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

G. H. Elgemeie * , H. Z. Shams, Y. M. Elkholy and N. S . Abbas

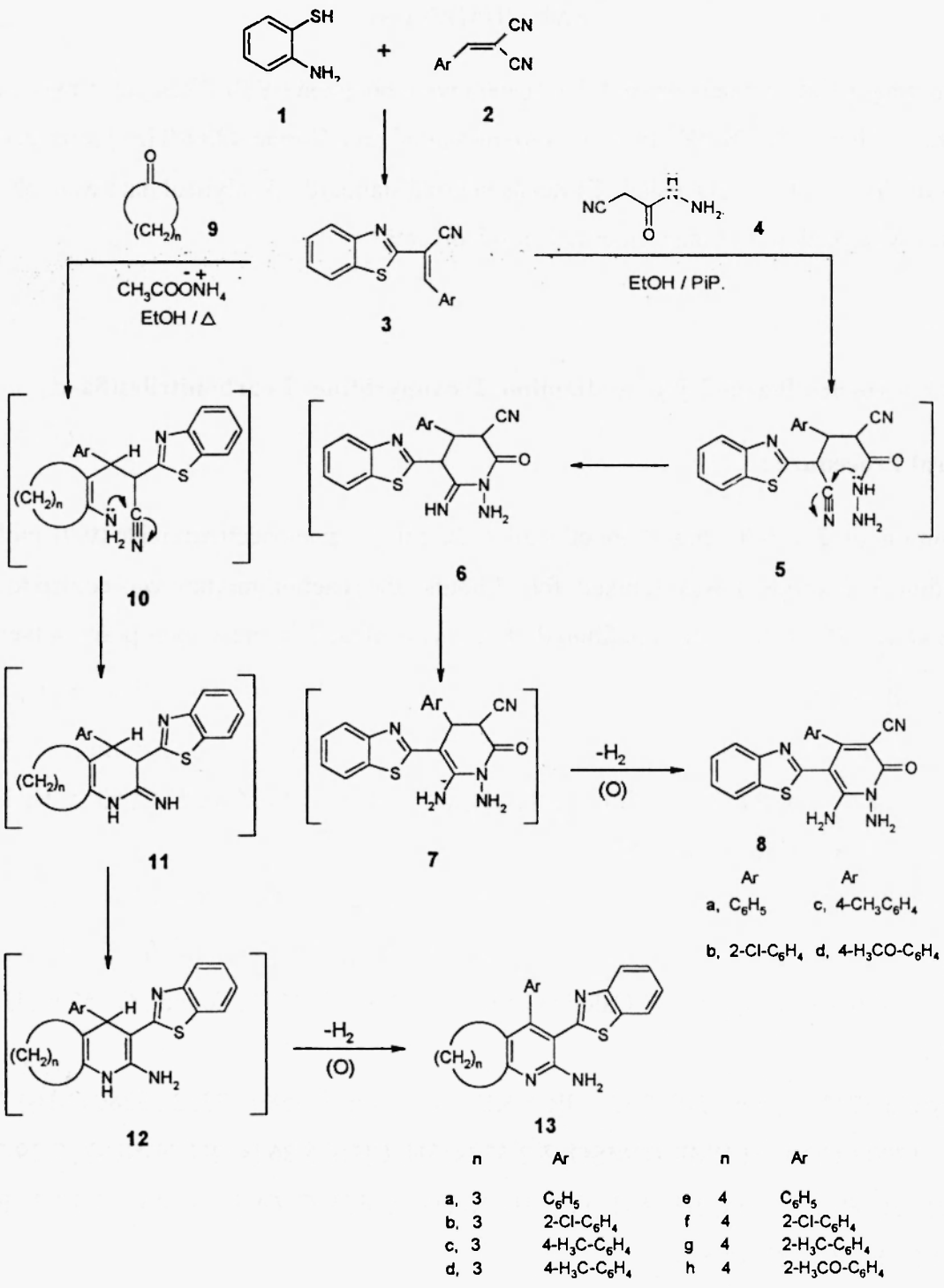
Chemistry department , Faculty of science , Helwan university , Ain – Helwan , Cairo, Egypt .

