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A New Synthesis for 1,2,4-Triazolo[1,5-*a*]-pyridines and 1,2,4-Triazolo[1,5-*a*]isoquinolines

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Summary. Condensation of cyano acid hydrazide **1** with cyclopentanone in refluxing ethanolic piperidine yields hydrazone **2**. With mixtures of aliphatic aldehydes and different active methylene reagents, **2** reacts to 1,2,4-triazolo[1,5-*a*]pyridines (**8a–f**). Compound **2** also reacts with arylidenes **9a–g** to give triazolopyridines **10a–g**. Reaction of **2** with aromatic aldehydes affords compounds **13a–c**. Diazotation of **2** with aryldiazonium chloride in ethanol at 0 °C leads to the azo adducts **15a–d**. The thieno-1,2,4-triazolopyridine **16** is obtained by reaction of **8a** with elementary sulfur. **16** undergoes cycloaddition with ω-nitrostyrene, maleic anhydride, N-arylmalemide, and acrylonitrile yielding the isoquinolines **21–24**. All new compounds have been characterized by their IR, ^{1}H NMR, and mass spectra.

Keywords. 1,2,4-Triazolo[1,5-*a*]pyridines; 1,2,4-Triazolo[1,5-*a*]isoquinolines; IR; ^{1}H NMR.

Ein neuer Syntheseweg für 1,2,4-Triazolo[1,5-*a*]pyridine und 1,2,4-Triazolo[1,5-*a*]isochinoline

Zusammenfassung. Kondensation des Cyanohydrazids **1** mit Cyclopentanon in ethanolischem Piperidin bei Rückflußtemperatur ergibt das Hydrazon **2**. Mit Gemischen aus aliphatischen Aldehyden und verschiedenen Verbindungen mit aktiven Methylengruppen reagiert **2** zu 1,2,4-Triazolo[1,5-*a*]pyridinen (**8a–f**). Verbindung **2** reagiert außerdem mit den Arylidenen **9a–g** zu den Triazolopyridinen **10a–g**. Umsetzung von **2** mit aromatischen Aldehyden führt zu den Verbindungen **13a–c**. Diazotierung von **2** mit Aryldiazoniumchloriden in Ethanol bei 0 °C ergibt die Azoaddukte **15a–d**. Das Thieno-1,2,4-triazolylpyridin **16** erhält man durch Reaktion von **8a** mit elementarem Schwefel. **16** geht mit ω-Nitrostyrol, Maleinsäureanhydrid, N-Arylmaleimid und Acrylnitril eine Cycloaddition zu den Isochinolinen **21–24** ein. Alle neuen Verbindungen wurden durch ihre IR-, ^{1}H-NMR- und Massenspektren charakterisiert.

Introduction

Polyfunctionally substituted nitriles are versatile reagents, and their chemistry has recently received considerable attention [1], especially because of their potential utility as biodegradable agrochemicals [2–4]. In the past few years we have been involved in research project aimed at the development of new efficient synthetic approaches to these heteroaromatic compounds utilizing inexpensive starting materials. In previous publications *Elnagdi* et al. [5–7] have shown that cyano acid hydrazide **1** is an excellent adduct for the synthesis of heterocyclic systems including

pyrazoles, 1,2,4-oxadiazoles, 1,3,4-thiadiazoles, pyridazolines, and pyridines. In conjunction with this work, we report here the results of our investigations on cyanoacetic acid hydrazide **1**.

