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FACILE SYNTHESIS OF SEVERAL NEW PYRIDINE AND FUSED PYRIDINE DERIVATIVES WITH ANTICIPATED BIOLOGICAL ACTIVITY

By

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دراسات على مركبات السيانوميثيل أزول

جـلال نـوار

تحضير سهل لمركبات الثيازول المحتوية على حلقة البيريدين ذات احتمال التأثير البيولوجي .

تم تحضير المركبات المستهدفة والمذكورة في العنوان من خلال تفاعل مادة البنزوثيازول - ٢ - ن - أستيل اسيتوهيدرازيد مع مركبات الالدهيدات والكيتونات غير المشبعة ومع مركبات الداي كيتواستر .

كذلك تم الوصول إلى المركبات المستهدفة عن طريق تفاعلات مواد البنزوثيازوليل أريليدين مع عديد من المركبات المحتوية على مجموعة الميثيلين النشطة .

Keywords: Benzothiazole, Pyridine, Michael addition, Ammonium acetate

ABSTRACT

The reactions of benzothiazol-2-N-acetylacetohydrazide **1** with α, β-unsaturated aldehyde, ketone, ester or diketoester led to the formation of the titled ring systems. The same target was also achieved through the reactions of the benzothiazolylarylidenes **8** with several active methylene containing compounds.

INTRODUCTION

The benzothiazole and pyridine moieties have been of continous chemical interest[1,2]. They were incorporated separately in several agrochemicals[3]. Following our laboratory program, we have recently reported the synthesis of several benzoazoles with anticipated pesticidal activity[4,5]. We describe in the present work the preparation of several new pyridine and condensed pyridine derivatives, as they seem of promising structures in the area of our interest.

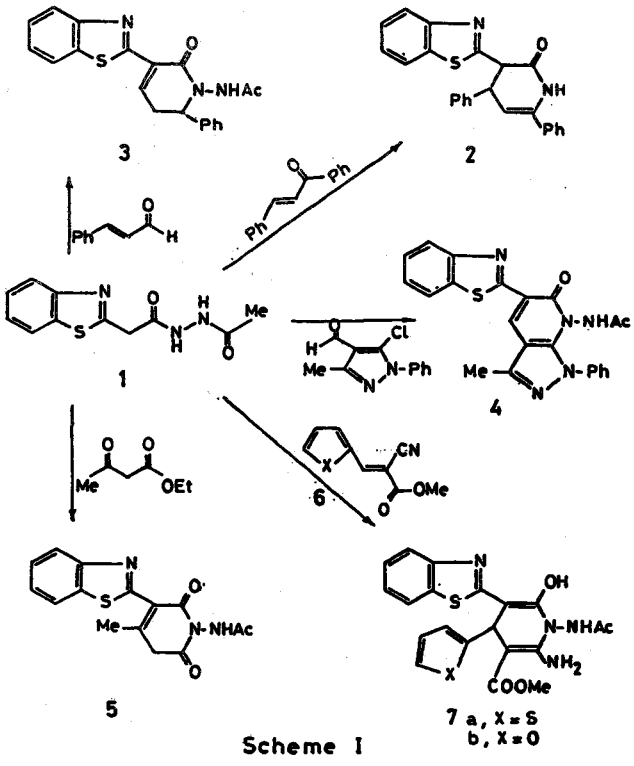
EXPERIMENTAL

All melting points were uncorrected. The IR spectra were recorded in KBr with a Pye-Unicam Sp-1000 spectrometer. The ^{1}H NMR spectra were run on a Jeol GLM EX (270 MHz) or Gemini-200 spectrometers using TMS as an internal reference. The mass spectra were recorded at 70 ev with a Schimadzu Ge/MS QP 1000 EX spectrometer. Elemental analysis were performed by the Central Service Unit at Cairo University.

