Iranian Journal of Organic Chemistry Vol. 2, No. 3 (2010) 413-416

New synthesis of 2,4-diamino-10-(4-bromo-phenylamino)-10*H*-9-oxa-1-aza-anthracene-3-carbonitrile, 2,4-diamino-10-*p*-tolylamino-10*H*-9-oxa-1-anthracec-3-carbonitrile and 2-(2-amino-3-cyano-4*H*-chromen-4-yl)-malononitrile

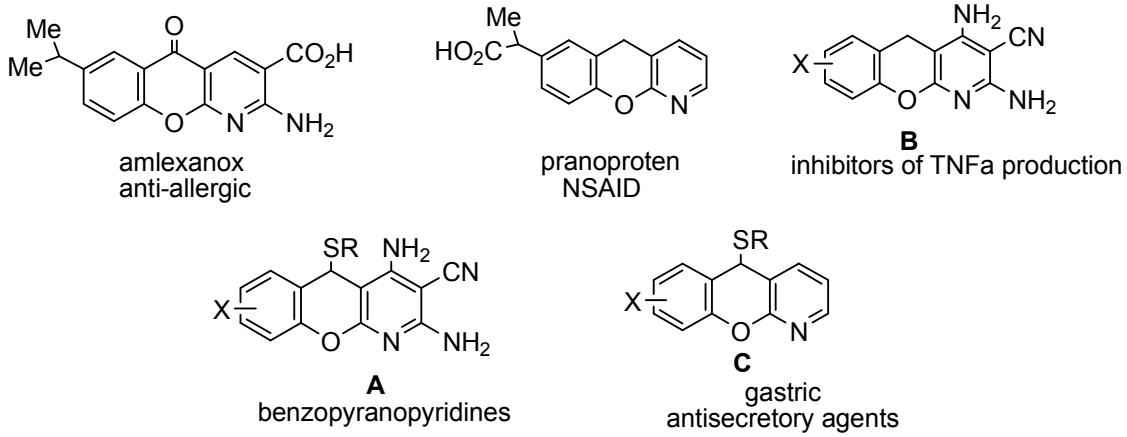
Mazarbanou Asnaashari Isfahani* and Maede Bayat
Department of Chemistry, Islamic Azad University, North Tehran Branch, Tehran, Iran.

Abstract: Benzopyrano[2,3-*b*]pyridine is an important privileged medicinal scaffold. In this work, the three-component synthesis of 2,4-diamino-10-(4-bromo-phenylamono)-10*H*-9-oxa-1-aza-anthracene-3-carbonitrile **(4),** 2,4-diamino-10-p-tolylamino-10*H*-9-oxa-1-anthracec-3- carbonitrile **(5)** and 2-(2-amino-3-cyano-4*H*-chromen-4-yl)-malononitrile **(6)** from the reaction of salicylaldehyde **(1)** with *p*-bromobenzaniline or *p*-tolylamine **(3)** in presence of 2 equiv of malononitrile **(2)**, is described.

Keywords: Salicylaldehyde; Cycloaddition; Malononitrile; Nucleophilic Addition.

Introduction

The rapid assembly of molecular diversity utilizing multi-component reactions has received a great deal of attention, most notably for the construction of heterocyclic drug-like libraries [1]. These methodologies are of particularly great utility when they lead to the formation of "privileged medicinal scaffolds', defined as molecular frameworks serving as the basis for the generation of ligands for functionally and structurally discreet biological receptors [2]. Such chemistry greatly facilitates the development of pharmaceutical agents for diverse applications.
Benzopyrano-(2, 3-b)-pyridine scaffold is of a significant medicinal relevance. The examples of approved therapeutic agents incorporating this molecular frameworh include amlexanox and pranoprofen (Scheme. **1**).