Results and Discussion

It has been found that condensation of **1** with cyclopentanone in refluxing ethanolic piperidine yields the hydrazones **2** or **3**. The possibility that the ketone reacts with the active methylene function in **1** was excluded on the basis of IR, ^{1}H NMR and MS data. The IR spectrum of the reaction product reveals the absence of an NH_2 group and the ^{1}H NMR spectrum exhibits a signal at $\delta = 2.8$ ppm for a CH_2 moiety. Recently, we have shown that a mixture of an aliphatic aldehyde and malononitrile can be used as synthetic equivalent to ylidenemalononitriles [8]. Thus, compound **2** reacts with mixtures of acetaldehyde/malononitrile, acetaldehyde/ethyl cyanoacetate, and acetaldehyde/cyanothioacetamide as well as with mixtures of formaldehyde/malononitrile, formaldehyde/ethyl cyanoacetate, and formaldehyde/cyanothioacetamide to yield the product of addition and hydrogen elimination which may be formulated as the oxidized adduct **6** or the 1,2,4-triazolopyridines **8a–f**. Structures **8a–f** were considered to be the only reaction products based on spectroscopic data. Thus no NH_2 signal can be detected in the IR spectrum of **8a**, whereas the ^{1}H NMR spectrum of **8a** shows two signals at $\delta = 9.5$ ppm and $\delta = 10.5$ ppm for two NH groups. Compound **8a** is assumed to be formed *via* an intermediate adduct **4** which is converted to **5** and subsequently cyclized and aromatized.

Compound **2** also reacts with arylidenemalononitriles **9a–c**, furylidenemalononitrile **9d**, furylideneethylcyanocetate **9e**, arylidenecyanothioacetamide **9f**, and furylidenecyanothioacetamide **9g** to yield the triazolo[1,5-*a*]pyridines **10a–g**.

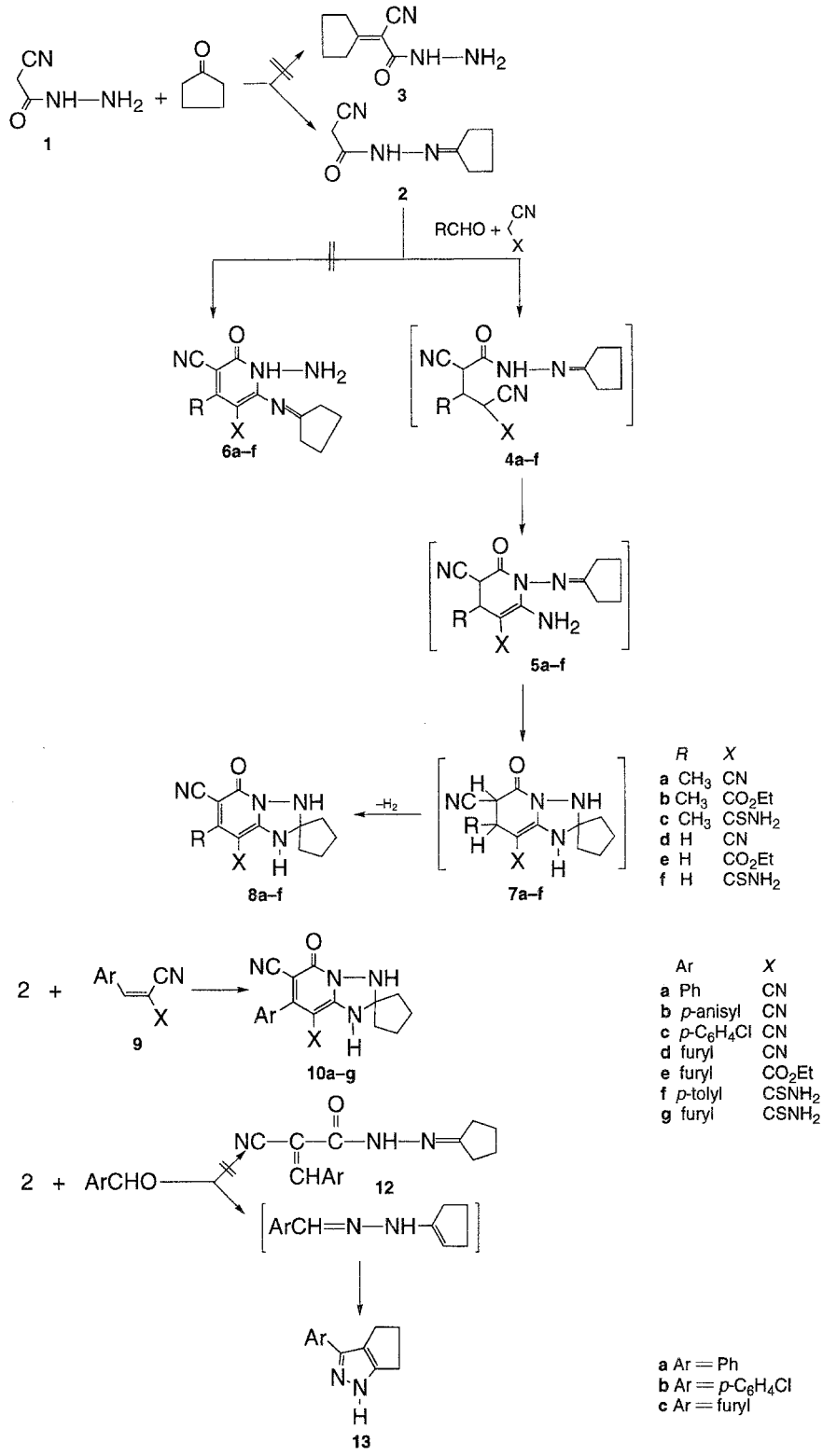
Attempts were made to condense **2** with aromatic aldehydes to form **12**. However only **13a–c** were formed under a variety of conditions. The structure of compounds **13a–c** was confirmed by spectroscopic data (IR, ^{1}H NMR, and MS). It is interesting to report that compounds **13a, b** cannot be readily obtained by direct condensation of cyclopentanonehydrazone and aromatic aldehydes or by condensation of arylhydrazone with cyclopentanone.