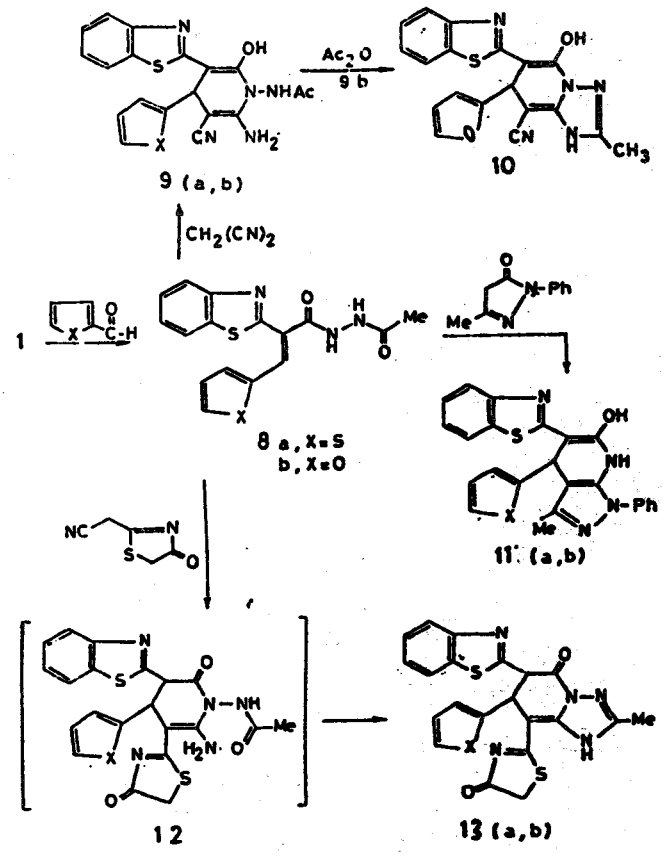
General Procedure

3-(2-Benzothiazolyl)-4,6-diphenyl-3,4-H-pyridin-2-one (2) and 1-phenyl-3-methyl-4-(2-heteroaryl)-5-(2-benzothiazolyl)-6-hydroxypyrazolo[4,5-b]pyridines (11a,b)

A mixture of compound **1** (0.01 mole, 2.49 g) and 1,3-diphenylpropene-1-one (0.01 mole, 2.08 g) or each of compounds **8a,b** (0.01 mole) and 1-phenyl-3-methylpyrazol-5-one (0.01 mole, 1.74 g) was refluxed in ethanol (30 ml) in presence of ammonium acetate (0.08 moles, 6.17 g). The reflux duration was 12 hours for the reaction of **1** and 2 hours for the reactions of **8a,b.** The reaction mixture was then partially concentrated and left over night at room temperature, the precipitate formed was collected and crystallized.



Scheme I



Scheme II

1-Acetamido-3-(2-benzothiazolyl)-6-phenyl-5,6-H-pyridin-2-one(3) and 1-phenyl-3-methyl-5-(2-benzothiazolyl)-7-acetamidopyrazolo[4,5-b]pyridin-6-one(4):

A mixture of compound **1** (0.01 mole, 2.49 g) and cinnamaldehyde (0.01 mole, 1.32 g) or 1-phenyl-3-methyl-5-chloropyrazol-4-aldehyde (0.01 mole, 2.2 g) was refluxed in pyridine (15 ml) for 12 hours. The reaction mixture was then partially concentrated, left overnight at room temperature to precipitate. The solid formed was collected, washed with water then heated in methanol, filtered and finally crystallized.

1-Acetamido-3(2-benzothiazolyl)-4-methylpyridin-2,6-dione(5):

A mixture of **1** (0.01 mole, 2.49 g) and ethyl acetoacetate (0.01 mole, 1.3 g) was refluxed in ethanolic sodium hydroxide (25 ml) for 30 minutes. A solid separated out on hot, filtered off and crystallized.

Methyl 1-acetamido-2-hydroxy-3-(2-benzothiazolyl)-4-(heteroaryl)-6-amino-4H-pyridin-5-carboxylates (7a, b):

Compound **1** (0.01 mole, 2.49 g) was refluxed with each of the arylidines **6** (0.01 mole) in ethanol (30 ml) in presence of piperidine (3 drops) for 6 hours. The solution was then partially concentrated and left to precipitate. The product formed was collected by filtration and crystallized.

1-(2-Benzothiazolyl)-1-(arylidene)-4-acetylacetohydrazides (8a, b):

Compound **1** (0.01 mole, 2.49 g) was refluxed with thiophen-2-aldehyde or 2-furaldehyde (0.01 mole) in ethanol (30 ml) in presence of piperidine (1 drop) for 6 hours. The solid product formed was collected by filtration.

