A NOVEL SYNTHETIC ROUTE TO NITROSOPYRIDINE-2(1H)-THIONES AND NITROSO-*N*-ARYLPYRIDONES

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Abstract –A novel and efficient method for the synthesis of a new variety of nitrosopyridine-2(1H)-thiones and nitroso-*N*-arylpyridones by the reaction of oxime derivatives of β-diketones and β-ketoesters with cyanothioacetamide and cynoacetanilides, respectively. The synthetic potential of the method is demonstrated.

Continuing our interest in the development of efficient and simple procedures for the synthesis of antimetabolites[1-3], we have recently reported different successful approaches for the synthesis of pyridine-2(1H)-thiones[4]. The importance of the synthesized compounds as intermediates for the synthesis of the biologically active deaza and folic acid ring system, prompted our interest in the synthesis and chemistry of this class of compounds. The present research deals with a novel synthesis of nitrosopyridine-2(1H)-thiones and N-arylpyridones by the reaction of oxime derivatives of β-diketones and β-ketoesters with cyanothioacetamide and cynoacetanilides, respectively. As far as I know this is the first examples to be reported for pyridine-2(1H)-thione and N-substituted pyridone derivatives. Thus, it has been found that cyanothioacetamide **1** reacted with isonitroso derivatives of β-diketones and β-ketoesters **3a,b** in boiling ethanolic sodium ethoxide to give the corresponding 5-nitroso-pyridine-2(1H)-thiones **6**. The structures of **6** were established on the basis of elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The analytical data for **6a** revealed a molecular formula $C_8H_7N_3OS$ (M^+=193). The ^{1}H NMR spectrum revealed two bands at δ 2.32 and 2.50 ppm assignable for two methyl groups and a broad singlet at δ 13.80 ppm assignable to an SH group. The ^{13}C NMR spectrum was characterized by a signal at δ 17.44 ppm and 22.20 attributed to two methyl carbons and a signal at δ 114.18 ppm attributed to the CN carbon. Moreover, signals appeared at δ =177.31, 105.91, 149.03, 157.20 and 160.31 ppm corresponding to C-2, C-3, C-5, C-4 and C-6, respectively. The formation of **6** from the reaction of **1** with **3** is assumed to proceed via Michael addition of active methylene of **1** to the double bond in **3**, The formed Michael adducts then cyclized smoothly via elimination of two moles of water to give the stable 5-nitroso-pyridine-2(1H)-thiones **6**. Similarly, reaction of cyanothioacetamide **1** with β-ketoesters **8** leads to 5-nitroso-6-hydroxy-pyridine-2(1H)-thiones **9**. In order to investigate the scope of this reaction further, we studied the reaction of **3** with oxo nitriles. Thus, in a typical experiment, when isonitroso derivatives of β-diketones **3a,b** reacted with cyanoacetanilide **10** in refluxing

ethanolic sodium ethoxide, the *N*-aryl-5-nitroso-2-oxo-pyridines **12** were obtained in good yields. The structures of **12** were established and confirmed for reaction products on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). The analytical data for **12a** revealed a molecular formula $C_{15}H_{13}N_3O2$ (M$^+$=267), ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR revealed two bands at δ 2.44 and 2.68 ppm assignable for two CH_3 groups, a multiplet at 7.05-7.99 ppm assigned for aromatic protons. The formation of **12** from the reaction of **3** and cyanoacetanilide **10** is assumed to proceed via intermediacy of Michael adducts, which cyclized to yield the final *N*-aryl-5-nitroso-2-pyridones **12**. In order to establish whether the reaction of isonitroso derivatives of β-diketones and β-ketoesters with activated nitriles could be extended to provide a general approach to nitrosopyridone derivatives, we found in a typical experiment, when oxime derivatives of β-diketones **3** and β-ketoesters **8** reacted with cyanoacetohydrazide **14** in refluxing ethanolic sodium ethoxide, the 5-nitroso-*N*-amino-2-pyridones **15** and **16** were obtained in good yields, respectively. The structures of **15** and **16** were established and confirmed for reaction products on the basis of their elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). Thus, the analytical data for **15a** revealed a molecular formula $C_8H_8N_4O_2$ (M =192), ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR revealed two bands at δ 2.46 and 2.68 ppm assignable to two methyl groups and a broad singlet at δ 5.52 ppm assignable for an amino group. The formation of **15** from the reaction of **3** and cyanoacetohydrazide **14** is assumed to proceed via intermediacy of Michael adducts, which cyclized to yield the final 5-nitroso-*N*-amino-2-oxopyridines **15**.

