4$ / 4c	80	93	> 350 (> 350)
4	C_6H_5 / 4d	85	87	304 (304-306)
5	4-ClC_6H_4 / 4e	95	92	346 (344-346)
6	4-$MeOC_6H_4$ / 4f	100	90	308 (308-310)
7	2,4-$Cl_2C_6H_3$ / 4g	110	87	> 350 (> 350)
8	3,4-$(MeO)_2C_6H_3$ / 4h	95	90	233 (230-232)
9	1,4-phenylene / 4i	95	88	> 350 (> 350)
10	4-FC_6H_4 / 4j	85	90	308 (306-308)
11	4-Br C_6H_4 / 4k	95	89	348-350[d]
12	2-$MeOC_6H_4$ / 4l	95	90	279-281[d]
13	4-isopropyl / 4m	75	89	293 (292-295)
14	2-Furyl / 4n	85	88	> 350 (> 350)
15	2-thienyl / 4o	95	90	306 (303-305)
16	pyridin-3-yl / 4p	100	86	306 (302-305)
17	pyridin-4-yl / 4q	90	90	307-310[d]

[a] All Compounds were identified by spectroscopic (FT-IR, ^{1}H NMR, and ^{13}C NMR) data and elemental analyses; [b] Yields of the isolated products; [c] Melting points of more compounds are consistent with reported values[26]; [d] New synthesized compounds.



(5) (6) (4a-q)

Scheme 2 : Plausible mechanism of formation of (4a-q)

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. FT-IR spectra were determined on a Shimadzo FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz Bruker DRX-500 in DMSO-d_6 as solvent and TMS as an internal standard. Elemental analyses were done on a

Carlo-Erba EA1110 CNNO-S analyser and agreed with the calculated values. Chemicals were purchased from Merck and Aldrich. All solvents used were dried and distilled according to the standard procedures. The development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure for the synthesis of (4a-q) compounds

A solution of 5-amino-3-methyl-1*H*-pyrazole (1 mmol), 6,6-dimethyl-1,3,5-trioxane-2,4-dione (1 mmol), aryl aldehydes (1 mmol) were reacted in refluxing EtOH (7 mL) in a water bath for the required reaction times (TABLE 1). After completion of the reaction, which was checked by TLC the solvent was evaporated under vacuum and the residue was purified by recrystallization from a mixture of EtOH and H_2O to furnish the desired products **(4a-q)**

Spectral data of some representative compounds

(4o)

White solid, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.80 (s, 3H); 2.50 (m, 1H); 2.76 (m, 1H); 4.12 (m, 1H); 7.09 (t, *J* = 1.65, 8.45 Hz, 2H); 7.46 (m, 2H); 10.28 (s, 1H, NH); 11.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 9.9, 33.8, 40.8, 101.9, 120.1, 129.7, 132.0, 135.2, 143.7, 149.2, 169.8 (C=O). ν_{max}/cm^{-1} (KBr): 1090, 1500, 1540, 1650, 2910, 3000, 3060, 3130, 3170. Anal. cald. for $C_{13}H_{12}BrN_3O$ (261.71): C, 51.00; H, 3.95; N, 13.72 %; Found: C, 51.10; H, 3.90; N, 13.60%.

(4p)

White solid, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.82 (s, 3H); 2.45 (m, 1H); 2.74 (m, 1H); 3.78 (s, 3H); 4.36 (m, 1H); 6.78 (m, 2H); 6.96 (d, *J* = 8.15 Hz, 1H); 7.17 (m, 1H); 10.20 (s, 1H, NH); 11.76 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 9..8, 28.0, 40.6, 55.8, 101.5, 111.4, 120.8, 127.6, 128.3, 131.5, 134.9, 149.8, 156.7, 170.2 (C=O). ν_{max}/cm^{-1} (KBr): 1100, 1540, 1600, 1625, 1650, 2910, 3000, 3040, 3120, 3195. Anal. cald. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.35; H, 5.88; N, 16.33 %; Found: C, 65.15; H, 5.75; N, 16.44%.

