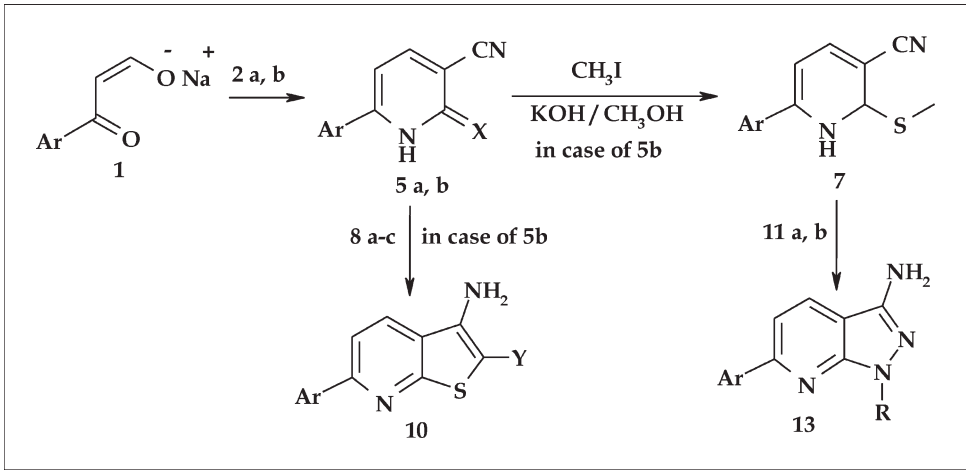
Mahmoud A. Mohamed*

Textile Department, Faculty of Industrial Education, Beni-Suef University, Beni-Suef, Egypt
*E-mail: mahmoud71_2000@yahoo.com
Received August 25, 2010
DOI 10.1002/jhet.802
Published online 25 August 2011 in Wiley Online Library (wileyonlinelibrary.com).



Cyclocondensation of cyanoacetamide and cyanothioacetamide with sodium salt of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one gave 6-oxo-[2,3′]bipyridine **5a** and 6-thioxo-[2,3′]bipyridine **5b** derivatives, respectively. Compound **5b** upon treatment with different methylenes **8** gave thieno[2,3-*b*]pyridines **10**. Treatment of **5b** with iodomethane gave bipyridine derivative **7**, which cyclocondensed with hydrazines **11** to give pyrazolo[3,4-*b*]pyridines **13**.