In summary, we have achieved a regiospecific synthesis of interesting nitrosopyridine-2(1H)-thiones and their corresponding oxo analogues by the reaction of oxime derivatives of β-diketones and β-ketoesters with cyanothioacetamide and cynoacetanilides, respectively. The compounds obtained seems promising as high potential intermediates for synthesizing antimetabolite agents.

Experimental

All melting points are uncorrected. The IR spectra were obtained (KBr, disk) on a Perkin Elmer /1650 FT-IR instrument .The ^{1}H NMR spectra were measured on a Varian 400 MHZ spectrometer for solutions in $(CD_3)_2SO$ with $SiMe_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical Data were obtained from the Microanalytical Data Center at Cairo University.

3-Cyano-4-methyl-5-nitroso-pyridine-2(H)-thiones 6a,b, 9a,b

General procedure. A mixture of cyanothioacetamide **1** (0.01 mol) and oximes **3a,b** or **8a,b** (0.01 mol) was dissolved in ethanol (30 ml) containing sodium ethoxide (0.01 mol). The mixture

was refluxed for 3h, then allowed to cool to room temperature and acidified with cold dilute hydrochloric acid. The resulting solid product was collected by filtration and recrystallized from ethanol.

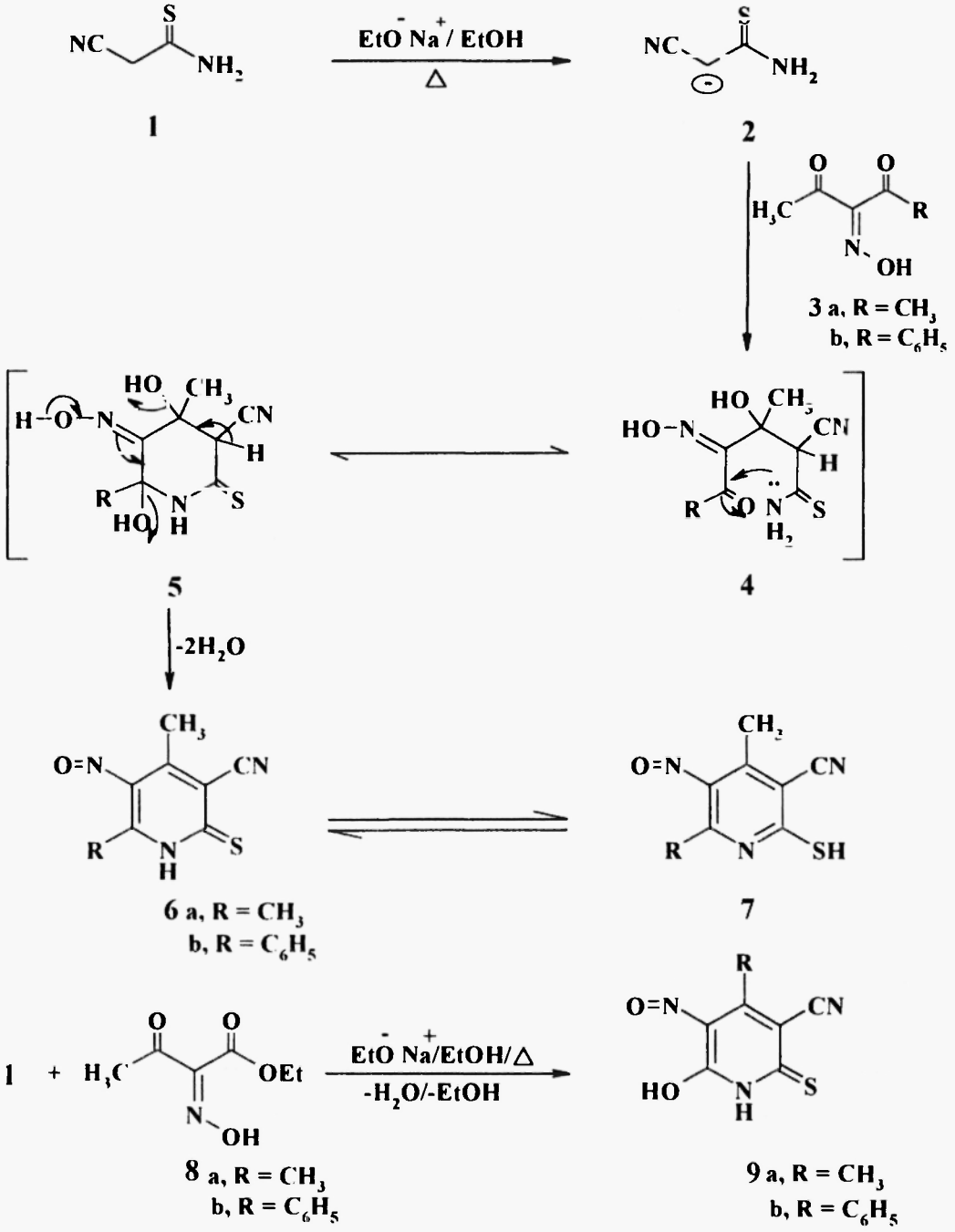
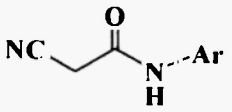


Chart (1)

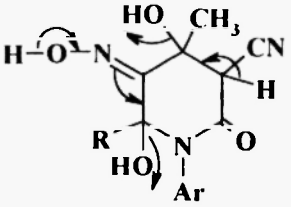


10

3a,b

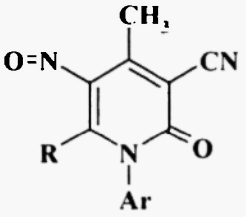
$EtO^- Na^+$ / EtOH

△



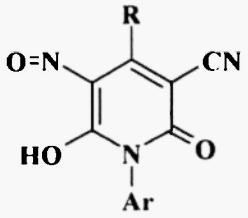
11

$-2H_2O$



12

8 + 10 $\xrightarrow[-H_2O/-EtOH]{EtO^- Na^+/EtOH/\triangle}$



13

12	R	Ar
a,	CH_3	4-CH_3-C_6H_4
b,	CH_3	4-Cl-C_6H_4
c,	C_6H_5	4-CH_3-C_6H_4

13	R	Ar
a,	CH_3	C_6H_5
b,	C_6H_5	4-CH_3-C_6H_4

Chart (2)