(4q)

White solid, ^{1}H NMR (DMSO-d_6, 500MHz): δ 1.85 (s, 3H); 2.55 (m, 1H); 2.81(m, 1H); 4.16 (m, 1H); 7.14 (d, *J* = 5.90 Hz, 2H); 8.45 (t, *J* = 1.3 Hz, *J* = 5.95 Hz, 2H); 10.32 (s, 1H, NH); 11.85 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 9.9, 33.6, 40.8, 100.1, 122.8, 135.3, 149.2, 150.4, 152.9, 169.6 (C=O). ν_{max}/cm^{-1} (KBr): 1100, 1600, 1650, 3180, 3160. Anal. cald. for $C_{12}H_{12}N_4O$ (228.25): C, 63.15; H, 5.30; N, 24.55 %; Found: C, 63.20; H, 5.25; N, 24.45%.

CONCLUSION

In summary, we develop an efficient and convenient procedure for the synthesis of 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridin-6(7*H*)-ones *via* three-component reaction of 5-amino-3-methyl-1H-pyrazole, Meldrum's acid and various aldehydes. This procedure offers advantages such as mild reaction conditions, higher yield, easy work-up, economic, simplicity, benign environmentally, and a waste free chemical process for the synthesis of dihydropyrazolopyrimidones.

ACKNOWLEDGEMENT

We thank the Research Council of University of Guilan, Payam Noor University of Tehran, and Damghan University.

REFERENCES

[1] **(a)** A.Strecker; Liebigs Ann.Chem., **75**, 27 **(1850)**; **(b)** A.Dömling, I.Ugi; Angew.Chem.Int.Ed., **39**, 3168 **(2000)**; **(c)** C.O.Kappe; Acc.Chem.Res., **33**, 879 **(2000)**; **(d)** A.Dömling, W.Wang, K.Wang; Chem.Rev., **112**, 3083 **(2012)**; **(e)** M.Syamala; Org.Prep.Proced.Int., **41**, 1 **(2009)**; **(f)** A.Dömling; Chem.Rev., **106**, 17 **(2006)**.

[2] **(a)** I.Ugi; Pure Appl.Chem., **73**, 187 **(2001)**; **(b)** V.A.Chebanov, K.A.Gura, S.M.Desenko; Top.Heterocycl.Chem., **23**, 41 **(2010)**; **(c)** M.Lei, L.Ma, L.Hu; Tetrahedron Lett., **52**, 2597 **(2011)**.

[3] H.V.Chavan, S.B.Babar, R.U.Hoval, B.P.Bandgar; Bull.Korean Chem.Soc., **32**, 3963 **(2011)**.

[4] S.R.Donohue, C.Halldin, V.W.Pike; Tetrahedron Lett., **49**, 2789 **(2008)**.

[5] G.Szabó, J.Fischer, Á.Kis-Varga, K.Gyires; J.Med.Chem., **51**, 142 **(2008)**.

[6] J.Quiroga, S.Cruz, B.Insuasty, R.Abonia, M.Nogueras, A.Sanchez, J.N.Low; J.Heterocycl. Chem., **38**, 53 **(2001)**.

[7] L.C.Chou, L.J.Huang, J.S.Yang, F.Y.Lee, C.M.Teng, S.C.Kuo; Bioorg.Med.Chem., **15**, 1732 **(2007)**.

[8] Y.Xia, C.D.Fan, B.X.Zhao, J.Zhao, D.S.Shin, J.Y.Miao; Eur.J.Med.Chem., **43**, 2347 **(2008)**.

[9] S.Schenone, O.Bruno, A.Ranise, F.Bondavalli, C.Brullo, P.Fossa, L.Mosti, G.Menozzi, F.Carraro, A.Naldini, C.Bernini, F.Manetti, M.Botta; Bioorg.Med.Chem.Lett., **14**, 2511 **(2004)**.

[10] J.Quiroga, J.Trilleras, B.Insuasty, R.Abonía, M.Nogueras, J.Cobo; Tetrahedron Lett., **49**, 2689 **(2008)**.

[11] J.Quiroga, S.Cruz, B.Insuasty, R.Abonía; Heterocycl.Commun., **6**, 275 **(2000**).

[12] C.L.Shi, D.Q.Shi, S.H.Kim, Z.B.Huang, S.J.Ji, M.Ji; Tetrahedron, **64**, 2425 **(2008)**.

[13] R.R.Crenshaw, G.M.Luke, P.Smirnoff; J.Med. Chem., **19**, 262 **(1976)**.

[14] R.Crenshaw, G.M.Luke, P.Smirnoff; Canadian Patent 10, **32**, 538 **(1978)**.

