NOVEL SYNTHESIS OF N-AMINO-2-PYRIDONES AND CYCLOALKANE RING-FUSED PYRIDINES CONTAINING BENZOTHAIAZOLE MOIETY

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Abstract : A variety of new N-amino-2-pyridone and cycloalkane ring-fused pyridine derivatives containing benzothiazole moiety could be prepared via the reaction of 2-Functionally Substituted methylbenzothiazoles with activated methylene compounds. The structures of the reaction products were established based on elemental analysis and spectral data (IR , ^1H NMR , ^{13}C NMR, MS).

Continuing our interest in development of efficient and simple procedures for the synthesis of fused heterocyclic nitrogen compounds ¹⁻⁵ , We have previously reported several new approaches for the synthesis of condensed heterocycles utilizing 2-substituted methylbenzothiazole derivatives as starting materials ⁶⁻⁹ . As an extension of this work , we report in this paper a new one step synthesis of N-amino-2-pyridones and cycloalkane ring fused pyridine derivatives containing benzothiazole moiety from the reaction of 2-(benzothiazol-2-yl)-arylidene methylcarbonitriles **3**¹⁰ with cyanoacethydrazide and cycloalkanones, respectively . Thus, it has been found that 2-aminothiophenol **1** reacted with arylmethylidenemalononitrile **2** to give the 1,3-benzothiazol-2-yl-substituted cinnamonnitriles **3** . Treatment of **3** with cyanoacethydrazide **4** in refluxing ethanol containing catalytic amounts of piperidine yielded the corresponding 4-Aryl-5-(benzothiazol-2-yl)-1,6-diamino-2-oxopyridin-3-carbonitrile **8** in good yields . The structure of compounds **8** was established on the basis of their elemental analysis and spectral data (IR , MS , ^1H NMR) . Thus , structure **8a** is supported by its mass spectrum which showed a molecular formula $\text{C}_{19} \text{H}_{13} \text{N}_5 \text{OS}$ ($m/e = 359$) . ^1H NMR was used to confirm this structure for the product .

Thus, ^1H NMR revealed two broad bands at $\delta = 5.47$ and 8.67 ppm assignable for two amino groups. The formation of **8** from the reaction of **3** and cyanoacethydrazide **4** is assumed to proceed via the initial Michael addition of the active methylene in **4** to the double bond of **3** to yield the intermediate **5**. This Michael adduct then cyclizes via addition to the cyano group to give the intermediate dihydropyridine **7**, which is oxidised under the reaction conditions to give the stable *N*-amino-2-pyridone derivatives **8**. The reaction of **3** with cyclic ketones can be utilized for the synthesis of interesting cycloalkane ring-fused pyridine derivatives. Thus, it has been found that **3** reacted with cycloalkanones **9** in refluxing ethanol containing catalytic amounts of ammonium acetate for 3 hrs to give the cycloalkane ring-fused 2-amino-4-aryl-3-(benzothiazol-2-yl)pyridines **13**. The structure of **13** could be established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (IR, MS, ^1H NMR, ^{13}C NMR). Thus, structure **13e** seemed to be logic according to the IR which revealed the absence of a CN band, its analytical data revealed a molecular formula $\text{C}_{22}\text{H}_{19}\text{N}_3\text{S}$ ($m/e = 357$). ^1H NMR spectroscopy was used to confirm this structure for the product. Thus, ^1H NMR spectroscopy revealed a broad band in the range $\delta = 7.37$ ppm assigned to an amino group. The ^{13}C NMR spectrum of **13e** contained a signal at $\delta = 157.28$ ppm corresponding to the C-2 atom of the benzothiazole, while signals appearing at $\delta = 146.63$, 149.94 and 154.26 ppm were assigned to C-4, C-6 and C-2 of pyridine, respectively. The formation of **13** from the reaction of **3** and **9** is assumed to proceed via the initial Michael addition of an active methylene group of the cycloalkanones **9** to the double bond of **3** to yield the intermediate **10**, which is cyclized and then oxidised under the reaction conditions to yield **13**.