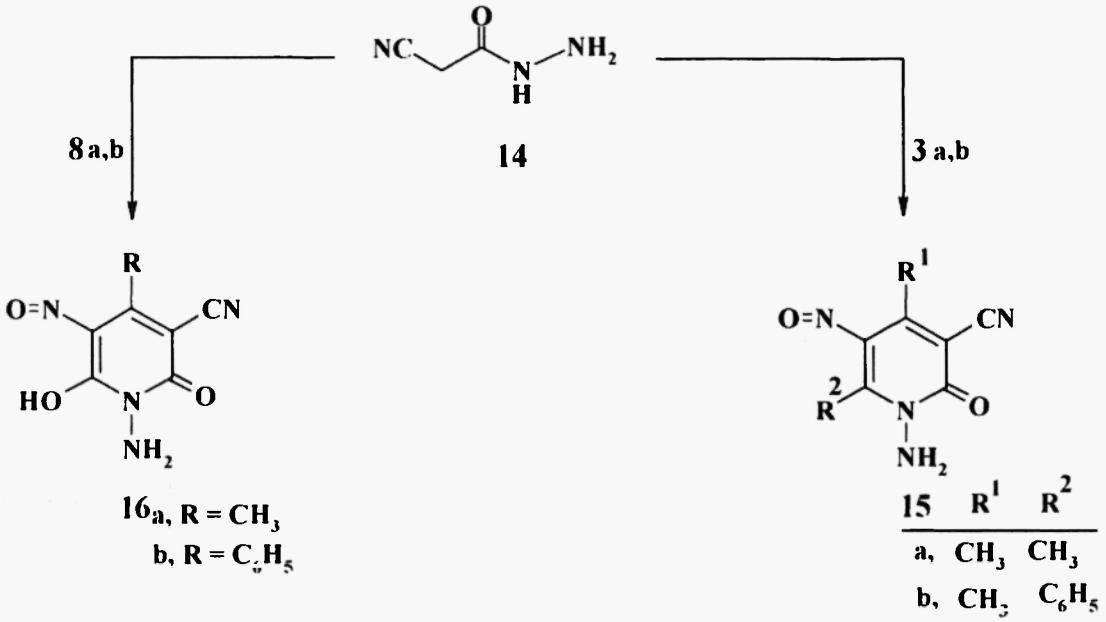


Chart (3)

6a: Yellow crystals, 60 % yield, m.p. > 300 °C. IR (cm^{-1}): 3300, 3230 (NH); 2215 (CN); 1675 (CO). ^1H NMR (δ ppm): 2.32 (s, 3H, CH_3); 2.50 (s, 3H, CH_3); 13.80 (s, 1H, SH). ^{13}C NMR (δ ppm): 17.44 (CH_3); 22.20 (CH_3); 114.18 (CN); 177.31 (C-2); 105.91 (C-3); 149.03 (C-4); 157.20 (C-5); 160.31 (C-6). Found: C, 49.5; H, 3.5; N, 21.6 %; Calcd. for $C_8H_7N_3OS$ (m/z=193): C, 49.7; H, 3.6; N, 21.8 %. **6b:** Brown crystals, 52 % yield, m.p. 295 °C. Found: C, 61.0; H, 3.4; N, 16.3 %, Calcd. for $C_{13}H_9N_3OS$: C, 61.2; H, 3.5; N, 16.5 %.

9a: Brown crystals, 65 % yield, m.p. 290 °C. IR (cm^{-1}): 3400, 3330 (NH); 2220 (CN); 1660 (CO). ^1H NMR (δ ppm): 2.40 (s, 3H, CH_3); 12.80 (s, 1H, OH), 13.67 (s, br, 1H, SH). Found: C, 42.9; H, 2.4; N, 21.4 %, Calcd. for $C_7H_5N_3O_2S$: C, 43.0; H, 2.6; N, 21.5 %. **9b:** Yellow crystals, 61 % yield, m.p. > 300 °C. Found: C, 55.9; H, 2.5, N, 16.1 %; Calcd. for $C_{12}H_7N_3O_2S$: C, 56.0; H, 2.7; N, 16.3 %.

***N*-Aryl-5-nitroso-2-pyridones 12a-c, 13a,b**

General procedure :To a mixture of compounds **3** or **8** (0.01 mol) and cyanoacetanilides **10** (0.01 mol), sodium ethoxide (0.01 mol) in dry ethanol (30 ml) was added .The reaction mixture was heated under reflux for 3h, then cooled in ice. The solid product was isolated after acidification with dil. HCl, filtered off, dried and then recrystallized from the appropriate solvent.

