ISSN: 0974 - 7516 Volume 8 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(3), 2012 [81-84]

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

Samy A.El-Assaly

Natural and Microbial Products Chemistry Department, National Research Center (NRC), Dokki, Giza, (EGYPT)

E-mail: samyassaly@yahoo.com

Received: 16th March, 2011 ; Accepted: 26th March, 2011

ABSTRACT

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

KEYWORDS

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] Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest from pharmaceutical groups.

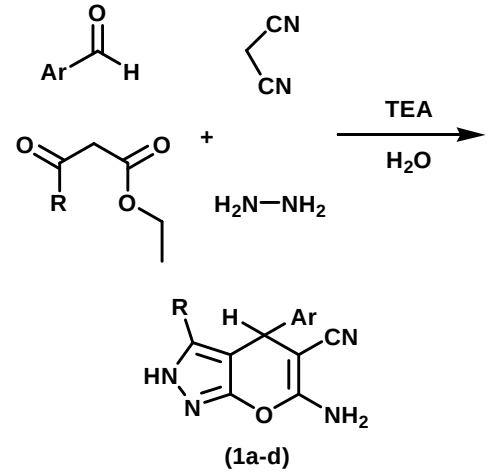
Designing organic reactions in aqueous media is another attractive area in green chemistry.[3] Water is an abundant and environmentally benign solvent. As a reaction medium, it offers several benefits including control over exothermic reactions, salting in and salting out and variation of pH. Work up 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.[4] Multicomponent reactions are suggested to have a negative activation volume.[5] Pyranopyrazoles are an important class of heterocyclic compounds. They find applications as pharmaceutical ingredients and biodegradable agrochemicals.[6-8] The first reported pyranopyrazole was synthesized from the reaction between 3-methyl-1-phenylpyrazolin5-one and tetracyanoethylene.[6] Various 6-amino-5-cyano-4-aryl-4Hpyrazolo[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.[7] Sharanin et al.[8] have developed a three-component

Full Paper

reaction between pyrazolone, an aldehyde and malononitrile in ethanolusing triethylamine as the catalyst. Shestopalov and co-workers[9] reported the synthesis of pyrazolopyran via a three-component condensation between Nmethylpiperidone, 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.[10]

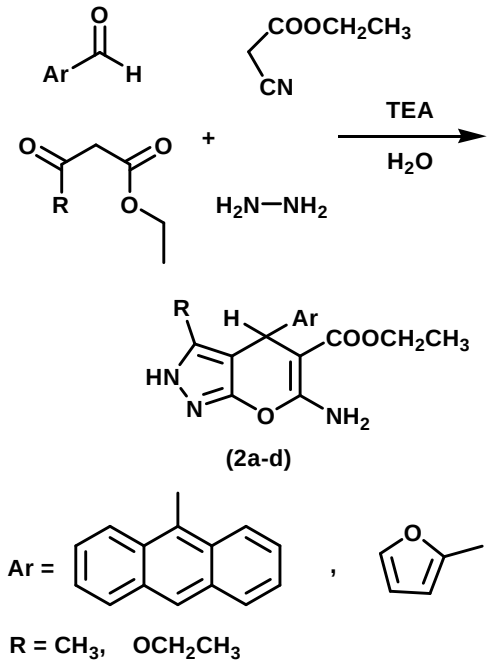
RESULTS AND DISCUSSION

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[11,12] malonitrile, a β-ketoester, and an aldehyde. 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 resulted in pyranopyrazoles **(1a-d)** in the presence of a catalytic amount triethyl amine in water mediam (Scheme 1).



Scheme 1

Interestingly enough, a closely related protocol was successfully proposed for the synthesis of 6-amino-4-aryl-3-alkyl-2,4dihydropyrano[2,3-c]pyrazole-5-carboxylate by using ethyl cyanoacetate as an alternative of malononitrile **(2a-d)**, (Scheme 2).



Scheme 2

EXPERIMENTAL

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. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer using DMSO-d6 or $CDCl_3$ 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-4aryl-3-alkyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-arbonitriles (1a-d)

To a stirred aqueous mixture of hydrazine hydrate

96% (0.107 g, 2 mmol) and ethyl acetoacetate (0.260 g, 2 mmol), aldehyde (2 mmol), malononitrile (0.132 g, 2 mmol) and triethylamine (1 ml) were added successively at room temperature under an open atmosphere with vigorous stirring for 15 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: 3354, 3311 (NH2), 2923, 2905, 2851 (CH stretching), 2205 (CN). ^{1}H-NMR (DMSO-d_6): 6.72–9.29 (m, 11H, Ar-H+NH2), 5.61 (s, 1H, pyran CH), 12.23 (s, 1H, NH). MS(m/z): 352(M^+, 85%). Anal. Calcd for $C_{22}H_{16}N_4O$: 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-(9-anthracenyl)-3-ethoxy-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (1b)

