An Efficient Synthesis of Some Novel 3-Cyano-4-imino-2-(methylthio) 4*H*-pyrido[1,2-*a*]pyrimidine and Their Derivatives

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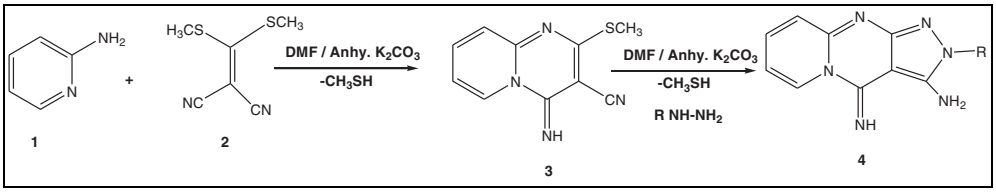

Pyrazolo pyrimido pyrimidine (**4a–k**) was prepared by the reaction of compound 3-cyano-4-imino-2-(methylthio)4*H*-pyrido[1,2-*a*]pyrimidine (**3**) with hydrazine hydrate, phenyl hydrazine, 2-hydrazino benzothiazole, and 6-substituted hydrazine benzothiazole in *N*,*N*-dimethylformamide and anhydrous potassium carbonate. These synthesized compounds were characterized by elemental analysis IR, ^{1}H NMR, and mass spectral data.

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INTRODUCTION

A novel method was successfully demonstrated toward the synthesis of pyrido[1,2-*a*]pyrimidines. The fused pyrimidines exhibit promising antiviral [1], antibacterial [2], anti-AIDS [3], and antinociceptive [4] activities. Fused pyrimidines are extensively used in neurology, particularly in the treatment of neurodegenerative disorders such as Parkinson's disease [5], anti-anxiety disorders [6], and depression [7]. Fused pyrimidines are selective inhibitors for multidrug resistance [8]. Folate metabolism has long been recognized as an attractive target for cancer chemotherapy because of indispensable role of fused pyrimidine antifolates as antitumor agents [9]. Risperidone is a derivative of pyrido[1,2-*a*]pyrimidines [10,11]. These compounds showed antipsychotic activity [12] and were used as α_2 antagonists [13–15]. They exhibit a high affinity for α2-adrenoceptor with high selectivity versus the α-receptor and possess potent *in vivo* central activity [16,17]. Wamho and Korte [18,19] have reported the synthesis of pyrido[1,2-*a*]pyrimidines by using 2-amino heterocyclic compounds and α-acetyl-γ-butyrolactone by refluxing dioxane or using PPA and have observed the formation of mixture of products. After a successful literature survey, it stimulated us to synthesize 3-amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo[3,4-*b*] pyrido[1,2-*a*]pyrimidine (**4**) by using 3-cyano-4-imino-2-(methylthio)4*H*-pyrido[1,2-*a*]pyrimidine (**3**) and 2-hydrazino benzothiazole by refluxing *N*,*N*-dimethylformamide and anhydrous potassium carbonate with new method and improved yield.