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 , ^{1}H 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)-arylidenemethylcarbonitriles **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-substitutedcinnamonitriles **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 ,^{1}H NMR) .Thus , structure **8a** is supported by its mass spectrum which showed a molecular formula C_{19} H_{13} N_5 OS (m/e = 359) . ^{1}H NMR was used to confirm this structure for the product .

Thus, ^{1}H NMR revealed two broad bands at δ = 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 cycoalkanones **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, ^{1}H 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 $C_{22}H_{19}N_3S$ (m/e = 357). ^{1}H NMR spectroscopy was used to confirm this structure for the product .Thus, ^{1}H NMR spectroscopy revealed a broad band in the range δ = 7.37 ppm assigned to an amino group.The ^{13}C NMR spectrum of **13e** contained a signal at δ= 157.28 ppm corresponding to the C-2 atom of the benzothiazole, while signals appearing at δ = 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)arylidenemethyl 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 bilogical testing studies.



n	Ar		n	Ar
a, 3	C_6H_5	e	4	C_6H_5
b, 3	2-Cl-C_6H_4	f	4	2-Cl-C_6H_4
c, 3	4-H_3C-C_6H_4	g	4	2-H_3C-C_6H_4
d, 3	4-H_3C-C_6H_4	h	4	2-H_3CO-C_6H_4

EXPERIMENTAL

All melting points are uncorrected . IR spectra were obtained (KBr discs) on a pye Unicam Spectra – 1000 . ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in (CD_3)$_2$ SO using $SiMe_4$ as internal standard . Analytical data were obtained from the Microanlytical 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 refuxed for 3 hours , the reaction mixture was cooled to room temperature . The precipitate was filtered off and crystallized from an appropraite solvent .

8a : yield (80 %) , m.p. 240^{0}C .IR (KBr) ν_{max}/cm^{-1} 3583, 3351, 3281 (NH_2) , 2256 (CN) , 1698 (CO) . ^{1}H 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) . $C_{19}H_{13}N_5OS$ (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 ^{0}C .IR (KBr) ν_{max} /cm^{-1} 3294 , 3170 (NH_2), 2212 (CN) 1653 (CO) ^{1}HNMR (DMSO) δ 5.86 (s, 2H, N-NH_2), 7.3 –7.9 (m , 8H ,2C_6H_4) , 9.8 (s, 2H , NH_2) .$C_{19}H_{12}ClN_5SO$ 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 ^{0} C . IR (KBr) ν_{max}/cm^{-1} 3580 , 3352 , 3280 (NH_2) 2182 . (CN) , 1700 (CO) ^{1}H NMR (DMSO) δ 2.52 (s, 3H, CH_3), 5.86 (s, 2H, N-NH_2) , 7.29-7.99 (m, 8H , 2C_6H_4), 8.40 (s, 2H , NH_2,) $C_{20}H_{15}N_5OS$, 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 ^{0} C.IR (KBr) ν_{max} / cm $^{-1}$ 3560 , 3351 , 3295 (NH_2) 2212 . (CN) ,1652(CO). $C_{20}H_{15}N_5O_2S$, 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 appropite solvent .

13a : yield (70 %), m.p. 180^{0} C .IR (KBr) ν_{max} / cm $^{-i}$ 3651 , 3352 , 3260 (NH_2) $C_{21}H_{17}N_3S$, 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^{0}C .IR (KBr) ν_{max} / cm $^{-i}$ 3650 , 3360 , 3265 (NH_2) $C_{21}H_{16}N_3SCI$, 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^{0}C .IR (KBr) ν_{max} / cm $^{-i}$ 3650 , 3360 , 3260 (NH_2). ^{1}H NMR (DMSO) δ 1.73–1.91 (m, 4H, $2CH_2$), 2.62 (s, 3H, CH_3), 2.79–3.00 (m, 2H ,CH_2) , 7.33–8.19 (m,10H ,$2C_6H_4$, NH_2) .$C_{22}H_{19}N_3S$, 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^{0}C .^{1}H NMR (DMSO) δ 1.82 – 1.96 (m,4H, $2CH_2$) , 2.85 – 3.01 (m, 2H ,CH_2) , 3.36 (s,3H,OCH_3) 7.47 – 8.20 (m,10H , $2C_6H_4$,NH_2) .