J. Heterocyclic Chem., **49**, 200 (2012).

INTRODUCTION

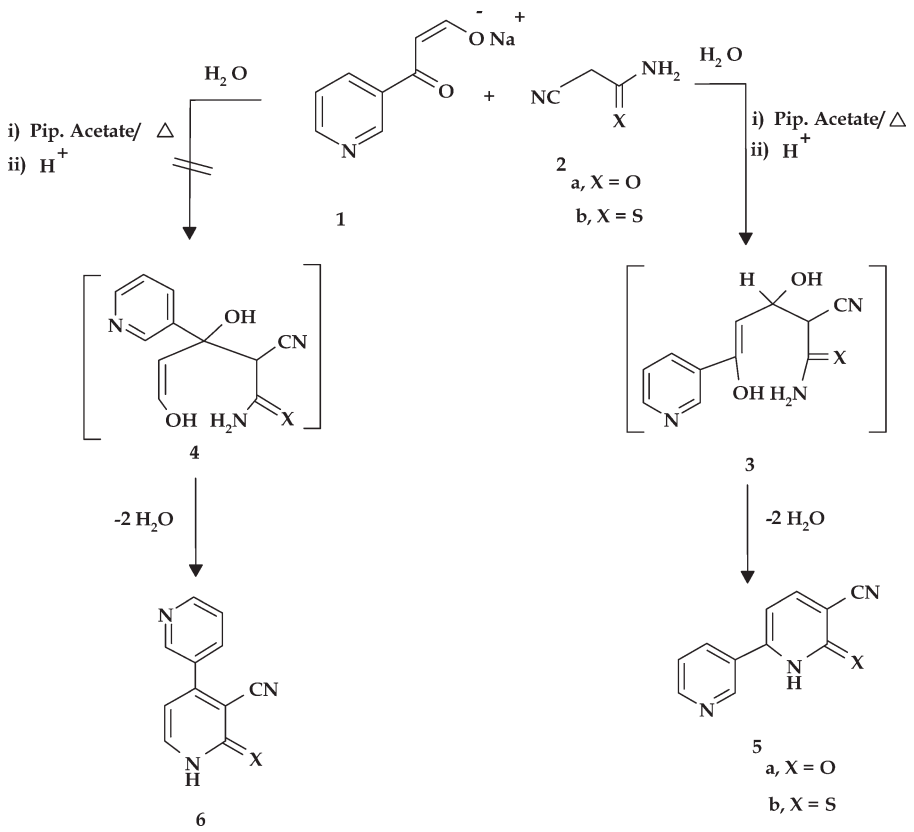
Pyridines and pyrazolopyridines have attained considerable interests due to their wide range of applications in medicine and agriculture, such as anti-inflammatory, antitumor, antimycobacterial, antifungal, and antiviral activities [1–3]. In the last decades, they are used as anticancer drugs, antihypertension, antifungal reagents, pesticides, herbicides, and plant growth reagents [4–7]. Similarly, thienopyridine derivatives are characterized by a very broad area of biological activities, such as antiallergic [8], antiatherosclerotic [9], antibacterial [10–12], anticancer [13], antiviral [14,15], antihypertensive [16,17], antidepressant [18], antihistaminic [19], antimicrobial, and neurotropic activities [20–23]. Recently, it has been reported that many pyridine derivatives showed strong cytotoxicity against several human cancer cell lines [24–26]. It was also found that many of these derivatives might block proliferation of various cancer cell lines [27].

In view of these reports and in continuation with the previous work, we have, herein, synthesized new derivatives of oxo(thioxo)bipyridine, thieno[2,3-*b*]pyridines, and pyrazolo[3,4-*b*]pyridines, which are expected to have anticancer properties.

RESULTS AND DISCUSSION

Pyridine derivatives are useful synthetic intermediates for synthesis of biologically active deazafolates' ring system and pyrimidine nucleosides, which are reported to be significantly active, both *in vitro* and *in vivo* [28,29], inhibitor for dihydrofolate reductase [30], cytotoxicity against various tumors as potentially as methotrexate [31,32] and one of the most effective antimetabolites currently used in treatment of various solid tumors [33,34]. Owing to our plane to develop an efficient and simple procedure for the synthesis of new antimetabolites [35,36], we have recently approached for the synthesis of this class of compounds. We report in this part new synthesis of bipyridine, thieno[2,3-*b*]pyridine, and pyrazolo[3,4-*b*]pyridine derivatives. Thus, it has been found that 2-acetylpyridine reacted with ethyl formate in dry ether containing sodium methoxide to give sodium salt of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one **1**. The structure of **1** was confirmed by chemical transformations. Compound **1** reacted with cyanamides **2** to give substituted bipyridines. Two modes of cyclization are feasible, giving a [2,3′]- or [3,4′]bipyridine-substituted products, as outlined in (Scheme 1). In the first, initial attack by a carbanion

Scheme 1



takes place at the formyl group of the salt **1** and subsequent Michael cyclization followed by elimination of two moles of water leads to the [2,3′]-substituted products **5**, whereas in the second, initial nucleophilic attack by the methylene carbon takes place at the ketonic group, followed by cyclization and elimination of water leads to [3,4′]bipyridine-substituted isomers **6**. In fact, only isomer **5** was obtained because of the fact that initial attack of the active methylene carbon at the unhindered formyl group being much more probable than attack at the hindered and electronically disfavored ketonic group. Spectral studies did not allow us to distinguish between structures **5** and **6**. To establish unambiguously the structure of the product, the crystal structure of a similar previous work, which confirms the exclusive presence of the regioisomer **5** in the solid state has been reported [35–39].