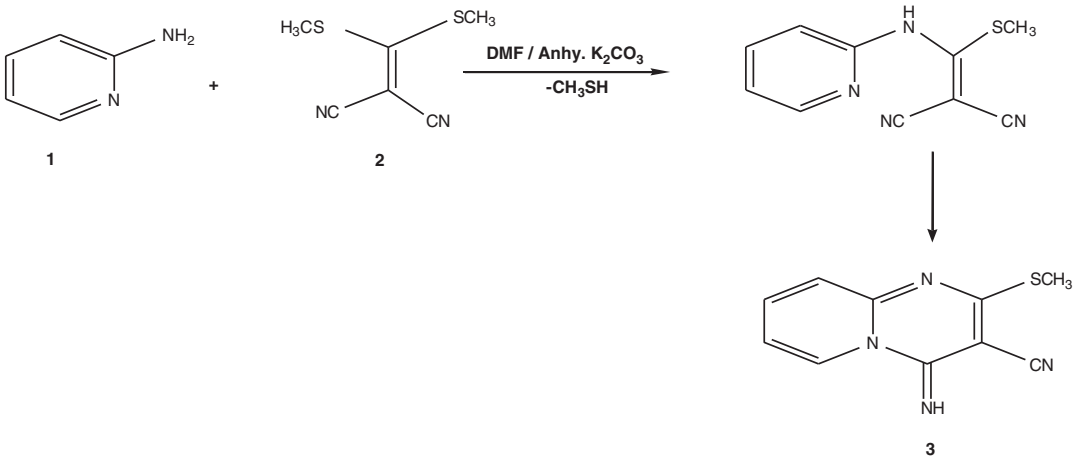
RESULTS AND DISCUSSION

In the present communication, we have developed a new methodology toward the synthesis of 3-amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo[3,4-*b*] pyrido[1,2-*a*] pyrimidine (**4**), as shown in Scheme 1. Our method gives a single product with high yield. The reaction started with 2-aminopyridines (**1**) and bis(methylthio)methylene malononitrile (**2**) refluxed in *N*,*N*-dimethylformamide in the presence of catalytic amount of anhydrous potassium carbonate to afford (**3**).

Compound (**3**) possesses replaceable active methylthio group at the 2-position, which is activated by the ring 1-nitrogen atom, electron withdrawing 3-cyano group. Compound (**3**) reacted with hydrazine hydrate in the presence of *N*,*N*-dimethylformamide, and the catalytic amount of anhydrous potassium carbonate afforded compound (**4a**) in 78% yield. The subsequent compound (**3**) was independently heated with phenyl hydrazine, 4-nitro phenyl hydrazine, 2,4-dinitro phenyl hydrazine, 2-hydrazino benzothiazole, 6-methyl 2-hydrazino benzothiazole, 6-methoxy 2-hydrazino benzothiazole, 6-chloro 2-hydrazino benzothiazole, 6-nitro 2-hydrazino benzothiazole, 2,4-dimethyl 2-hydrazino benzothiazole, and 6,7-chloro,fluoro 2-hydrazino benzothiazole to obtain 3-amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo[3,4-*b*] pyrido[1,2-*a*] pyrimidine derivatives (**4a–k**), respectively, as shown in Scheme 2.

The structure of these newly synthesized compounds was established on the basis of elemental analysis, IR, PMR, and mass spectral data; spectral studies of all

Scheme 1. Formation of fused pyrido[1,2-*a*]pyrimidine.



compounds show that compounds are stable and do not exhibit any tautomerism.

In conclusion, we have developed a new methodology toward the synthesis of 3-amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo[3,4-*b*]pyrido[1,2-*a*]pyrimidine by using a reaction of 2-aminopyridines and bis(methylthio) methylene malononitrile in DMF as a solvent in the presence of a catalytic amount of anhydrous potassium carbonate.

EXPERIMENTAL

Melting points were determined by open capillary tubes and were uncorrected. All the reactions were monitored by thin-layer chromatography, carried out on 0.2-mm silica gel-C plates using iodine vapors for detection. Infrared spectra were recorded in Nujol or as potassium bromide pellets on an infrared spectrophotometer; nuclear magnetic resonance spectra were obtained on Brukner avance spectrophotometer; 400 MHz mass spectra were recorded on FT-VC-7070H mass spectrometer with the use of the EI technique at 70 eV. All the reactions were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

General procedure.

3-Cyano-4-imino-2-(methylthio)4H-pyrido[1,2-a]pyriidine (3). A mixture of 2-aminopyridine (**2**) (0.01 mol) and (methylthio) methylene malononitrile (1) (0.01 mol) in 15 mL of *N*,*N*′-dimethylformamide and anhydrous potassium carbonate (10 mg) was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated solid product was filtered, washed with water, and recrystallized from a *N*,*N*′-dimethylformamide–ethanol mixture to give pure (**3**).

3-Amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo [3,4-b]pyrido[1,2-a]pyrimidine (4a–k). A mixture of **3** (0.001 mol) and independently with hydrazine hydrate (80%), phenyl hydrazine, 4-nitro phenyl hydrazine, 2,4-dinitro phenyl hydrazine, 2-hydrazino benzothiazole, 6-methyl 2-hydrazino benzothiazole, 6-methoxy 2-hydrazino benzothiazole, 6-chloro 2-hydrazino benzothiazole, 6-nitro 2-hydrazino benzothiazole, 2,4-dimethyl 2-hydrazino benzothiazole, and 6,7-chloro,fluoro 2-hydrazino benzothiazole (0.001 mol) in 15 mL of *N*,*N*′-dimethylformamide and anhydrous potassium carbonate (10 mg) was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated solid product was filtered, washed with water, and recrystallized from a *N*,*N*′-dimethylformamide–ethanol mixture to give pure (**4a–k**).