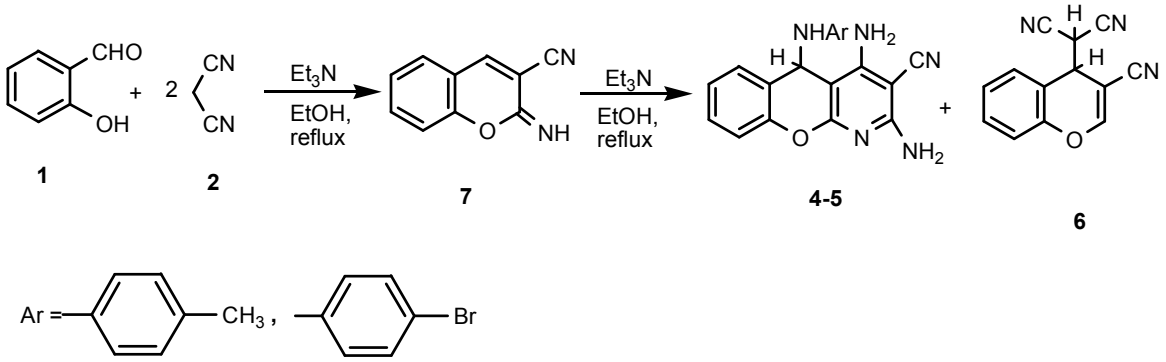


Scheme 1.

*Corresponding author. Tel: +98 21 22215670; Fax: + (98) 21 22214312; E-Mail: *mb_esnaashari@yahoo.com; m_asnaashari@iau-tnb.ac.ir*

In addition, many of these compounds possess anti-proliferative [3], cancer, chemopreventive [4], anti-bacterial (including anti-tubercular) [5], anti-myopic [6], anti-histaminic [7], hypotensive [8], anti-theumatic [9] and anti-asthmatic activities [10]. Many synthetic pathways to such medicinal libraries have been reported. [11] However; the diverse pharmacological properties associated with benzopyranopyridines warrant the development of novel processes allowing the synthesis of previously inaccessible analogues for biological evaluation. Also, Igor V. Magedov, Alexander Kornienko and et al. have described a multi-component strategy for the rapid preparation of library **A** [12] (Scheme. **1**).

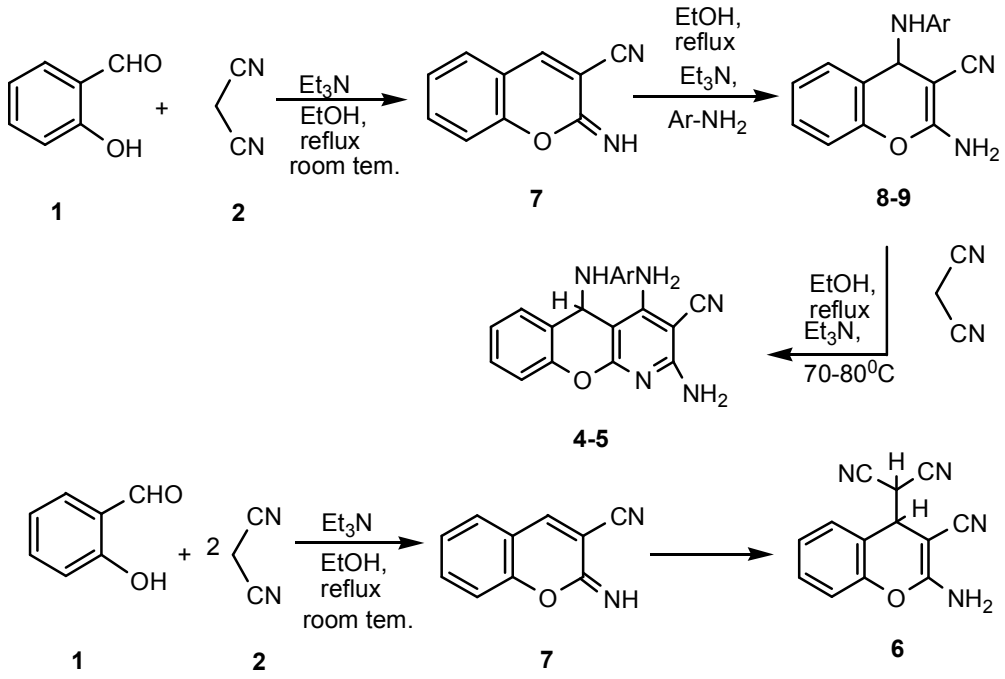
Therefore, in this work, we report the three-component synthesis of 2,4-diamino-10-(4-bromo-phenylamono)-10*H*-9-oxa-1-aza-anthracene-3-carbonitrile **(4),** 2,4-diamino-10-p-tolylamino-10*H*-9-oxa-1-anthracec-3-carbonitrile **(5)** and 2-(2-amino-3-cyano-4*H*-chromen-4-yl)-malononitrile **(6)** from the reaction of salicylaldehyde **(1)** with *p*-bromobenzaniline or *p*-tolylamine **(3)** in presence of 2 equiv of malononitrile **(2)**, is described (Scheme **2**).