Orange solid; m.p.261 °C., yield (78%). IR: 3395, 3364 (NH2), 2963, 2951, 2882 (CH stretching), 2213 (CN). ^{1}H-NMR (DMSO-d_6): 6.95–8.48 (m, 11H, Ar-H+NH2), 4.88 (s, 1H, pyran CH), 11.82 (s, 1H, NH). MS(m/z): 382(M^+, 92%). Anal. Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65; O, 8.37 Found: C, 72.69; H, 4.91; N, 14.28; O, 8.62

6-amino-4-(2-furyl)-3-methyl-2,4-dihydropyrano[2,3c]pyrazole-5-carbonitrile (1c)

Orange solid; m.p.293 °C., yield (75%). IR: 3362, 3319 (NH2), 2965, 2912, 2863 (CH stretching), 2211 (CN). ^{1}H-NMR (DMSO-d_6): 6.33– 8.65(m, 11H, Ar-H+NH2), 5.11 (s, 1H, pyran CH), 10.95 (s, 1H, NH). MS(m/z): 242(M^+, 51%). Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13; O, 13.21. Found: C, 59.66; H, 4.32; N, 23.35; O, 13.15

6-amino-4-(2-furyl)-3-ethoxy-2,4-dihydropyrano[2,3c]pyrazole-5-carbonitrile (1d)

Orange solid; m.p.251 °C., yield (81%). IR: 3361, 3325 (NH2), 2918, 2931, 2898 (CH stretching), 2214 (CN). ^{1}H-NMR (DMSO-d_6): 6.39–8.95 (m, 11H, Ar-H+NH2), 5.11 (s, 1H, pyran CH), 10.86 (s, 1H, NH). MS(m/z): 287(M^+, 11%). Anal. Calcd for $C_{14}H_{15}N_4O_3$: C, 58.53; H, 4.26; N, 19.50; O,16.71. Found: C, 58.62; H, 4.35; N, 19.66; O, 16.86.

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

To a stirred aqueous mixture of hydrazine hydrate 96% (0.107 g, 2 mmol) and ethyl acetoacetate (0.260 g, 2 mmol), aldehyde (2 mmol), ethyl cyanoacetate (0.250 g, 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-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate (2a)

Orange solid; m.p.253 °C., yield (83%). IR: 3361, 3323 (NH2), 2934, 2941, 2869 (CH stretching), 2214 (CN). ^{1}H-NMR (DMSO-d_6): 7.21–8.69 (m, 11H, Ar-H+NH2), 4.90 (s, 1H, pyran CH), 11.41 (s, 1H, NH). MS(m/z): 399(M^+, 15%). Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52; O,12.02. Found: : C, 72.25; H, 5.41; N, 11.10; O,12.23.

6-amino-4-(9-anthracenyl)-3-ethoxy-2,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate (2b)

Orange solid; m.p.275 °C., yield (85%). IR: 3362, 3340 (NH2), 2972, 2916, 2875 (CH stretching), 2212 (CN). ^{1}H-NMR (DMSO-d_6): 7.16–9.01 (m, 11H, Ar-H+NH2), 5.12 (s, 1H, pyran CH), 11.82 (s, 1H, NH). MS(m/z): 429(M^+, 64%). Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78; O,14.90. Found: C, 70.32; H, 5.53; N, 9.49; O, 14.68.

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

Orange solid; m.p.253 °C., yield (73%). IR: 3341, 3310 (NH2), 3009, 2916, 2874 (CH stretching), 2209 (CN). ^{1}H-NMR (DMSO-d_6): 6.41–8.65 (m, 11H, Ar-H+NH2), 3.92 (s, 1H, pyran CH), 11.35 (s, 1H, NH). MS(m/z): 305(M^+, 85%). Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76; O, 20.96 Found: C, 60.12; H, 6.29; N, 13.52; O, 20.35

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

Orange solid; m.p.265 °C., yield (77%). IR: 3395,

3367 (NH2), 2958, 2915, 2875 (CH stretching), 2212 (CN). ^{1}H-NMR (DMSO-d_6): 6.45–9.63 (m, 11H, Ar-H+NH2), 4.96 (s, 1H, pyran CH), 12.06 (s, 1H, NH). MS(m/z): 319(M^+, 6%). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16; O, 25.05. Found: C, 56.67; H, 5.46; N, 13.09; O, 24.87.