Compound **2** reacts with aryldiazonium chlorides **14** in ethanol in the presence of sodium acetate at 0 °C to the azo adducts **15a–d**. Their structures have been confirmed by spectroscopic data.

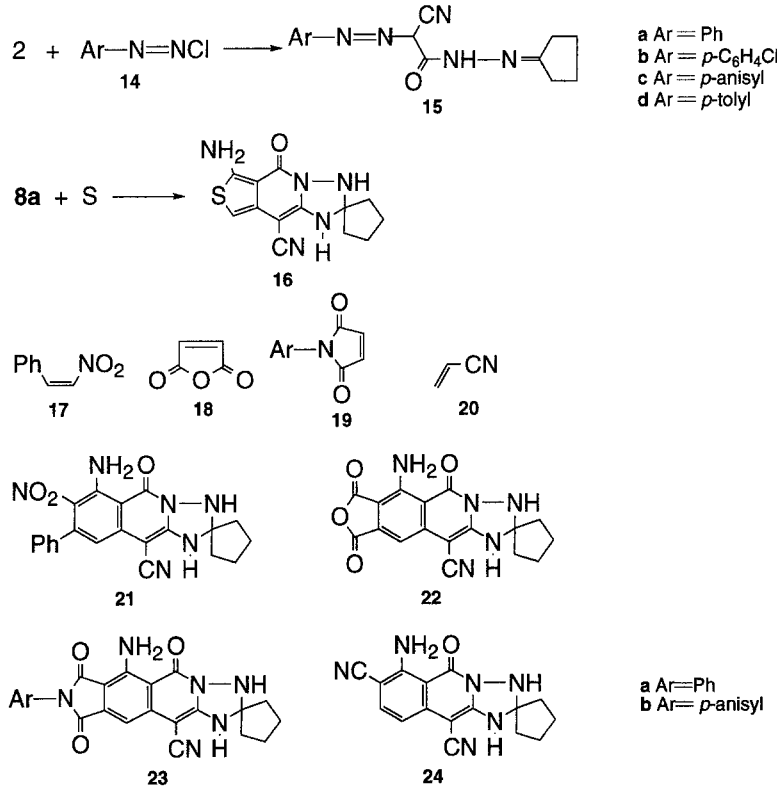
Synthetic approaches to benzoazines have been extensively studied [2]. These employ benzene or substituted benzene derivatives as starting materials. Recently, a new synthesis of benzoazines utilizing alkylazinycarbonitriles as starting materials has been reported [9, 10]. We have found that **8a** reacts with elementary sulfur to yield the thieno-1,2,4-triazolopyridine **16**. This undergoes cycloaddition with ω-nitrostyrene, maleic anhydride, N-arymalemide, and acrylonitrile yielding the isoquinolines **21–24**.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer, ^{1}H NMR spectra were measured with a Varian EM-390 spectrometer. Microanalyses were performed