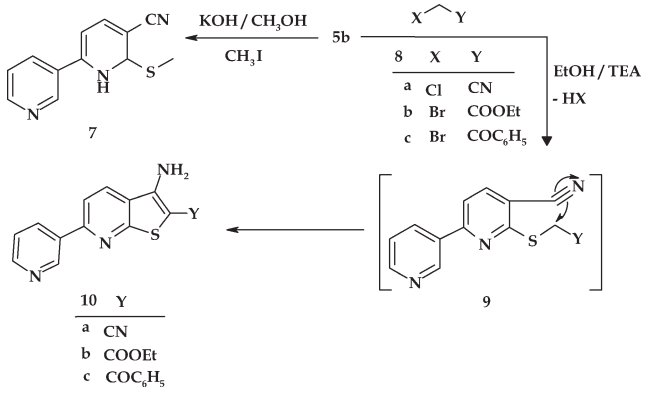
Treatment of bipyridine derivative **5b** with iodomethane in ethoxide solution gave 6-methylsulfonyl[2,3′]bipyridine derivative **7**. Treatment of **5b** with active methylene derivatives **8a–c** in methanolic potassium hydroxide solution afforded the corresponding thieno[2,3-*b*]pyridine derivatives **10a–c**, respectively (Scheme 2).

Finally, refluxing compound **7** with hydrazines **11** in ethanolic solution containing a catalytic amount of piperidine afforded pyrazolo[3,4-*b*]pyridines **13** (Scheme 3).

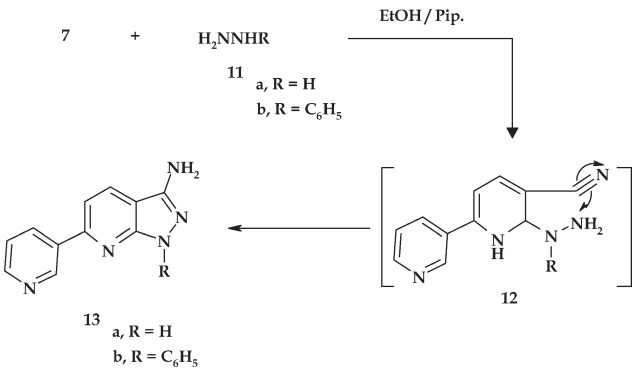
EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (KBr disk) on a Perkin Elmer 11650 FTIR instrument. ^{1}H NMR spectra were measured on a Varian 400 MHz

Scheme 2



Scheme 3



spectrometer for solutions in $(CD_3)_2SO$ using $Si(CH_3)_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were measured at the Microanalytical Data Center at Cairo University.

Sodium salt of 3-hydroxy-1-(pyridin-3-yl)prop-2-en-1-one (1). A mixture of (0.01 mol) 3-acetyl pyridine and (0.01 mol) ethyl format was dropped over a solution of (0.01 mol) of sodium methoxide in 65-mL dry ether with stirring. The formed solid product was collected and used directly in the following reactions.

1,6-Dihydro-[2,3′]bipyridinyl-5-carbonitriles (5a, b). A solution of (0.01 mol) sodium salt of 3-hydroxy-1-pyridin-3-yl-propenone **1**, (0.01 mol) cyanamides **2,** (1 mL) piperidine acetate in (3 mL) water was refluxed for 10 min. Acetic acid (1 mL) was added to the hot solution. The solid product was filtered off and recrystallized from the appropriate solvent.

5a. Pale yellow crystals, from DMF, (yield 70%), m.p. 230°C, ν_{max} (cm^{-1}) (KBr) 3350 (NH), 2211 (CN), 1680 (CO), 1622 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 6.88–8.99 (m, 6H, aromatic), 9.05 (s, br., 1H, NH); *m/z* 197 (Calcd. for $C_{11}H_7N_3O$ (197.19): C, 67.00; H, 3.58; N, 21.31% Found C, 67.14; H, 3.65; N, 21.11%).