These results indicate that the reaction of 2-(benzothiazol-2-yl)arylidene methyl carbonitrile **3** with suitable active methylene compounds can be utilized as an excellent route for the synthesis of several, otherwise difficulty accessible *N*-amino-2-pyridone and cycloalkane ring-fused pyridines containing benzothiazole moiety, in most cases via initial Michael addition. These compounds appear promising for further chemical transformations and for biological testing studies.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (KBr discs) on a pye Unicam Spectra – 1000. ^1H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(\text{CD}_3)_2\text{SO}$ using SiMe_4 as internal standard. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

4-Aryl-5-(benzothiazol-2-yl)-1,6-diamino-2-oxopyridine-3-carbonitriles(8a–d)

General Procedure :

A solution of **3** (0.01 mol) in ethanol (20 ml), cyanoacethydrazide (0.01 mol) and piperidine (3 drops) was refluxed for 3 hours, the reaction mixture was cooled to room temperature. The precipitate was filtered off and crystallized from an appropriate solvent.

8a : yield (80 %) , m.p. 240°C .IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3583, 3351, 3281 (NH_2), 2256 (CN), 1698 (CO). ^1H NMR (DMSO) δ 5.47 (s, 2H, N- NH_2), 7.11-7.86 (m, 9H, C_6H_5 , C_6H_4), 8.67 (s, br, 2H, NH_2). $\text{C}_{19}\text{H}_{13}\text{N}_5\text{OS}$ ($M^+ = 359$), Calcd : C, 63.5; H, 3.6; N, 19.4, Found : C, 63.6; H, 4.0; N, 19.2 %

8b : yield (75 %) , m.p. 290°C .IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3294, 3170 (NH_2), 2212 (CN) 1653 (CO) ^1H NMR (DMSO) δ 5.86 (s, 2H, N- NH_2), 7.3–7.9 (m, 8H, $2\text{C}_6\text{H}_4$), 9.8 (s, 2H, NH_2). $\text{C}_{19}\text{H}_{12}\text{ClN}_5\text{SO}$ Calcd : C, 57.7; H, 3.0; N, 17.7, Found : C, 57.6; H 3.3. N, 17.6 %.

8c : yield (75%) ,m.p. 270°C . IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3580, 3352, 3280 (NH_2) 2182. (CN), 1700 (CO) ^1H NMR (DMSO) δ 2.52 (s, 3H, CH_3), 5.86 (s, 2H, N- NH_2), 7.29-7.99 (m, 8H, $2\text{C}_6\text{H}_4$), 8.40 (s, 2H, NH_2), $\text{C}_{20}\text{H}_{15}\text{N}_5\text{OS}$, Calcd :C, 64.3; H, 4.0 N, 18.7, Found : C, 64.6; H, 4.1; N, 18.5 %.

8d : yield (75 %), m.p. 230 ° C. IR (KBr) $\nu_{\max}$ / cm^{-1} 3560 , 3351 , 3295 (NH₂) 2212 . (CN) , 1652(CO) . C₂₀ H₁₅ N₅ O₂ S, Calcd : C, 61.6 H , 3.8 ; N, 17.9 , Found : C , 61.7 ; H, 3.7 ; N , 17.8 %

Cycloalkane Ring Fused 2-amino-4-aryl-3-(benzothiazol-2-yl)pyridines
(13 a –h)

General Procedure :

A solution of **3** (0.01 mol) in ethanol (20 ml) , cycloalkanones **9** (0.01 mol) and ammonium acetate (0.02 mol) was refluxed for 3 hours . The reaction mixture was cooled to room temperature . The precipitated solid was collected by filtration and crystallized from the appropriate solvent .

13a : yield (70 %), m.p. 180 ° C .IR (KBr) $\nu_{\max}$ / cm^{-1} 3651 , 3352 , 3260 (NH₂) C₂₁ H₁₇ N₃ S, Calcd : C, 73.4 ; H, 4.9 ; N, 12.2 , Found : C, 73.5 H , 4.8 ; N, 12.3 % .

13b : yield (70 %) , m.p. 120 ° C .IR (KBr) $\nu_{\max}$ / cm^{-1} 3650 , 3360 , 3265 (NH₂) C₂₁ H₁₆ N₃ SCl , Calcd : C, 67.6 ; H, 4.3 ; N, 11.3 , Found : C, 67.6; H , 4.3 ; N , 11.6 % .

