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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLES: SYNTHESES OF POLYFUNCTIONALLY SUBSTITUTED ISOQUINOLINES

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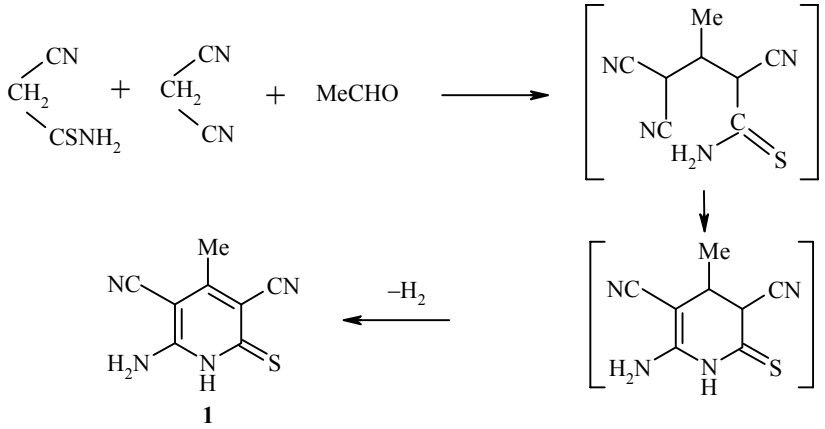
The three-component reaction of acetaldehyde, cyanothioacetamide, and malononitrile results in 6-amino-3,5-dicyano-4-methylpyridine-2(1H)-thione. The latter reacts with different chemical reagents to afford new substituted isoquinolines and their fused derivatives, which show high fungicidal and bactericidal activities.

Keywords: electrophilic reagents, isoquinoline, pyridinethiones, thieno[3,4-*c*]pyridine.

Alkylazinylcarbonitriles are important building blocks in synthetic heterocyclic chemistry, and their utility for the preparation of condensed azines has been reported recently [1-10]. In continuation of our research in this area, we report here results that enabled us to develop several new efficient syntheses for differently substituted isoquinolines and thieno[3,4-*c*]pyridines.

RESULTS AND DISCUSSION

Pyridinethione **1** was prepared *via* the three-component reaction of acetaldehyde, malononitrile, and cyanothioacetamide. The structure of the reaction product could be established *via* inspection of its mass, IR, and ^{1}H NMR spectra (see Experimental).



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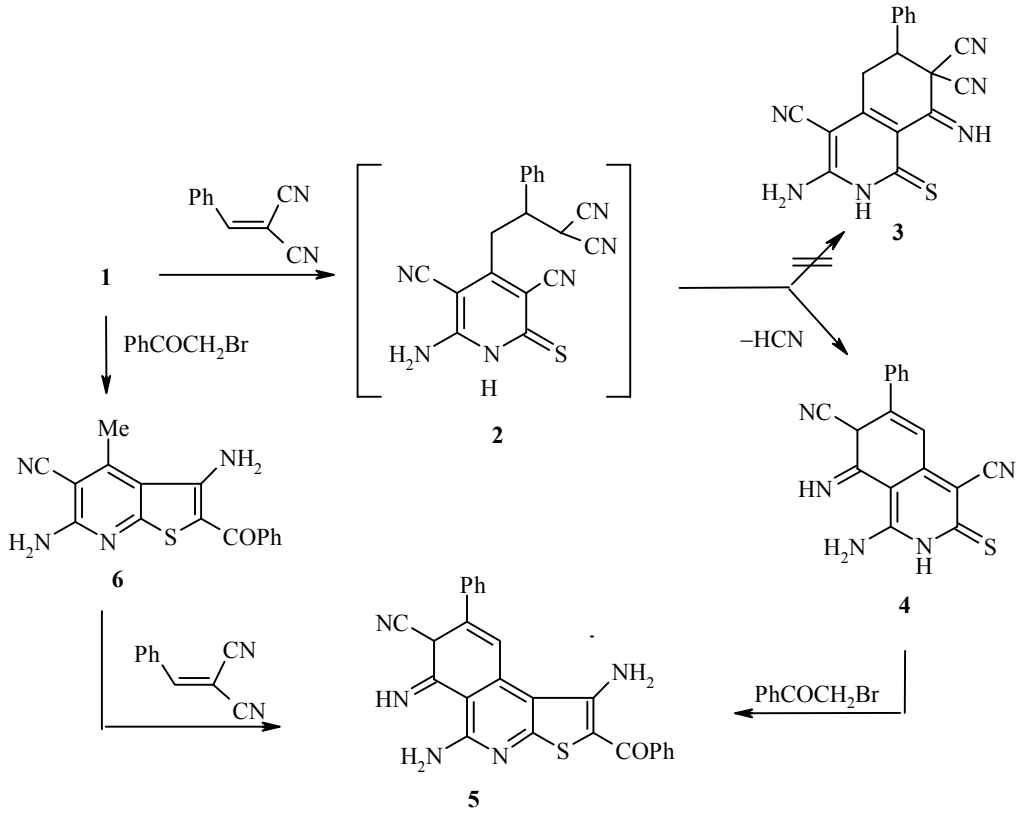
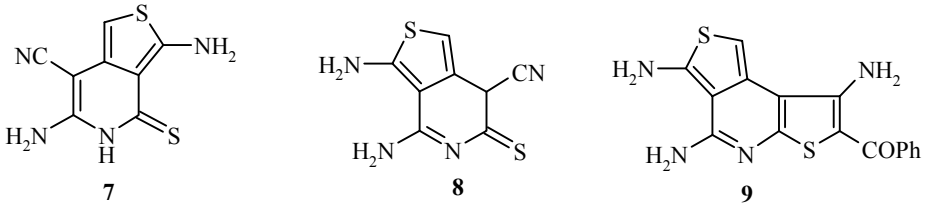
The methyl group in the pyridinethione **1** is highly active towards electrophilic reagents. Thus, compound **1** reacted readily with benzylidenemalononitrile to yield a 1:1 adduct which may be formulated as **2, 3**, or **4**. The "acyclic" structure **2** was ruled out based on the ^{1}H NMR spectrum since the latter revealed the absence of any multiplet for protons linked to sp^3 carbon atoms which might be expected for such adducts. The two isomeric forms **3** and **4** are expected to have almost the same ^{1}H NMR spectra. Structure **4** was established for the reaction product based on the chemical evidence: the substance reacted with phenacylbromide to yield the thienoisoquinoline derivative **5** which was also obtained *via* reacting the thienopyridine derivative **6** with benzylidenemalononitrile (Scheme 1).