Scheme 2.

Results and Discussion

In support of the proposed mechanism we obtained experimental evidence for each of the key steps in scheme **3**. Thus, the reaction between salicylaldehyde **(1)** with 1 equivalent of malononitrile **(2)**, in Et_3N and EtOH at room temperature leads to intermediate such as 2-iminochromene **(7).** This compound undergoes an addition with *p*-bromoaniline or *p*-tolylamine **(3)** to afford 2-amino-4-(4-bromo-phenylamino)-4*H*-chromene-3-carbonitrile **(8)** or 2-amino-4-*p*-tolylamino-4*H*-chromene-3-carbonitrile **(9)** at 70-80ºC. Finally, when **(8)** or **(9)** are treated under the same reaction conditions with another equivalent of malononitrile, bezopyranopyridine **(4-5)** forms in a good isolated yield. Also, the reaction between salicylaldehyde **(1)** with 2 equivalent of malononitrile **(2)**, in Et_3N and EtOH at room temperature leads to intermediate such as 2-iminochromene **(7)** and then leads to compounds **(6)** (Scheme **3**). The ^{1}H NMR spectrum of compound (**4**) exhibited tow broad singlet at δ=6.30 and δ=6.51 due to the tow NH_2 protons)(D_2O exchangeable), δ=7.02 (1 H, *d*, *J*=8.0) and δ=7.14 (1 H, *t*, *J*=7.2 and 7.4), δ=7.24 (1 H, *t*, *J*=7.4 and 8.0), δ=7.37 (1 H, *d*, *J*=7.2), 7.56 (2 H, *d*, *J*=8.2), δ=7.64 (2 H, *d*, *J*=8.2), and in the δ=8.43 (1 H, broad singlet, NH)(D_2O exchangeable), δ=8.94 (1 H, *d*, *J*=8.2, NH=*CH*), . The ^{1}H NMR spectrum of compound (**5**) exhibited one singlet at δ=2.08 (3 H, *s*, CH_3) and tow broad singlet at δ=6.67 and δ=7.06 due to the NH_2 protons), (D_2O exchangeable). The ^{1}H NMR spectrum of compound (**6**) exhibited displayed tow doublet at δ=4.60 and δ=4.80 (*J*=3.8) and a singlet at δ=6.82 due to the NH_2 protons (D_2O exchangeable).



Scheme 3.

Conclusion

In conclusion, we have developed a simple method for the synthesis of novel 2-aminochrimenes and benzopyranopyridines in Et_3N and ethanol at 70-80 °C. Advantages of this method are its generality, short reaction tim and easy work-up.

Experimental

All compounds in these reactions were obtained from Merck co. and were used without further purification. Mp: Thomas-Hoover capillary. FT-IR spectra: Bruker VERTEX-70. ^{1}H and ^{13}CNMR spectra: Bruker DRX-500Avance instrument; in $CDCl_3$ or DMSO at 500.1 and 125.7 MHz, respectively; δ in part per million, J in hertz.

Typical experimental procedure:

To a stirred solution of malononitrile **(2)** (3 mmol), salicylaldehyde **1** (1.5 ml), in Et_3N (0.1 mL) and 7 mL of ethanol was added *p*-bromobenzaniline (1.5 mmol) at room temperature and then 70-8 °C. The resulting mixture was refluxed for 3-4 h and 70-8 °C and then allowed to cool to room temperature. The formed precipitate was isolated by filtration. To the filtrate was added water (4 ml), which resulted in the crystallization of the product. The formed crystals were isolated by filtration to yield a corresponding pure benzopyranopyridine (**4-5**).