12a: Yellow crystals, from EtOH, 50 % yield, m.p. 290 °C. IR (cm^{-1}): 2210 (CN); 1665 (CO). ^1H NMR (δ ppm): 2.44 (s, 3H, CH_3); 2.68 (s, 3H, CH_3); 7.05-7.99 (m, 5H, C_6H_5). Found: C, 67.1; H, 4.8; N, 15.6 %; Calcd. for $C_{15}H_{13}N_3O_2$ (m/z=267): C, 67.4; H, 4.9; N, 15.7 %. **12b**:

Yellow crystals, from EtOH/DMF 60 % yield, m.p. > 300 °C. Found: C, 58.3; H, 3.3; N, 14.5 %; Calcd. for $C_{14}H_{10}ClN_3O_2$: C, 58.4; H, 3.5; N, 14.6 %. **12c**: Brown crystals, from DMF 50 % yield, m.p. 295 °C. Found: C, 72.8; H, 4.3; N, 12.6 %; Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.9; H, 4.6; N, 12.8 %.

13a: Brown crystals, from EtOH 65 % yield, m.p. > 300 °C. IR (cm^{-1}): 2220 (CN); 1685 (CO). ^1H NMR (δ ppm): 2.40 (s, 3H, CH_3); 7.00-7.88 (m, 5H, C_6H_5), 11.87 (s, br, 1H, OH). Found: C, 61.0, H, 3.3; N, 16.4 %; Calcd. for $C_{13}H_9N_3O_3$: C, 61.2, H, 3.5; N, 16.5 %. **13b**: Yellow crystals, from EtOH/DMF, 55 % yield, m.p. 285 °C. Found: C, 68.7; H, 3.8; N, 12.5 %; Calcd. for $C_{19}H_{13}N_3O_3$: C, 68.9; H, 3.9; N, 12.7 %.

***N*-Amino-5-nitroso-pyridin-2-ones 15a,b, 16a,b**

General procedure :A mixture of oximes **3a,b** or **8a,b** (0.01 mol) and cyanoacetohydrazide **14** (0.01 mol) was refluxed in presence of sodium ethoxide (0.01 mol) and ethanol (30 ml) for 5h. The reaction mixture was cooled, poured over ice/water mixture and neutralized with dil. HCl. The pricipitated product was collected by filtration and recrystallized from ethanol

15a: Brown crystals, 50 % yield, m.p. > 300 °C. IR (cm^{-1}): 3420, 3250 (NH_2, NH); 2210 (CN); 1680 (CO). ^1H NMR (δ ppm): 2.46 (s, 3H, CH_3); 2.68 (s, 3H, CH_3); 5.52 (s, br, 2H, NH_2). Found: C, 50.1; H, 4.4; N, 29.0 %; Calcd. for $C_8H_8N_4O_2$ (m/z=192): C, 50.0; H, 4.2; N, 29.2 %. **15b**: Yellow crystals, 55 % yield, m.p. 285 °C. Found: C, 61.6; H, 4.1; N, 22.1 %; Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.4, H, 3.9; N, 22.0 %.

16a: Yellow crystals, 60 % yield, m.p. > 300 °C. IR (cm^{-1}): 3470, 3350 (NH_2, NH); 2218 (CN); 1670 (CO). ^1H NMR (δ ppm): 2.38 (s, 3H, CH_3); 5.43 (s, br, 2H, NH_2), 11.46 (s, br, 1H, OH). Found: C, 43.1; H, 2.3; N, 28.7 %; Calcd. for $C_7H_6N_4O_3$: C, 43.3; H, 3.1; N, 28.9 %. **16b**: Yellow crystals, 60 % yield, m.p. > 300 °C. Found: C, 56.2; H, 3.2; N, 22.1 %; Calcd. for $C_{12}H_8N_4O_3$: C, 56.3; H, 3.1; N, 21.9 %.

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