1-Acetamido-2-hydroxy-3-(2-benzothiazolyl)-4-(2-heteroaryl)-5-cyano-4H-6-aminopyridines (9a, b) and 2-methyl-4-carboxy-5-(2-benzothiazolyl)-6-(2-heteroaryl)-7-(thiazol-4-one)-1,5,6-H-triazolo [2,3-a] pyridine (13a, b):

Each of compounds **8a,b** (0.01 mole) was refluxed with malononitrile (0.01 mole, 0.66 g) or 2-cyanomethylthiazol-4-one (0.01 mole, 1.4 g) in ethanol (25 ml) in presence of triethylamine (4 drops) for 2 hours. The solution was cooled and the precipitate formed was filtered and crystallized from the appropriate solvent.

2-Methyl-4-hydroxy-5-(2-benzothiazolyl)-6-(2-furyl)-7-cyano-triazolo [2,3-a] pyridine (10):

Compound **9b** (0.01 mole 3.93 g) was refluxed in acetic anhydride (20 ml) for 4 hours. The reaction mixture was then poured onto crushed ice, the solid obtained was filtered off and crystallized.

RESULTS AND DISCUSSION

Our previously reported benzothiazole-2-N-acetylacetohydrazide **1**[6] reacted with 1,3-diphenylpropen-2-one in ethanol-ammonium acetate. A new product was obtained showing an ABX ^{1}H-NMR pattern at δ 4.5 (dd), 4.69 (d) and 5.6 (d) ppm. It showed the absence of the methylene and acetyl protons found in the parent compound at δ 4.1 and δ 2.0 ppm respectively. Also the mass spectrum showed a molecular formula $C_{24}H_{18}N_2OS$ (m/z = 382). These data propose the 3-

benzothiazolyl-4, 6-diphenyl-3, 4-H-pyridin-2-one structure **2** for the isolated compound. The formation of **2** is assumed to proceed via initial Micheal addition and amination with the liberated ammonia, followed by cyclization via loss of the acetylhydrazine moiety.

Compound **1** reacted also with cinnamaldehyde in pyridine affording a product showing an ABX ^{1}H NMR at δ 4.7, 5.4 and 6.4 ppm in addition to the acetyl and benzothiazole protons found in the parent compound. Besides, the mass spectrum showed a molecular formula $C_{20}H_{17}N_3O_2S$ (m/z = 363). Accordingly, the N-acetamido-3-benzothiazolyl-6-phenyl-5,6-H-Pyridin-2-one **3** was given to this product. It is assumed that compound **3** was formed via condensation with a subsequent intra-Michael addition with the hydrazino nucleophile.

A similar approach was achieved when **1** was treated with 1-phenyl-3-methyl-5-chloropyrazol-4-aldehyde in pyridine. The reaction afforded the 1-phenyl-3-methyl-5-benzothiazolylpyrazolo[4,5-b]-pyridin-6-one **4** in a moderate yield. Its formation is also assumed to occur via initial condensation followed by nucleophilic displacement with the hydrazino nitrogen. Structure **4** was assigned based on microanalytical and spectral data, where it showed the absence of chlorine and evidence of the pyrazolo- pyridine H-4 at δ 8.2 ppm and two singlets at δ 2.45 and δ 2.0 ppm attributed to the methyl groups of the pyrazole and the acetyl group, respectively. Also the mass spectrum showed a molecular formula compatible with $C_{22}H_{17}N_5O_2S$ (m/z = 415). Compound **1** was refluxed with ethyl acetoacetate in ethanolic sodium hydroxide to form the benzothiazolylpyridin-2,6-dione **5** in a good yield. The IR spectrum showed C=O absorptions at ν 1660 and 1650 cm^{-1} and the ^{1}H NMR revealed two methyl signals at δ 1.65 and 2.5 ppm in addition to the pyridine methylene at δ 2. 25 ppm. A similar proposal has been previously reported [7]. Other pyridine derivatives could also be synthesized via the reaction of **1** with the arylidines of methyl cyanoacetate **6**. The products obtained were given the N-acetamido-6-aminopyridine-5-carboxylate structure **7**. Their IR showed NH_2, NH, OH and CO absorption bands at ν 3400-3100, 1660 and 1620 cm^{-1} respectively. The ^{1}H-NMR singlets at δ 5.5 ppm were attributed to the pyridine H-4. The microanalysis was also in accordance with the structure **7**.