5b. Pale yellow crystals, from ethanol, yield (73%), m.p. 230–32°C; ν_{max} (cm^{-1}) (KBr) 2218 (CN); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 7.14–8.92 (m, 6H, aromatic), 14.25 (s, br., 1H, SH); *m/z* 213 (Calcd. for $C_{11}H_7N_3S$ (213.26): C, 61.95; H, 3.31; N, 19.70; S, 5.03% Found C, 62.12; H, 3.22; N, 19.80; S, 15.11%).

6-Methylsulfanyl-[2,3′]bipyridinyl-5-carbonitrile (7). Equimolar amounts of bipyridine derivative **5b** and iodomethane were stirred in methanolic potassium hydroxide solution for 1 h. The solution was poured over ice-water mixture and then neutralized by HCl. The solid product was filtered off and recrystallized from ethanol.

Colorless crystals, from EtOH, yield (71%), m.p. 170–72°C; ν_{max} (cm^{-1}) (KBr) 2210 (CN), 1665 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 2.75 (s, 3H, SCH_3), 7.27–9.31 (m, 6H, aromatic); *m/z* 227 (Calcd. for $C_{12}H_9N_3S$ (227.28): C, 63.41; H, 3.99; N, 18.49; S, 14.11% Found: C, 63.31; H, 4.12; N, 18.35; S, 14.00%).

3-Amino-6-(pyridin-3-yl)thieno[2,3-*b*]pyridines (10a–c). A mixture of (0.01 mol) bipyridine **5b**, (0.01 mol) active methylenes **8** and (0.01 mol) KOH was stirred in methanol for 1 h. The solution was poured over ice-water mixture and then neutralized by HCl. The solid products were filtered off and recrystallized from the appropriate solvent.

10a. Colorless crystals, from Dioxan, yield (71%), m.p. 280–82°C; ν_{max} (cm^{-1}) (KBr) 3320, 3180 (NH_2), 2184 (CN), 1663 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 6.92 (s, br, 2H, NH_2), 7.34–9.33 (m, 6H, aromatic); *m/z* 252 (Calcd. for $C_{13}H_8N_4S$ (252.29): C, 61.89; H, 3.20; N, 22.21; S, 12.71% Found C, C, 62.00; H, 3.33; N, 22.12; S, 12.93%.

10b. Colorless crystals, from Dioxan, yield (85%), m.p. 270–72°C; ν_{max} (cm^{-1}) (KBr) 3320, 3180 (NH_2), 1672 (CO), 1622 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 2.30 (t, 3H, $CH_2\mathbf{CH_3}$), 3.81 (q, 2H, $\mathbf{CH_2}CH_3$), 6.54 (s, br, 2H, NH_2), 7.33–9.33 (m, 6H, aromatic); *m/z* 299 (Calcd for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.19; H, 4.38; N, 14.04; S, 10.71% Found: C, 60.00; H, 4.45; N, 14.17; S, 10.94%.

10c. Colorless crystals, from EtOH, yield (78%), m.p. 210–12°C; ν_{max} (cm^{-1}) (KBr) 3360, 3180 (NH_2), 1700 (CO), 1599 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 7.01 (s, br, 2H, NH_2), 7.27–7.55 (m, 5H, C_6H_5), 7.80–9.13 (m, 6H, aromatic); *m/z* 331 (Calcd for $C_{19}H_{13}N_3OS$ (331.40): C, 68.86; H, 3.95; N, 12.68; S, 9.68% Found C, 68.65; H, 4.13; N, 12.74; S, 9.53%.

6-(Pyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-ylamines (13a, b). A solution of (0.01 mol) bipyridine **7** and (0.01 mol) hydrazines **11** was refluxed in ethanol containing a catalytic amount of pip. for 3 h. The solution was poured over ice-water mixture and then neutralized by HCl. The solid products were filtered off and recrystallized from water.