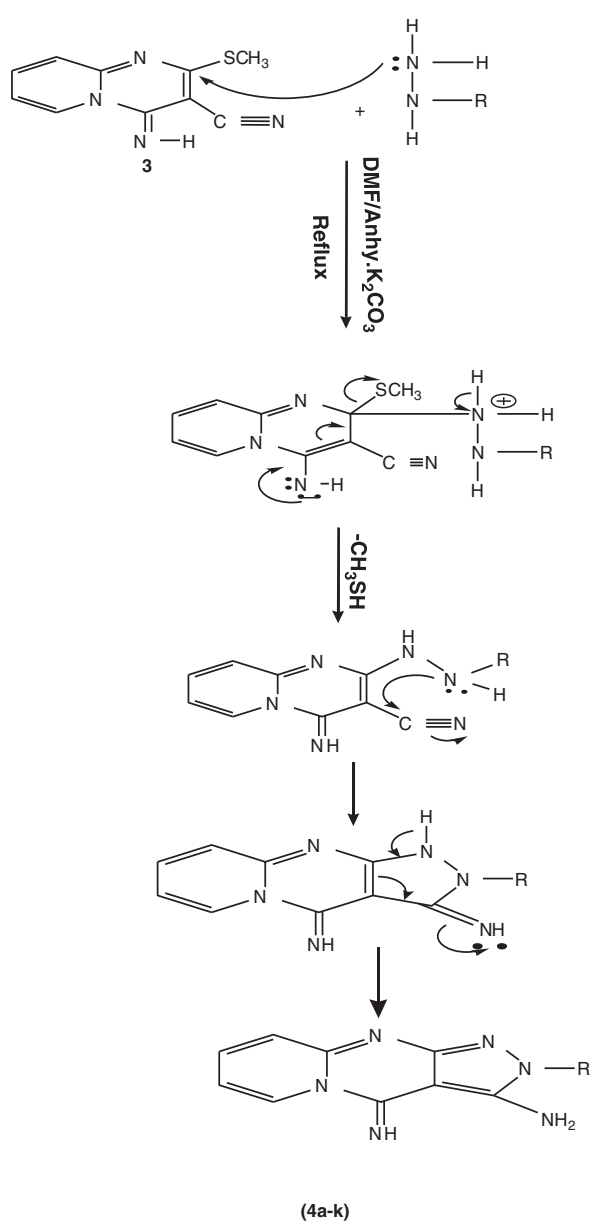
3-Cyano-4-imino-2-(methylthio)4H-pyrido[1,2-a]pyrimidine (3). Orange powder, yield 60%, mp 230 °C (dec.). IR (KBr/cm^{-1}) 3350 (=NH), 2225 (CN). ^{1}H NMR (400 MHz, DMSO-d_6): 2.59 (s, 3H, SCH_3), 6.4–6.5 (d, 2H, J = 8 Hz), 6.1–6.3 (d, 2H, J = 7.5–8 Hz), 9.2 (br s, 1H, =NH). EI-MS (*m*/*z*: RA %): 217 (M + I), 100%, 215 (35). ^{13}C NMR (300 MHz, DMSO-d_6): δ 16, 40, 79, 109, 115, 122, 134, 138, 151, 165. *Anal*. Calcd for $C_{10}H_8N_4S$; C, 60.35; H, 3.55; N, 24.85. Found: C, 60.30; H, 3.50; N, 24.80.

3-Amino-4-imino-2-(2H)pyrazolo[3,4-b]pyrido[1,2-a]pyrimidine (4a). Brown powder, yield 75%, mp 187 °C (dec.). IR (KBr/cm^{-1}) 3380 (=NH), 3321 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.0 (s, 2H, x-NH_2), 5.1–5.3 (d, 2H J = 7.3–8 Hz), 6.1–6.5 (d, 2H, J = 7.8–8 Hz), 9.2 (br s, 1H, =NH), 13.6 (s, 1H, NH). *Anal*. Calcd for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98. Found: C, 53.32; H, 3.61; N, 41.30.