CN
NH—NH2
O
1
3
2
RCHO + CN
X
6a–f
4a–f
5a–f
7a–f
8a–f
–H2
R X
a CH3 CN
b CH3 CO2Et
c CH3 CSNH2
d H CN
e H CO2Et
f H CSNH2
2 +
9
10a–g
Ar X
a Ph CN
b p-anisyl CN
c p-C6H4Cl CN
d furyl CN
e furyl CO2Et
f p-tolyl CSNH2
g furyl CSNH2
2 + ArCHO
12
ArCH=N—NH
13
a Ar = Ph
b Ar = p-C6H4Cl
c Ar = furyl

(*continued*)



Scheme

by the microanalytical facility at Cairo University. Mass spectra were recorded on a mass spectrometer MS 30 MS 9 (AEI) at 70 ev.

1-Cyclopentylidene-2-cyanoacetylhydrazine (**2**)

To a solution of cynoacetic acid hydrazide (**1**, 0.01 mol) in ethanol (30 ml), cyclopentanone (0.01 mol) was added. The reaction mixture was treated with a few drops of piperidine and refluxed for 3 h. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Table 1).

Preparation of **8a–f**; *general procedure*

Equimolar amounts of **2** (0.01 mol) and a mixture of the appropriate aliphatic aldehyde and the appropriate active methylene reagent (0.01 mol) in ethanol (30 ml) were treated with a few drops of piperidine. The reaction mixture was refluxed for 3 h. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

Preparation of **10a–g**; *general procedure*

A suspension of **2** (0.01 mol) and the appropriate arylidene or furylidene **9a–g** (0.01 mol) in ethanol (50 ml) was treated with a few drops of triethylamine and then refluxed for 3 h. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

Table 1. Yields, melting points, and elemental analyses of compounds **2**, **8a–f**, **10a–g**, **13a–c**, **15a–d**, **16**, **21**, **22**, **23a**, **b**, and **24**