REFERENCES

[1] **(a)** P.T.Anastas, J.C.Warner; Green Chemistry: Theory and Practice, Oxford University Press: Oxford, UK, **(1998)**; **(b)** P.T.Anastas, T.Williamson; Green Chemistry, Frontiers in Benign Chemical Synthesis and Process, Oxford University Press: Oxford, UK, **(1998)**.

[2] **(a)** J.Zhu, H.Bienayme; In Multicomponent Reactions, J.Zhu, H.Bienayme, (Eds); WILEY-VCH Verlag GmbH & Co: KGaA, Weinheim, **(2005)** and references cited therein; **(b)** D.Tejedor, F.Garcia-Tellado; Chem.Soc.Rev., **36**, 484 **(2007)**; **(c)** I.Ugi; Pure Appl.Chem., **73**, 187 **(2001)**; For MCR based Heterocyclic Libraries see: **(d)** F.Lie'by-Muller, C.Simon, T.Constantieux, J.Rodriguez; QSAR Comb.Sci., **25**, 432 **(2006)**; **(e)** C.Simon, T.Constantieux, J.Rodriguez; Eur.J.Org.Chem., 4957 **(2004)**; **(f)** N.M.Evdokimov, A.S.Kireev, A.A.Yakovenko, M.Y.Antipin, I.V.Magedov, A.J.Kornienko; Org.Chem., **72**, 3443 **(2007)**; For Drug Discovery see: **(g)** L.Weber; Drug Discovery Today, **7**, 143 **(2002)**; **(h)** C.Hulme, V.Gore; Curr.Med.Chem., **10**, 51 **(2001)**.

[3] **(a)** C.I.Herrerias, X.Yao, Z.Li, C.Li; Chem.Rev., **107**, 2546 **(2007)**; **(b)** Comprehensive Organic Reactions in Aqueous Media; C.J.Li, T.H.Chan, (Eds); John Wiley & Sons, **(2007)**; **(c)** P.A.Grieco; Organic Reactions in Water, Thomson Science: Glasgow, Scotland, **(1998)**; **(d)** For recent examples, see: R.S.Varma; Org.Chem.High., **(2007)**, February 1, Clean Chemical Synthesis in Water; **(e)** V.D.B.Bonifacio; Org.Chem.High., **(2005)**, July 25, Organic Reactions in Water.

[4] **(a)** J.E.Kljin, J.B.N.Engberts; Nature, **435**, 746 **(2005)**; **(b)** S.Narayan, M.G.Fokin, H.C.Kolb, K.B.Sharpless; Angew.Chem., Int.Ed., **44**, 3275 **(2005)**; **(c)** I.Kanizsai, S.Gyónfalvi, Z.Szadonyi, R.Sillanpää, F.Fülöp; Green Chem., **9**, 357 **(2007)**.

[5] **(a)** M.C.Pirrung, K.Das Sarma; Tetrahedron, **61**, 11456 **(2005)**; **(b)** M.C.Pirrung, K.Das Sarma; J.Am.Chem.Soc., **126**, 444 **(2004)**; **(c)** H.C.Hailes; Org.Process Res.Dev., **11**, 114 **(2007)**.

[6] H.Junek, H.Aigner; Chem.Ber., **106**, 914 **(1973)**.

[7] **(a)** H.Wamhoff, E.Kroth, K.Strauch; Synthesis, **11**, 1129 **(1993)**; **(b)** G.Tacconi, G.Gatti, G.Desimoni; J.Prakt.Chem., **322**, 831 **(1980)**; **(c)** L.G.Sharanina, V.P.Marshtupa, A.Sharanin Yu; Khim.Geterosikl. Soedin., **10**, 1420 **(1980)**.

[8] A.Sharanin Yu, L.G.Sharanina, V.V.Puzanova; Zh. Org.Khim., **19**, 2609 **(1983)**.

[9] **(a)** A.M.Shestopalov, Y.M.Emeliyanova, A.A.Shestopalov, L.A.Rodinovskaya, Z.I.Niazimbetova, D.H.Evans; Tetrahedron, **59**, 7491 **(2003)**; **(b)** A.M.Shestopalov, Y.M.Emeliyanova, A.A.Shestopalov, L.A.Rodinovskaya, Z.I.Niazimbetova, D.H.Evans; Org.Lett., **4**, 423 **(2002)**.

[10] Y.Peng, G.Song, R.Ruiling Dou; Green Chem., **8**, 573 **(2006)**.

[11] **(a)** A.S.Nagarajan, B.S.R.Reddy; Synlett., 2002-2004 **(2009)**.

[12] G.Vasuki, K.Kumaravel; Tetrahedron Lett., **49**, 5636-5638 **(2008)**.