13a. Colorless crystals, from water, yield (77%), m.p. 105–106°C; ν_{max} (cm^{-1}) (KBr) 3350, 2316, 2189 (NH, NH_2), 1627 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 6.52 (s, 2H, NH_2), δ = 10.31 (s, br., H, NH), 7.26–9.63 (m, 6H, aromatic); *m/z* 211 (Calcd. for $C_{11}H_9N_5$ (211.22): C, 62.55; H, 4.29; N, 33.16% Found: C, 62.35; H, 4.12; N, 33.32%).

13b. Colorless crystals, from water, yield (80%), m.p. 110–112°C; ν_{max} (cm^{-1}) (KBr) 3350, 2316 (NH_2), 1627 (C=N); ^1H NMR (200 MHz, $(CD_3)_2SO$): δ = 5.21 (s, br., 2H, NH_2), 7.26–8.87 (m, 11H, aromatic); *m/z* 211; *m/z* 287 (Calcd for $C_{17}H_{13}N_5$: C, 71.07; H, 4.56; N, 24.37% Found C, 71.07; H, 4.56; N, 24.37%).

REFERENCES AND NOTES

[1] Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, F. M. E. Biorg Med Chem 2008, 16, 7102.

[2] Shaheen, F.; Badashah, A.; Gielen, M.; Gieck, C.; Jamil, M.; de Vos, D. J. Organometallic Chem 2008, 693, 1117.

[3] Son, J.; Zhao, L.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.;Ch. Jeong, T.; Jeong, B.; Lee, C.;Lee E. Eur J Med Chem 2008, 43, 675.

[4] Highfield, J. A.; Mehta, L. K.; Parrick, J.; Wardman, P. Bioorg Med Chem 2000, 8, 1065.

[5] Wu, X. M.; Wu, X. S.; Xu, J. Y.; Hua, W. J Chin Pharm Univ 1996, 27, 641.

[6] Wlime ová, V.; Otŏcená.ck, M.; Waissor, K. Eur J Med Chem 1996, 31, 389.

[7] Qian, X. H.; Tang, J.; Chen, W. D. Chem J Chin Univ [in Chinese]. 1998, 10, 1620.

[8] Bol'but, A. V.; Vovk, M. V. Abstracts of International Confeerence on the Chemistry of Nitrogen Containing Heterocycles, CNH-2003; Kharkiv (Ukraine), 2003, 68.

[9] Allan, J. D.; Rliopoulos, G. M.; Reiszner, E.; Moellering, R. C. Antimicrob Agents Chemother 1987, 31, 1997.

[10] Hozien, Z. A.; Abdel-Wahab, A. A.; Hassan, K. M.; Atta, F. M.; Ahmed, S. A. Pharmazie 1997, 52, 753.

[11] Munchhof, M. J.; Sobdov-Jaynes, S.; Marx, Malthew Arnold (Pfizer Inc.). U.S. Pat. 6,492,383 (Cl, 514–301; A 61 K 31/44), 10 Dec 2002, US Appl. PV 65,097. 11 Nov 2001, 37 pp, cont-in-part of Appl. No. PCT/IB98/1691; Chem Abstr 2003, 138, 24721.

[12] Kharizomenova, I. A.; Grinev, A. N.; Samsonova, N. V.; Panisheva, E. K.; Kaplina, N. V.; Nikolaeva, I. S.; Pushkina, T. V.; Pershin, G. N. Khim-farm Zh 1981, 15, 40.

[13] Kaplina, N. V.; Grinev, A. N.; Bogdanova, G. A.; Alekseeva, L. N.; Pushkina, T. V.; Fomina, A. N. Khim-farm Zh 1987, 21, 197.

[14] Pathak, U. S.; Alagarsamy, V. Acta Pharm Turc 1999, 41, 37.

[15] Ismail, M. A.-H.; Aboul-Einein, M. N. Y.; Abouzid, K. A. M.; Kandil, S. B. A. Alex J Pharm Sci 2002, 16, 143.