	yield (%)	Molecular formula (molecular weight)	Mp (°C) (Solvents)	Calculated (Found)			
				C	H	N	S
2	85	$C_8H_{11}N_3O$ (165)	165 (EtOH)	58.16 (58.3)	6.70 (6.5)	25.43 (25.4)	
8a	80	$C_{13}H_{13}N_3O$ (255)	210 (EtOH)	61.16 (61.0)	5.13 (5.0)	27.43 (27.6)	
8b	85	$C_{15}H_{18}N_4O_3$ (302)	300 (EtOH/*DMF*)	59.59 (59.8)	5.94 (6.1)	18.54 (18.8)	
8c	77	$C_{13}H_{15}N_5OS$ (289)	280 (EtOH/*DMF*)	54.00 (53.7)	5.22 (5.4)	24.22 (24.4)	11.08 (11.2)
8d	82	$C_{12}H_{11}N_5O$ (241)	275 (EtOH/*DMF*)	59.69 (59.8)	4.58 (4.6)	29.08 (29.3)	
8e	72	$C_{14}H_{16}N_4O_3$ (288)	320 (Dioxane)	58.32 (58.5)	5.58 (5.6)	19.43 (19.3)	
8f	79	$C_{12}H_{13}N_5OS$ (275)	300 (Dioxane)	52.34 (52.2)	4.75 (4.8)	25.43 (25.6)	11.64 (11.8)
10a	67	$C_{18}H_{15}N_5O$ (317)	245 (EtOH/*DMF*)	68.12 (68.3)	4.76 (4.8)	22.06 (22.2)	
10b	70	$C_{22}H_{17}N_5O_2$ (383)	180 (EtOH)	65.69 (65.8)	4.90 (5.0)	20.14 (20.3)	
10c	73	$C_{18}H_{14}N_5OCl$ (351.5)	200 (EtOH)	61.44 (61.6)	4.00 (4.1)	19.90 (20.6)	
10d	78	$C_{16}H_{13}N_5O_2$ (307)	190 (EtOH)	62.44 (62.6)	4.25 (4.4)	22.75 (23.0)	
10e	76	$C_{18}H_{18}N_4O_4$ (354)	260 (EtOH/*DMF*)	61.01 (61.3)	5.11 (5.3)	15.81 (15.2)	
10f	65	$C_{19}H_{19}H_5OS$ (365)	175 (EtOH)	62.46 (62.6)	5.23 (5.4)	19.16 (19.4)	
10g	74	$C_{16}H_{15}N_5O_2S$ (341)	295 (EtOH/*DMF*)	56.30 (56.6)	4.42 (4.5)	20.50 (20.6)	9.39 (9.5)
13a	82	$C_{12}H_{12}N_2$ 184	215 (EtOH)	78.23 (78.4)	6.56 (6.7)	15.20 (15.4)	
13b	79	$C_{12}H_{11}N_2Cl$ (218.5)	210 (EtOH)	65.89 (66.0)	5.06 (5.3)	12.80 (13.0)	
13c	75	$C_{10}H_{10}N_2$ (158)	250 (EtOH)	75.92 (76.0)	6.36 (6.5)	17.70 (17.9)	
15a	85	$C_{14}H_{15}N_5O$ (269)	270 (Dioxane)	62.44 (62.6)	5.61 (5.7)	26.00 (26.3)	
15b	83	$C_{14}H_{14}N_5OCl$ (303.5)	290 (Dioxane)	55.35 (55.5)	4.64 (4.8)	23.05 (23.3)	
15c	85	$C_{15}H_{17}N_5O_2$ (299)	250 (Dioxane)	60.19 (60.4)	5.71 (5.9)	23.39 (23.6)	
15d	80	$C_{15}H_{17}N_5O$ (283)	280 (Dioxane)	63.59 (63.8)	6.04 (6.3)	24.71 (24.9)	

(*continued*)

Table 1. (*Continued*)

	yield (%)	Molecular formula (molecular weight)	Mp (°C) (Solvents)	Calculated (Found)			
				C	H	N	S
16	73	$C_{13}H_{13}N_5OS$ (287)	280 (EtOH/*DMF*)	54.45 (54.5)	4.55 (4.7)	24.37 (24.6)	11.16 (11.3)
21	71	$C_{21}H_{18}N_6O_3$ (402)	>300 (EtOH/*DMF*)	62.68 (62.7)	4.50 (4.6)	20.88 (21.1)	
22	72	$C_{17}H_{13}N_5O_4$ (351)	260 (Dioxane)	58.12 (58.3)	3.72 (3.9)	19.93 (20.1)	
23a	73	$C_{23}H_{18}N_6O_3$ (426)	263 (Dioxane)	64.79 (64.9)	4.25 (4.4)	19.71 (19.9)	
23b	70	$C_{24}H_{20}N_6O_4$ (456)	>300 (EtOH/*DMF*)	63.15 (63.4)	4.41 (4.6)	18.41 (18.6)	
24	76	$C_{16}H_{14}N_6O$ (306)	130 (EtOH)	62.73 (62.9)	4.60 (4.7)	27.43 (27.6)	