3-Amino-4-imino-2-(phenyl)pyrazolo[3,4-b]pyrido[1,2-a] pyrimidine (4b). Brown powder, yield 62%, mp 140 °C (dec.). IR (KBr/cm^{-1}) 3370 (=NH), 3327 cm^{-1} (NH_2 asym.), 3217 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.9 (s, 2H, –NH_2), 5.1–6.5 (d, 4H, J = 7–8 Hz), 7.4–7.6 (m, 5H), 9.8 (s, 1H, =NH). *Anal*. Calcd for $C_{15}H_{12}N_6$: C, 65.21; H, 4.38; N, 30.42. Found: C, 64.78; H, 3.03; N, 30.02.

3-Amino-4-imino-2-(4′-nitro phenyl)pyrazolo[3,4-b]pyrido [1,2-a]pyrimidine (4c). Brown powder, yield 79%, mp 156 °C (dec.). IR (KBr/cm^{-1}) 3380 (=NH), 3335 cm^{-1} (NH_2 asym.), 3220 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.4 (s, 2H, –NH_2), 5.9–6.4 (d, 4H, J = 6.7 Hz), 7.3 (d, 2H, J = 8 Hz), 7.4 (d, 2H, J = 7.5 Hz), 9.1 (br s, 1H, =NH). *Anal*. Calcd for

Scheme 2. 3-Amino-4-imino-2-(6′-substituted benzothiazolyl)pyrazolo[3,4-*b*]pyrido[1,2-*a*]pyrimidine derivatives (**4a–k**).



Comp.No	R
4a	H
4b	
4c	O_2N
4d	O_2N, NO_2
4e	
4f	H_3C
4g	H_3CO
4h	Cl
4i	O_2N
4j	H_3C, CH_3
4k	F, Cl

$C_{15}H_{11}N_7O_2$: C, 56.07; H, 3.45; N, 30.52. Found: C, 53.32; H, 3.61; N, 30.01.

3-Amino-4-imino-2-(2′,4′-dinitro phenyl)pyrazolo[3,4-b]pyrido [1,2-a]pyrimidine (4d). Brown powder, yield 68%, mp 168 °C (dec.). IR (KBr/cm^{-1}) 3380 (=NH), 3343 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.3 (s, 2H, –NH_2), 5.6–6.5 (d, 4H, J = 6.5–7.5 Hz,), 7.3 (s, 1H), 7.2 (d, 2H, J = 8 Hz), 8.4 (br s, 1H, =NH). *Anal*. Calcd for $C_{15}H_{10}N_8O_4$: C, 49.19; H, 2.75; N, 30.59. Found: C, 48.60; H, 2.21; N, 30.02.

3-Amino-4-imino-2-(2′-benzothiazolyl)pyrazolo[3,4-b]pyrido [1,2-a]pyrimidine (4e). Brown powder, yield 74%, mp 192 °C (dec.). IR (KBr/cm^{-1}) 3367 (=NH), 3336 cm^{-1} (NH_2 asym.), 3226 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.2 (s, 2H, –NH_2), 5.4–6.7 (d, 4H, J = 6.5 Hz), 7.4–8.3 (d, 4H, J = 8.5 Hz), 8.6 (br s, 1H, =NH). *Anal*. Calcd for $C_{16}H_{11}N_7S$: C, 57.64; H, 3.33; N, 29.41. Found: C, 57.06; H, 2.67; N, 28.90.

3-Amino-4-imino-2-(6′-methyl-2′-benzothiazolyl)pyrazolo [3,4-b] pyrido[1,2-apyrimidine (4f). Brown powder, yield 68%, mp 150 °C (dec.). IR (KBr/cm^{-1}) 3380 (=NH), 3321 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.4 (s, 2H, –NH_2), 5.4–6.7 (d, 4H), J = 7–8 Hz, 7.1 (s, 1H), 7.2–8.3 (d, 2H, J = 7.2–7.5 Hz), 2.4 (s, 3H, Ar–CH_3), 9.1 (br s, 1H, =NH). *Anal*. Calcd for $C_{17}H_{13}N_7S$: C, 58.77; H, 3.77; N, 28.22. Found: C, 58.23; H, 3.20; N, 27.60.