2,4-Diamino-10-(4-bromo-phenylamino)-10H-9-oxa-1-aza-anthracine-3-carbo-nitrile **(4)**:

Yellow powder; 71%; mp 243-245 °C; IR (KBr) (ν_{max}/cm^{-1}): 3348 (NH), 3288 (NH_2), 3152 (CH aromatic), 2204 (CN), 1663 (C=C), 1588 (N-H bending) cm^{-}1. ^{1}H NMR (500.1 MHz, TMS, DMSO): δ= 6.30 (2 H, *s*, NH_2) (D_2O exchangeable), 6.51 (2 H, *s*, NH_2), 7.02 (1 H, *d*, *J*=8.0 Hz, ArCH), 7.12 (1 H, *t*, *J*=7.2 and 7.4 Hz ArCH), 7.23 (1 H, *t*, *J*=7.4 and 8.0 Hz ArCH), 7.37 (1 H, *d*, *J*=7.2 Hz, ArCH), 7.49 (2 H, *s*, NH_2) (D_2O exchangeable), 7.56 (2 H, *d*, *J*=8.2 Hz, 2 bromoCH), 7.64 (2 H, *d*, *J*=8.2 Hz, 2 bromoCH), 8.43 (1 H, *s*, NH), 8.93 (1 H, *d*, *J*=8.2 Hz, NH–*CH*) ppm. ^{13}C NMR (125.7 MHz, TMS, DMSO): δ=161.3, 161.2, 157.8, 152.4, 131.0, 129.8, 124.9, 118.7, 117.7, 117.1, 114.3, 113.7 84.6 and 71.3 (aromatic C and 3 CN), 35.5 (CH aliphatic) ppm.

2,4-Diamino-10-p-tolylamino-10H-9-oxa-1-aza-anthracene-3-carbonitrile **(5)**:

Brown powder, 62%; mp 258-260 °C; IR (KBr) (ν_{max}/cm^{-1}): 3385 (NH), 3348 (NH_2), 3181 (CH aromatic), 2201 (CN), 2823 (CH aliphatic), 1640 (C=C), 1601 (N-H bending) cm^{-}1. ^{1}H NMR (500.1 MHz, TMS, DMSO): δ=2.08 (3 H, *s*, CH_3), 7.03 (1 H,

d, *J*=8.0 Hz, ArCH), 7.12 (1 H, *t*, *J*=7.3 and 7.5 Hz ArCH), 7.23 (1 H, *t*, *J*=7.5 and 8.0 Hz ArCH), 7.37 (1 H, *d*, *J*=7.3 Hz, ArCH), 7.47 (2 H, *s*, NH_2), 7.54 (2 H, *d*, *J*=8.3 Hz, 2 CH of tolyl), 7.77 (2 H, *s*, NH_2) (D_2O exchangeable), 7.78 (2 H, *d*, *J*=7.3 Hz, 2 CH of tolyl), 8.93 (1 H, *d*, *J*=8.2 Hz, NH–*CH*), 9.17(1 H, *br s*, NH) ppm. ^{13}C NMR (125.7 MHz, TMS, DMSO): δ=163.3, 162.8, 154.7, 152.8, 150.2, 135.2, 130.0, 128.3, 126.2125.7, 125.0, 123.0, 119.4, 118.6, 117.2, 116.7, 98.1, 78.7, 75.9, 70.6 and 25.1 ppm.

2-(2-Amino-3-cyano-4H-chromen-4-yl)-malononitrile **(6)**:

White Powder; 80%; mp 140-142 °C; IR (KBr) (ν_{max}/cm^{-1}): 3195 (NH_2), 2201 (CN), 1608 (C=C), cm^{-1}. ^{1}H NMR (300.1 MHz, TMS, Acetone): δ= 4.60 (1 H, *d*, *J*=3.8 Hz, CH), 4.79 (1 H, *d*, *J*=3.8 Hz, CH), 6.82 (1 H, *s*, NH_2) (D_2O exchangeable), 7.16 (1 H, *d*, *J* = 8.2 Hz ArCH), 7.32 (1 H, *t*, *J* = 7.5 and 7.6 Hz ArCH), 7.47 (1 H, *t*, *J* = 7.6 and 8.2 Hz ArCH), 7.60 (1 H, *d*, *J*=7.5 Hz, ArCH), ppm. ^{13}C NMR (125.7 MHz, TMS, DMSO): δ 33.2 (*C*-H), 37.9 (*C*–H), 49.7 (*C*N), 113.7 (*C*N), 113.9 (*C*N), 117.2, 118.8, 120.2, 125.9, 129.7 and 131.1 (aromatic 6C), 150.6 and 164.3, (Chromen 2C).

References

[1] For recent reviews, see: (a) Gerencsér, J.; Dormán, G.; Darvas, F. *QSAR Comb. Sci*. **2006**, 439–448; (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed*. **2005**, *44*, 1602–1634; (c) Orru**,** R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (e) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen* **2001**, *4*, 1–34; (f) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366–374.

[2] The term 'privileged scaffolds or structures' was originally introduced by Merck researchers in their work on benzodiazepines: (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem*. **1988**, *31,* 2235–2246; For review, see: (b) Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem*. **2000**, *35*, 289–298.

[3] Kolokythas, G.; Pouli, N.; Marakos, P.; Pratsinis, H.; Kletsas, D. *Eur. J. Med. Chem*. **2006**, *41*, 71–79.

[4] Azuine, M. A.; Tokuda, H.; Takayasu, J.; Enjyo, F.; Mukainaka, T.; Konoshima, T.; Nishino, H.; Kapadia, G. *J. Pharmacol. Res*. **2004**, *49*, 161–169.

[5] (a) Srivastava, S. K.; Tripathi, R. P.; Ramachandran, R. *J. Biol. Chem*. **2005**, *280*, 30273–30281; (b) Brötz-Oesterhelt, H.; Knezevic, I.; Bartel, S.; Lampe, T.; Warnecke-Eberz, U.; Ziegelbauer, K.; Ha¨bich, D.; Labischinski, H. *J. Biol. Chem*. **2003**, *278*, 39435–39442.

[6] Toshiro, S.; Noriko, W. Eur. Pat. Appl. EP 647445 A1, 19950412, 1995.

[7] Ito, Y.; Kato, H.; Yasuda, S.; Kato, N.; Iwasaki, N.; Nishino, H.; Takeshita, M. Jpn. Kokai Tokkyo Koho, JP, 06107664 A2 19940419, 1994.

[8] Goto, K.; Yaoka, O.; Oe, T. PCT Int. Appl. WO 8401711, A1, 19840510, 1984.

[9] Maruyama, Y.; Goto, K.; Terasawa, M. Ger. Offen. DE, 3010751, 19810806, 1981.

[10] Ukawa, K.; Ishiguro, T.; Kuriki, H.; Nohara, A. *Chem., Pharm. Bull*. **1985**, *33*, 4432–4437.

[11] For recent synthetic work, see: (a) Abdel-Rahman, A. H.; Hammouda, M. A. A.; El-Desoky, S. I. *Heteroat. Chem*., **2005**, *16*, 20–27; (b) Langer, P.; Appel, B. *Tetrahedron Lett*. **2003**, *44*, 5133–5135; (c) Daia, D. E.; Gabbutt, C. D.; Heron, B. M.; Hepworth, J. D.; Hursthouse, M. B.; AbdulMalik, K. M. *Tetrahedron Lett*. **2003**, *44*, 1461–1464; (d) Fujiwara, H.; Kitagawa, K. *Heterocycles* **2000**, *53*, 409–418; (e) O'Callaghan, C. N.; McMurry, T. B. H.; O'Brien, J. E.; Draper, S. M. *J. Chem. Res*. (S) **1997**, 312–313; (f) O'Callaghan, C. N.; McMurry, T. B. H.; O'Brien *J. Chem.*, *Soc*., *Perkin Trans. 1,* **1995**, 417– 420.

[12] Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Yu.; Magedov, I. M.; Kornieko, A. *Tetrahedron Lett.* **2006,** *47,* 9309-9312.