Table 2. Spectroscopic data of new compounds

	IR (cm^{-1})	^1H NMR (δ, ppm)
2	3300–3200 (NH), 2220 (CN), 1680 (CO)	2.5 (m, 8H, CH_2), 2.8 (s, 2H, CH_2), 10.8 (s, 1H, NH)
8a	3350–3100 (2NH), 2220 (2CN), 1670 (CO)	1.8 (s, 3H, CH_3), 2.8 (m, 8H, CH_2), 9.5 (s, 1H, NH), 10.5 (s, 1H, NH)
8b	3350–3200 (2NH), 2220 (CN), 1710 (CO ester, 1680 (CO)	1.8 (t, 3H, CH_3), 3.1 (s, 3H, CH_3), 3.5 (m, 8H, CH_2), 4.2 (q,2H, CH_2), 8.8 (s, 1H, NH), 9.5 (s, 1H, NH)
8c	3450–3350 (NH_2), 3350–3200 (2NH), 2220 (CN), 1650 (CO)	
8d	3300–3200 (2HN), 2190 (CN), 1680 (CO)	3.5 (m, 8H, CH_2), 6.5 (s, 1H, pyridine CH), 10.5 (s, 1H, NH), 11.0 (s, 1H, NH)
8e	3350–3220 (2NH), 2210 (CN), 1720 (CO ester, 1680 (CO)	1.6 (t, 3H, CH_3), 3.5 (m, 8H, CH_2), 4.3 (q, 2H, CH_2), 6.5 (s, 1H, pyridine CH), 11.5 (s, 1H, NH), 12.0 (s, 1H, 2NH)
8f	3390–3300 (NH_2), 3200–3100 (NH), 2208 (CN), 1690 (CO)	
10a	3400–3300 (2NH), 2224 (CN), 1644 (CO)	3.3 (m, 8H, CH_2), 7.2–7.8 (m, 5H, aryl protons), 11.0 (s, 1H, NH), 12.4 (s, 1H, NH)
10b	3350–3300 (2NH), 2190 (CN), 1650 (CO)	3.3 (m, 8H, CH_2), 7.2–7.6 (m, 4H, aromatic protons), 3.8 (s, 3H, OCH_3), 10.8 (s, 1H, NH), 12.2 (s, 1H, NH)
10c	3300–3200 (2NH), 2200 (CN), 1650 (CO)	
10d	3350–3280 (2NH), 2200 (CN), 1670 (CO)	3.3 (m, 8H, CH_2), 6.9–7.4 (m, 3H, furyl CH), 11.2 (s, 1H, NH), 12.3 (s, 1H, NH)
10e	3330–2200 (2NH), 2224 (CN), 1710 (CO ester), 1680 (CO)	1.6 (t, 3H, CH_3), 3.3 (m, 8H, CH_2), 4.2 (q, 2H, CH_2), 7.0–7.5 (m, 3H, furyl H), 10.8 (s, 1H, NH), 11.5 (s, 1H, NH)

(*continued*)

Table 2. (*Continued*)