$C_{22}H_{19}N_3OS$, 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 ^{0} C.IR (KBr) ν_{max} / cm $^{-1}$ 3650 , 3366 , 3261 (NH_2). ^{1}H NMR (DMSO) δ : 1.61 – 1.65 (m, 2H , CH_2) , 1.75 – 1.79 (m, 2H , CH_2) , 2.14 – 2.18 (m, 2H , CH_2),2.74 – 2.75 (m, 2H , CH_2) ,7.37 (s,br, 2H , NH_2) , 7.48 – 8.03 (m, 9H , C_6H_5 , C_6H_4). ^{13}C NMR (DMSO) δ 21.73, 22.12, 25.27, 32.07 ($4CH_2$), 117.48-135.31 (aromatic carbons), 146.63 (C-4), 149.9 (C-6), 154.25 (C-2), 157.23 (benziazole C-2). $C_{22}H_{19}N_3S$ (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 ^{0}C .IR (KBr) ν_{max} / cm $^{-i}$ 3650 , 3377 , 3261 (NH_2) .

^{1}H NMR (DMSO) δ :1.62 –1.77 (m, 2H ,CH_2) , 2.03 – 2.16 (m, 2H , CH_2,), 2.51- 2.52 (m,2H,CH_2) , 2.73 – 2.67 (m, 2H , CH_2) ,7.29–7.40 (s,br, 2H, NH_2,),7.47 – 8.05 (m, 8H $2C_6H_4$) . $C_{22}H_{18}N_3SCl$ (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. 170^{0}C .IR (KBr) ν_{max} /cm^{-1} 3645 , 3366 , 3265 (NH_2) $C_{23}H_{21}N_3S$, 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. 200^{0}C .IR (KBr) ν_{max} / cm^{-1} 3645 , 3377 , 3261 (NH_2) $C_{23}H_{21}N_3S$, Calcd : C, 71.3 ; H , 5.4 ; N, 10.8 , Found: C, 71.5 ; H , 5.5 ; N , 10.8%. ^{1}H NMR (DMSO) δ 1.88–1.92 (m, 4H, $2CH_2$) , 2.80 – 3.00 (m, 2H ,CH_2) , 3.22 (s,3H,OCH_3) 7.37 – 8.11 (m,10H , $2C_6H_4$,NH_2) .

References

1) Elgemeie , G. E. H. ; Hussain , B. A., Tetrahedron , 1994 , **50** , 199 .
2) Elgemeie , G. E. H.; Fathy , N. M.. ,Tetrahedron , 1995 , **51** , 3345 .
3) Elgemeie, G. E. H.; Regaila , H. A.,Shehata ,N., J. Chem. Soc. Perkin Trans. 1, 1990 1267.
4) Elgemeie , G. E. H.; Elzanate , A. H.; Mansour , A. K., J. Chem . Soc. Perkin Trans. 1 , 1992 , 1073 .
5) Elgemeie G. E. H. , Elghandour A. H. , Elzanate A. M. and Ahmed S. A , J . Chem . Soc. Perkin Trans 1 , 1997 , 3285 .
6) Elgemeie , G. E. H.; Ali H. A.; Elzanate , A. H. ,J. Chem Res. (S) , 1996 , 340.
7) Azzem , M.A. .; Elgemeie , G. E. H.; Neguid , N. A., Fahmy , H. M.;Elmassry , Z.M., J.Chem Soc. Perkin Trans 2 , 1990 , 545 .
8) Elgemeie , G E. H.; Abdel Aal , F. M., Heterocycles , 1986 , **24** , 349 .
9) Elgemeie , G. E. H.; Fathy N. M., Sulfur Lett ., 1988 , 7 , 189 .
10) Saito , K.; Kampe , S. and Nanano . Y , Synthesis , 1983 , 210 .

Received on June 28, 2000