Moreover compound **1** was treated in ethanolic piperidine with 2-furaldehyde , 2- thiophenaldehyde respectively to give the condensation products **8a, b** in good yields. Structures **8** were deduced from the analytical and spectral data that showed the ylidine proton at δ 7.9 ppm.

Table 1
Physical and chemical data for compounds **2,3,4,5,7a,b** and **8a**

Compd. No.	Yield %	Solvent/ M.P (°C)	Molecular Formula Mol. Wt	Analysis (Calcd/Found) (%) C	H	N	S
2	55	Ethanol 286-70	$C_{24}H_{18}N_2OS$ (382.46)	(75.4) 75.2	(4.7) 4.5	(7.3) 7.1	(8.4) 8.2
3	45	Benzene 198-201	C20H17N3O2S (363.42)	(66.1) 66.2	(4.7) 4.5	(11.6) 11.2	(8.8) 8.7
4	48	Ethanol 225-228	$C_{22}H_{17}N_5O_2S$ (415.46)	(63.6) 63.5	(4.1) 4.0	(16.9) 16.6	(7.7) 7.5
5	75	Methanol 276-279	$C_{15}H_{13}N_3O_3S$ (315.33)	(57.1) 56.9	(4.2) 4.0	(13.3) 13.1	(10.2) 9.9
7a	45	Dioxane 155-157	$C_{20}H_{18}N_4O_4S_2$ (442.49)	(54.3) 54.1	(4.1) 3.8	(12.7) 12.3	(14.5) 14.1
7b	55	Dioxane 260-262	$C_{20}H_{18}N_4O_5S$ (426.43)	(54.3) 54.1	(4.1) 3.8	(12.7) 12.3	(14.5) 14.1
8a	65	AcOH 219-221	$C_{16}H_{13}N_3O_2S_2$ (343.4)	(56.0) 55.8	(3.9) 3.6	(12.2) 12.0	(18.7) 18.3
8b	60	AcOH 188-190	$C_{16}H_{13}N_3O_3S$ (327.34)	(58.7) 58.6	(4.0) 4.1	12.8 12.6	(9.8) 9.5
9a	70	AcOH 180-183	$C_{19}H_{15}N_5O_2S_2$ (409.47)	(55.7) 55.5	(3.7) 3.6	(17.1) 16.8	(15.7) 15.5
9b	72	AcOH 175-177	$C_{19}H_{15}N_5O_3S$ (393.41)	(58.0) 57.8	(3.8) 3.7	(17.8) 17.5	(8.2) 8.0
10	35	AcOH >300	$C_{19}H_{13}N_5O_2S$ (375.394)	(60.8) 60.4	(3.5) 3.4	(18.7) 18.5	(8.5) 8.3
11a	45	Ethanol 179-181	$C_{24}H_{18}N_4OS_2$ (442.53)	(65.1) 65.0	(4.1) 4.2	(12.7) 12.5	(14.5) 14.2
11b	58	Ethanol 172-72	$C_{24}H_{18}N_4O_2S$ (426.47)	(67.6) 67.4	(4.3) 4.1	(13.1) 13.1	(7.5) 7.4
13a	60	AcOH 188	$C_{21}H_{15}N_5O_2S_3$ (465.56)	(54.2) 54.0	(3.3) 3.1	(15.0) 14.9	(20.7) 20.4
13b	55	AcOH 166	$C_{21}H_{15}N_5O_3S_2$ (449.49)	(56.1) 56.2	(3.4) 3.4	(15.6) 15.3	(14.3) 14.0

Table 2

Spectral data for the compounds listed in Table 1.