[16] Ninomya, K.; Nitsuta, K.; Tobe, A.; Egawa, M.; Kikumoto, R. Jpn Kokai Tokkyo Koho JP 06 16,557 [94 16,557]. (Cl. A61K31/505), 25 Jan. 1994, Appl. 92/340,658, 21 Dec. 1992; 12 p; Chem Abstr 1994, 120, 290120.

[17] Shishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. Eur J Med Chem 2000, 35, 351.

[18] Moneer, A. A. Bull Fac Pharm (Cairo Univ) 2001, 39, 27.

[19] Ammar, Y. A.; Ismail, M. M.; El-Gaby, M. S. A.; Zahran, M. A. Indian J Chem 2002, 41B, 1486.

[20] Chambhare, R. V.; Bobade, A. S.; Khadse, B. G. Indian J Heterocycl Chem 2002, 12, 67.

[21] Sayed, A. Z. Adv Colour Sci Technol 2002, 5, 24; Chem Abstr 2002, 137, 141818.

[22] Shah, M.; Patel, P.; Parekh, H. Orient J Chem 2002, 18, 159; Chem Abstr 2002, 137, 310886.

[23] Oganisyan, A. Kh.; Noravyan, A. S.; Dzhagatspanyan, I. A.; Melikyan, G. G. Pharm Chem J 2003, 37, 13; Chem Abstr 2004, 140, 122553.

[24] Zhao, L. X.; Sherchan, J.; Park, J. K.; Jhang, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. Arch Pharm Res 2006, 29, 1091.

[25] Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. Bioorg Med Chem 2007, 15, 4351.

[26] Cesarini, S.; Spallarossa, A.; Ranise, A.; Schenone, S.; Rosano, G.; La Colla, P.; Sanna, G.; Bernardetta, B.; Loddo, R. Eur J Med Chem 2009, 44, 1106.

[27] Krystof, V.; Moravcova, D.; Paprskarova, M.; Barbier, P.; Peyrot, V.; Hlobikova, A.; Havlicek, L.; Stramd, M. Eur J Med Chem 2006, 41, 1405.

[28] Temple, C.; Elliot, R. D.; Montgomery, J. A. J Org Chem 1982, 47, 761.

[29] Taylor, E. C.; Palmer, D. C.; George, T. J.; Fletcher, S. R.; Tseng, C. P.; Horrion, P. J.; Beardsley, G. P. J Org Chem 1983, 48, 4852.

[30] Stone, S. R.; Montgomery, J. A.; Morrision, J. F. Biochem Pharmcol 1974, 33, 175.

[31] Grivsky, E. M.; Lee, S.; Sigel, S. W.; Durch, D. S.; Nichol, C. A. J Med Chem 1980, 23, 327.

[32] Ensminger, W. D.; Grindey, G. B.; Hoglind, J. A. In Advances in Cancer Chemotherapy;Rosowsky, A., Ed.;Marcel Dekker:New York, 1976; Vol. 1, p 61.

[33] DeGraw, J. I.; Christine, P. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. J Med Chem 1990, 33, 673.

[34] Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. J Med Chem 1985, 28, 914.

[35] Elgemeie, G. H.; Elghandour, A. H.; Elzanate, A. M.; Mohamed, M. A. Mansora Sci Bull 2004, 31.

[36] Elgemeie, G. H.; Mohamed, M. A.; Jones, P. G. Acta Cryst E58, 2002, 1293.

[37] Ahmed, S. A.; Hussein, A. M.; Hozayen, W. G. M.; El-Ghandour, A. H. H.; Abdelhamid, A. O. J Heterocycl Chem 2007, 44, 803.

[38] Ahmed, O. M.; Mohamed, M. A.; Ahmed, R. R.; Ahmed, S. A. E. J Med Chem 2009, 44, 3519.

[39] Mohamed, M. A. J Heterocycl Chem 2010, 47, 517.