[15] **(a)** L.A.Smyth, T.P.Matthews, I.Collins; Bioorg. Med.Chem., **19**, 3569 **(2011)**; **(b)** R.P.Wurz, L.H.Pettus, S.Xu, B.Henkle, L.Sherman, M.Plant, K.Miner, H.J.McBride, L.M.Wong, C.J.M.Saris, M.R.Lee, S.Chmait, C.Mohr, F.Hsieh, A.S.Tasker; Bioorg.Med.Chem.Lett., **20**, 1680 **(2010)**; **(c)** B.Wu, H.L.Wang, L.Pettus, R.P.Wurz, E.Doherty, B.Henkle, H.J.McBride, C.J.M.Saris, L.M.Wong, M.H.Plant, L.Sherman, M.R.Lee, F.Hsieh, A.S.Tasker; J.Med.Chem., **53**, 6398 **(2010)**.

[16] S.A.Saggar, J.T.Sisko, T.J.Tucker, R.M.Tynebor, D.S.Su, N.J.Anthony; U.S.Patent Appl.US, 2007021442 **(2007)**.

[17] **(a)** R.W. Allcock, H.Blakli, Z.Jiang, K.A.Johnston, K.M.Morgan, G.M.Rosair, K.Iwase, Y.Kohno, D.R.Adams; Bioorg.Med.Chem.Lett., **21**, 3307 **(2011)**; **(b)** A.Straub, J.Benet-Buckholz, R.Fröde, A.Kern, C.Kohlsdorfer, P.Schmitt, T.Schwarz, H.M.Siefert, J.P.Stasch; Bioorg.Med.Chem., **10**, 1711 **(2002)**.

[18] R.G.Stein, J.H.Biel, T.J.Singh; J.Med.Chem., **13**, 153 **(1970)**.

[19] D.B.Kendre, R.B.Toche, M.N.Jachak; Tetrahedron, **63**, 1100 **(2007)**.

[20] A.Feurer, J.Luithle, S.Wirtz, G.Koenig, J.Stasch, E.Stahl, R.Schreiber, F.Wunder, D.Lang; PCT Int.Appl.WO, 2004009589 **(2004)**.

[21] M.R.Bell, J.H.Ackerman; US Patent 4, 920, 128 **(1990)**.

[22] F.Gatta, M.Pomponi, M.J.Marta; Heterocycl. Chem., **28**, 1301 **(1991)**.

[23] S.Wenglowsky, K.A.Ahrendt, A.J.Buckmelter, B.Feng, S.L.Gloor, S.Gradl, J.Grina, J.D.Hansen, L.R.Laird, P.Lunghofer, S.Mathieu, D.Moreno, B.Newhouse, L.Ren, T.Risom, J.Rudolph, J.Seo, H.L.Sturgis, W.C.Voegtli, Z.Wenb; Bioorg.Med. Chem.Lett., **21**, 5533 **(2011)**.

[24] **(a)** G.P.Sagitullina, L.A.Lisitskaya, M.A.Vorontsova, R.S.Sagitullin; Mendeleev Commun., **17**, 192 **(2007)**; **(b)** A.Rahmati; Tetrahedron Lett., **51**, 2967 **(2010)**; **(c)** M.N.Jachak, A.B.Avhale, C.D.Tantak, R.B.Toche, C.Reidlinger, W.J.Stadlbauer; J.Heterocycl.Chem., **42**, 1311 **(2005)**; **(d)** G.Lavecchia, S.Berteina-Raboin, G,Guillaumet; Tetrahedron Lett., **45**, 2389 **(2004)**.

[25] **(a)** H.A.Samimi, M.Mamaghani, K.Tabatabaeian; Heterocycles, **75**, 2825 **(2008)**; **(b)** M.Nikpassand, M.Mamaghani, F.Shirini, K.Tabatabaeian; Ultrason.Sonochem., **17**, 301 **(2010)**; **(c)** M.Mamaghani, S.Dastmard; Ultrason. Sonochem., **16**, 445 **(2009)**; **(d)** M.Nikpassand, M.Mamaghani, K.Tabatabaeian, H.A.Samimi; Synth.Commun., **40**, 3552 **(2010)**; **(e)** M.Nikpassand, M.Mamaghani, K.Tabatabaeian, M.Koupaei Abiazi; Mol.Divers., **13**, 389 **(2009)**; **(f)** M.Mamaghani, A.Loghmanifar, M.R.Taati; Ultrason.Sonochem., **18**, 45 **(2011)**.

[26] A.Azimi Roshan, M.Mamaghani, N.O.Mahmoodi, F.Shirini; Chin.Chem.Lett., **23**, 399 **(2012)**.