Comd. No.	IR (cm^{-1})	^1H NMR δ (ppm)
2	3150 (NH), 1670 (CO)	4.5 (dd, J= 5Hz, J = 11 Hz, 1H, Pyridine H-4), 4.6 (d, J = 11Hz, 1H, Pyridine H-3), 5.6 (dd, J = 5 Hz, 1H, Pyridine H-5), 7.1-8.1 (m, 14 H, ArH), 10.2 (s, 1H, NH).
3	3250 (NH), 1650 (CO)	1.9 (s, 3H, CH_3), 4.7 (m, 2H, CH_2), 5.4 (dd, 1 H, Pyridine H-6), 6.4 (dd, 1H, Pyridine H-4), 7.0-8.1 (m, 9H, C_6H_5 and C_6H_4), 9.6 (s, br, 1H, NH)
4	3450 (OH)	2.0 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.6-7.8 (m, 5H, C_6H_5), 8.15 (s, 1H, Pyrazolopyridine H-4), 8.3 (m, 2H, benzothiazole H-5, H-6), 8.5 (m, 2H, benzothiazole H-4, H-7).
5	3400 (NH), 1660 (CO), 1650 (CO)	1.65 (s, 3H, CH_3), 2.25 (s, 2H, CH_2), 2.5 (s, 3H, CH_3), 5.85 (s, br, 1H, NH), 7.35-7.65 (m, 4H, C_6H_4).
7a	3400-3100 (OH, NH, NH_2) 1660 (CO), 1620 (CO amide)	2.0 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 5.5 (s, 1H H-5, pyridine H-4), 6.8-8.1 (m, 7H, C_6H_4 and thiophene H-3, 4, 5), 10.0 (s, br, 1H, NH), 10.5 (s, br, 2H, NH_2), 11.8, (s, br, 1H, OH).
7b	3400-3150 (OH, NH, NH_2) 1665 (CO) 1620 (CO)	2.0 (s, 3H, CH_3 H-3,4), 3.7 (s, 3H, OCH_3), 5.4 (s, 1H, pyridine H-4), 6.2-6.3 (m, 2H, furan H-3,4), 7.2-8.2 (m, 5H, C_6H_4 and furan H-5), 10.0 (s, br, 1H, NH), 10.5 (s, br, 2H, NH_2), 11.7 (s, br, 1H, NH).
8a	3180-2900 (NH), 1650-1605 (CO)	2.0 (s, 3H, CH_3), 7.2 (q, 1H, thiophene, H-3), 7.5 (m, 2H, thiophene H-4,5), 7.5 (m, 2H, thiophene H-4, H-5), 7.8 (m, 2H, benzothiazole H-5, H-6), 7.9 (s, 1H, CH), 7.95-8.15 (m, 2H, benzothiazole H-4, H-7), 10.3 (s, br, 1H, NH), 10.9 (s, br, 1H, NH).
8b	3150-2950 (NH), 1665-1620 (CO)	2.0 (s, 3H, CH_3), 6.2 (q, 1H, furan, H-3), 6.6 (q, 1H, furan H-4), 7.5 (m, 3H, benzothiazole H-5, H-6 and furan H-5), 7.85 (s, 1H, CH), 8.0-8.1 (m, 2H, benzothiazole H-4, H-7), 10.2 (s, br, 1H, NH), 10.6 (s, br, 1H, NH).
9a	3500-3100 (OH, NH_2, NH), 2190 (CN), 1650 (CO)	2.0 (s, 3H, CH_3), 5.1 (s, 1H, pyridine H-4), 6.4 (s, 2H, NH_2), 6.8-7.7 (m, 7H, C_6H_4 and thiophene H-3,4,5), 10.0 (s, 1H, NH).
9b	3500-3150 (OH, NH_2, NH), 2190 (CN), 1650 (CO)	2.0 (s, 3H, CH_3), 4.9 (s, 1H, Pyridine H-4), 6.1 (q, 1H, furan H-4), 6.5 (s, br, 2H, NH_2), 7.1-7.7 (m, 5H, C_6H_4 and furan H-5), 9.9 (s, 1H, NH), 11.7 (s, 1H, OH).
10	3450-3200 (OH, NH), 2200 (CN)	2.7 (S, 3H, CH_3), 5.1 (s, H, pyridine H-4) 6.2-6.4 (m, 2H, furan H-3 and H-4), 7.2-7.8 (m, 5H, C_6H_4 and furan H-5), 10.1 (s, 1H, NH).
11a	3500-3350 (OH, NH)	2.3 (s, 3H, CH_3), 5.1 (s, 1H, pyridine H-4), 6.7-7.7 (m, 12H, C_6H_5, C_6H_4, and thiophen H-3, 4, 5), 13.9 (s, 1H, OH).
11b	3500-3350 (OH, NH)	2.2 (s, 3H, CH_3), 4.1 (s, 1H, NH), 5.0 (s, 1H, pyridine H-4), 6.1 (q, 1H, furan H-3), 6.4 (q, 1H, furan H-4), 7.2-8.0 (m, 10H, C_6H_5, C_6H_4 and furan H-5), 13.8 (s, br, 1H, OH).
13a	3250 (NH), 1680 (CO), 1660 (CO)	3.0 (s, 3H, CH_3), 4.05 (2d, 2H, CH_2), 5.3 (d, 1H, pyridine H-4), 5.5 (d, 1H, pyridine H-3), 6.8-8.0 (m, 7H, C_6H_4 and thiophen H-3,4, 5), 10.1 (s, br, 1H, NH), 10.7 (s, br, 1H, OH).
13b	3250 (NH), 1680 (CO), 1660 (CO)	3.0 (s, 3H, CH_3), 4.1 (2d, 2H, CH_2), 5.3 (d, 1H, pyridine H-4), 5.5 (d, 1H, pyridine H-3), 6.2-6.4 (m, 2H, furan H-3, H-4), 7.0-8.0 (m, 5H, C_6H_4 and furan H-5), 10.7 (s, br, 1H, OH).