13c : yield (70 %) , m.p. 120 ° C .IR (KBr) $\nu_{\max}$ / cm^{-1} 3650 , 3360 , 3260 (NH₂) . ¹H NMR (DMSO) δ 1.73–1.91 (m, 4H, 2CH₂), 2.62 (s, 3H, CH₃), 2.79–3.00 (m, 2H ,CH₂) , 7.33–8.19 (m, 10H , 2C₆H₄, NH₂) . C₂₂ H₁₉ N₃ S , Calcd : C, 73.9 ; H , 5.3 ; N , 11.7 , Found : C , 74.0; H , 5.5 ; N , 11.3 % .

13d : yield (70 %) , m.p. 110 ° C .¹H NMR (DMSO) δ 1.82 – 1.96 (m, 4H, 2CH₂), 2.85 – 3.01 (m, 2H ,CH₂) , 3.36 (s, 3H, OCH₃) 7.47 – 8.20 (m, 10H , 2C₆ H₄ ,NH₂) . C₂₂ H₁₉ N₃ OS , Calcd : C, 70.8 ; H, 5.1 ; N , 11.3 Found : C, 70.9 ; H , 5.4 ; N, 11.6 % .

13e : yield (80 %) , m.p. 207 ° C. IR (KBr) $\nu_{\max}$ / cm^{-1} 3650 , 3366 , 3261 (NH₂) . ¹H NMR (DMSO) δ : 1.61 – 1.65 (m, 2H , CH₂) , 1.75 – 1.79 (m, 2H , CH₂ ,) , 2.14 – 2.18 (m, 2H , CH₂), 2.74 – 2.75 (m, 2H , CH₂) , 7.37 (s, br, 2H , NH₂ ,) , 7.48 – 8.03 (m, 9H , C₆H₅ , C₆H₄) . ¹³C NMR (DMSO) δ 21.73, 22.12, 25.27, 32.07 (4CH₂), 117.48–135.31 (aromatic carbons), 146.63 (C-4), 149.9 (C-6), 154.25 (C-2), 157.23 (benziazole C-2). C₂₂H₁₉ N₃ S (M⁺ = 357), Calcd : C, 73.9 ; H , 5.3 ; N , 11.7 , Found : C, 73.6 ; H , 5.5 ; N , 11.6 % .

13f : yield (75 %) , m.p. 230 ° C .IR (KBr) $\nu_{\max}$ / cm^{-1} 3650 , 3377 , 3261 (NH₂) .

^1H NMR (DMSO) δ :1.62 –1.77 (m, 2H ,CH₂) , 2.03 – 2.16 (m, 2H , CH₂ ,), 2.51- 2.52 (m,2H,CH₂) , 2.73 – 2.67 (m, 2H , CH₂) ,7.29–7.40 (s,br, 2H, NH₂),7.47 – 8.05 (m, 8H 2C₆H₄) . C₂₂ H₁₈ N₃ SCl (M⁺ = 391) , Calcd : C,67.5 ; H , 4.6 ; N, 10.7 , Found C, 67.6 ; H, 4.3 ; N,10.6 %.

13g : yield (75 %) , m.p. 170⁰C .IR (KBr) ν_{max} /cm⁻¹ 3645 , 3366 , 3265 (NH₂) C₂₃ H₂₁ N₃ S , Calcd : C, 74.4 ; H , 5.7 ; N, 11.3 , Found: C, 74.0 ; H, 5.9 ; N, 11.5 %.

13h : yield (75 %) , m.p. 200⁰C .IR (KBr) ν_{max} / cm⁻¹ 3645 , 3377 , 3261 (NH₂) C₂₃ H₂₁ N₃ S , Calcd : C, 71.3 ; H , 5.4 ; N, 10.8 , Found: C, 71.5 ; H , 5.5 ; N , 10.8%. ^1H NMR (DMSO) δ 1.88–1.92 (m, 4H, 2CH₂) , 2.80 – 3.00 (m, 2H ,CH₂) , 3.22 (s,3H,OCH₃) 7.37 – 8.11 (m,10H , 2C₆ H₄ ,NH₂) .

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