3-Amino-4-imino-2-(6′-methoxy-2′-benzothiazolyl)pyrazolo [3,4-b]pyrido[1,2-a]pyrimidine (4g). Brown powder, yield 72%,

mp 183 °C (dec.). IR (KBr/cm^{-1}) 3435 (=NH), 3321 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.), 2208 (CN). ^{1}H NMR (400 MHz, DMSO-d_6): 3.9 (s, 3H, Ar–OCH_3), 4.4 (s, 2H, NH_2), 5.1–5.4 (d, 2H, J = 6.5–7 Hz), 6.2–6.7 (d, 2H, J = 7.3–8 Hz), 7.0–7.7 (d, 2H), 8.3 (s, 1H), 9.7 (br s, 1H, =NH). EI-MS (*m/z*: RA %): 364 (M + I), 261, 236 (100), 231, 216, 178, 165, 122. *Anal*. Calcd for $C_{17}H_{13}N_7OS$: C, 56.19; H, 3.61; N, 26.98. Found: C, 55.74; H, 3.02; N, 26.32.

3-Amino-4-imino-2-(6′-chloro-2′-benzothiazolyl)pyrazolo [3,4-b]pyrido[1,2-a]pyrimidine (4h). Brown powder, yield 67%, mp 260 °C (dec.). IR (KBr/cm^{-1}) 3368 (=NH), 3334 cm^{-1} (NH_2 asym.), 3216 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.2 (s, 2H, NH_2), 5.2–5.6 (d, 2H, J = 6.5–7.3 Hz), 6.1–6.7 (d, 2H, J = 6.5–7 Hz), 7.6 (s, 1H), 8.0–8.3 (d, 2H, J = 7.5–8 Hz), 9.2 (br s, 1H, =NH). EI-MS (*m/z*: RA %): 368 (M + I), 353, 336. *Anal*. Calcd for $C_{16}H_{10}ClN_7S$: C, 52.25; H, 2.74; N, 26.66. Found: C, 51.72; H, 2.15; N, 26.10.

3-Amino-4-imino-2-(6′-nitro-2′-benzothiazolyl)pyrazolo[3,4-b] pyrido[1,2-a]pyrimidine (4i). Brown powder, yield 67%, mp above 300 °C (dec.). IR (KBr/cm^{-1}) 3342 (=NH), 3230 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.7 (s, 2H, NH_2), 5.2–5.5 (d, 2H, J = 6.3–7 Hz), 6.0–6.6 (d, 2H, J = 6.5–7 Hz), 8.0–8.3 (d, 2H, J = 7–8 Hz), 9.2 (s, 1H), 8.8 (br s, 1H, =NH). *Anal*. Calcd for $C_{16}H_{10}N_8O_2S$: C, 50.79; H, 2.66; N, 29.61. Found: C, 53.32; H, 3.61; N, 41.30.

3-Amino-4-imino-2-(4′,6′-dimethyl-2′-benzothiazolyl)pyrazolo [3,4-b]pyrido[1,2-a]pyrimidine (4j). Brown powder, yield 74%, mp 130 °C (dec.). IR (KBr/cm^{-1}) 3386 (=NH), 3342 cm^{-1} (NH_2 asym.), 3224 cm^{-1} (NH_2 sym.). *Anal*. Calcd for $C_{18}H_{14}N_6S$: C, 62.41; H, 4.07; N, 24.26. Found: C, 61.84; H, 3.69; N, 23.85.

3-Amino-4-imino-2-(6′,7′-chloro,floro-2′benzothiazolyl)pyrazolo [3,4-b]pyrido[1,2-a]pyrimidine (4k). Brown powder, yield 48%, mp 195 °C (dec.). IR (KBr/cm^{-1}) 3380 (=NH), 3321 cm^{-1} (NH_2 asym.), 3213 cm^{-1} (NH_2 sym.). ^{1}H NMR (400 MHz, DMSO-d_6): 4.2 (s, 2H, NH_2), 5.0–5.6 (d, 2H, J = 6.3–7 Hz), 6.3–6.9 (d, 2H, J = 7–8 Hz), 7.3–7.9 (d, 2H, J = 7.5–8 Hz), 9.1 (br s, 1H, =NH) *Anal*. Calcd EI-MS (*m/z*: RA %): 385 (M), 217, 216 (100). For $C_{16}H_9ClFN_6S$: C, 51.83; H, 2.35; N, 22.67. Found: C, 51.32; H, 1.61; N, 22. 03.

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