Starting with the ylidines **8a, b,** a number of fused pyridines were achieved through their reactions with active mehtylene containing compounds. Thus, the furylidene derivative **8b** was treated with malononitrile in ethanol-triethylamine. The product obtained showed spectral features similar to those detected for compound **7b** except the absence of the acetoxy band at ν 1665 cm^{-1} and the presence of the CN band at n 2190 cm^{-1}. Hence the structure **9b** was given to this product. The microanalytical data were also in accordance with that structure. The pyridines **9** are probably formed via initial addition of the methylene group to the olefinic double bond in a Michael type reaction followed by cyclization involving the CN and imino groups. Similar proposals have previously been reported[8].

The resultant N-acetamidocyanopyridine **9b** was then treated with acetic anhydride. A new product was formed that shows the absence of CO absorption and the presence of a CN absorption. The ^1H NMR revealed two signals at δ 2.7 (3H) and 5.2 (1H) ppm. Also the mass spectra showed a molecular formula compatible with the molecular formula $C_{19}H_{13}N_5O_2S$ (m/z = 375). According to these informations and previous reports[9] the triazolopyridine structure **10** was given to this product.

The ylidines **8a, b** were also treated with active methylene containing heterocycles. Thus, N-phenyl-3-mehtylpyrazol-5-one was refluxed with **8a, b** in ethanol-ammonium acetate. The ^1H NMR of the product revealed a singlet at δ 5.1 ppm attributed to the pyridine-H. These along with the microanalytical and IR data could be explained in terms of the benzothiazolylpyrazolopyridine structure **11**. Moreover, the presence of a mass fragment ion at (m/z = 267, 25%) corresponding to the 1-phenyl-3-methyl-4-thienelydene-5-iminopyrazol molecule together with the one at (m/z = 175, 50%) corresponding to the 1-(2-benzothiazolyl) ketene moiety, confirms the proposed structure. The formation of structure **11** could also be interpreted in terms of the proposed mechanism of product **2**.

Persuing of the target compounds, the reaction of **8a, b** with 2-cyanomethylthiazolin-4-one was examined. Using the ylidene derivative **8a** the present reaction provides a new product with a molecular formula $C_{21}H_{15}N_5O_2S_3$ (m/z = 465). Its ^1H NMR showed four aliphatic signals at δ 3.0 (3H), 4.05 (2H), 5.3 (1H) and 5.5 (1H) ppm. Among several probabilities the present data fit with the triazolopyridine structure **13 a**.

In a previous report, we have investigated the reaction of arylidenemalonitrile with the same reactant, 2-cyanomehtylthiazolin-4-one. A thiazolopyridine ring system was obtained via a Michael addition followed by an intracyclization involving the thiazolo ring nitrogen nucleophile[10]. However, in the present case of the arylidines **8a, b**, the reaction also began with a Michael type addition but the following intra-cyclization step occurred via the hydrazino nitrogen nucleophile rather than via the thiazolone favoring the intermediates **12**, these further self condensed to form the triazolo moiety. A similar triazole ring formation has been proposed[9].

As a conclusion, some pyridines and fused pyridines could be prepared using simple procedures with available starting compounds.

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