	IR (cm^{-1})	^1H NMR (δ, ppm)
10f	3400–3300 (NH_2), 3300–3220 (2NH), 2200 (CN), 1660 (CO)	
10g	3420–3300 (NH_2), 3300–3200 (2NH), 2200 (CN), 1660 (CO)	
13a	3200–3100 (NH), 3050 (CH aromatic), 2900 (CH_2 aliphatic)	3.4 (m, 6H, $3CH_2$), 7.1–7.6 (m, 5H, aromatic 8.9 (s, 1H, NH)
13b	3300 (NH), 3050 (CH aromatic), 2980 (CH_2 aliphatic	
13c	3300 (NH), 2980 (CH_2 aliphatic)	3.4 (m, 6H, $3CH_2$), 6.4 (s, 1H, NH), 6.8–7.6 (m, 3H, furyl H)
15a	3250–3150 (NH), 2220 (CN), 1680 (CO)	3.3 (m, 8H, CH_2), 7.2–7.8 (m, 5H, aromatic protons), 10.5 (s, 1H, NH), 11.6 (s, 1H, NH)
15b	3300–3200 (NH), 2220 (CN), 1680 (CO)	
15c	3300–3150 (2NH), 2220 (CN), 1680 (CO)	3.3 (m, 8H, CH_2), 3.8 (s, 1H, OCH_3), 7.1–7.6 (m, 4H, aromatic protons), 10.6 (s, 1H, NH), 11.0 (s, 1H, NH)
15d	3320–3200 (2NH), 2222 (CN), 1670 (CO)	3.4 (m, 9H, CH_2, CH_3), 7.1–7.5 (m, 4H, aromatic protons), 11.2 (s, 1H, NH), 11.8 (s, 1H, NH)
16	3400–3280 (NH_2), 3280–3150 (2NH), 2200 (CN), 1650 (CO)	3.4 (m, 8H, CH_2), 7.6 (s, 1H, thiophene H), 8.9 (br, 2H, NH_2), 11.2 (s, 1H, NH), 12.5 (s, 1H, NH)
21	3400–3300 (NH_2), 3300–3200 (NH), 2190 (CN), 1660 (CO)	3.3 (m, 8H, CH_2), 7.2–7.8 (m, 6H, aromatic protons), 9.2 (br, 2H, NH_2), 11.3 (s, 1H, NH), 12.0 (s, 1H, NH)
22	3450–3300 (NH_2), 3300–3200 (2NH), 2220 (CN), 1650 (CO)	3.4 (m, 8H, CH_2), 7.2–7.5 (s, 1H, aromatic protons), 8.9 (br, 2H, NH_2), 11.3 (s, 1H, NH), 11.8 (s, 1H, NH)
23a	3400–3320 (NH_2), 3320–3200 (NH), 2210 (CN), 1710 (CO), 1660 (CO)	
23b	3450–3300 (NH_2), 3300–3200 (2NH), 2220 (CN), 1700 (CO), 1670 (CO)	3.4 (m, 8H, CH_2), 3.7 (s, 3H, OCH_3) 7.1–7.8 (m, 5H, aromatic protons), 8.5 (br, 2H, NH_2), 11.0 (s, 1H, NH), 11.5 (s, 1H, NH)
24	3400–3300 (NH_2), 3300–3150 (NH), 2210 (CN), 1660 (CO)	3.3 (m, 8H, CH_2), 7.2 (d, 2H, aromatic protons), 7.9 (br, 2H, NH_2), 10.8 (s, 1H, NH), 11.2 (s, 1H, NH)

Preparation of **13a–c**; *general procedure*

A mixture of **2** (0.01 mol) and aromatic aldehyde (0.01 mol) in acetic acid (30 ml) containing 1 g of sodium acetate was refluxed for 3 h. The reaction mixture was poured into water. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

Preparation of **15a–d**; *general procedure*

To a solution of **2** (0.01 mol) in ethanol (50 ml) containing 1g of sodium acetate, the diazonium chloride (prepared from the corresponding aromatic amine with sodium nitrite in HCl) was added and left

overnight in the refrigerator. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

5-Amino-4-oxo-1H-2,3-dihydrothieno[3,4-c]-2-spiro[cyclopentan-1,2,4-triazolo[1,5-a]pyridine]-8-carbonitrile (**16**)

A mixture of **8a** (0.01 mol) and elementary sulfur (0.01 gatom) in 50 ml ethanol was treated with a little amount of triethylamine and then refluxed for 3 h. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

Preparation of **21–24**; *general procedure*

Method A: To a solution of **16** (0.01 mol) in a dioxan/acetic acid mixture (50:10 ml), compounds **17–20** were added. The reaction mixture was refluxed for 3 h and then poured into icewater. The solid product was collected by filtration and recrystallized from the proper solvent (*cf.* Tables 1 and 2).

Method B (*preparation of* **24**): Equimolar amounts of **8a** (0.01 mol) and a mixture of malononitrile and formaldehyde (0.01 mol) in ethanol (30 ml) were treated with a few drops of piperidne. The reaction mixture was refluxed for 3 h. The solid product was collected by filtration and recrystallized from ethanol.

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