Scheme 1



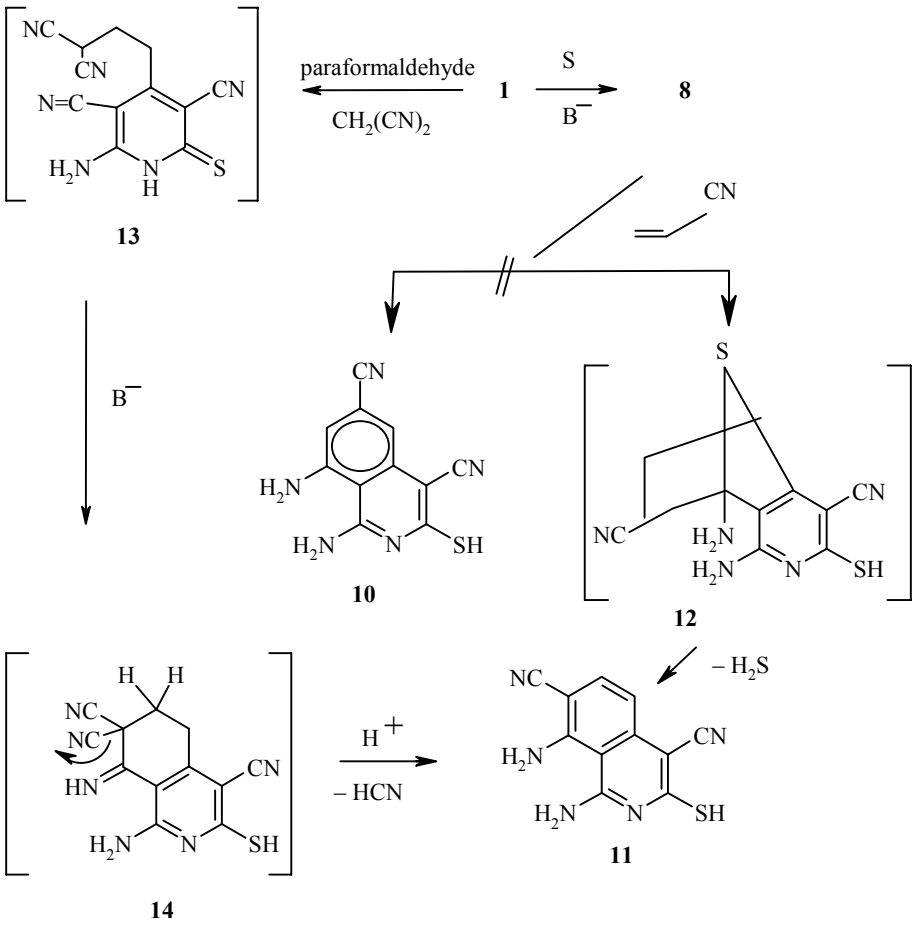
Although in **1** the cyano group at C(3) is expected to be more reactive than the one at C(5), cyclization took place at the latter CN perhaps as hydrogen bonding between NH and NH_2 in structure **4** is more efficient in stabilizing the system than the hydrogen bonding that is expected to happen between the C=NH and C=S group in structure **3**.

The pyridinethione **1** reacted with sulfur to yield a product that may be formulated as **7** or isomeric **8**. Structure **8** was considered for the reaction product as its reaction with phenacylbromide gave compound **9** which has been obtained *via* treatment of thieno[2,3-*b*]pyridine **6** with sulfur. Spectral data are in agreement with the proposed structure **8**.

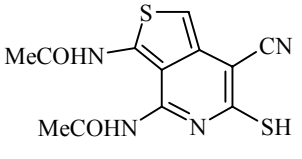


Thieno[3,4-*c*]pyridine **8** reacted with acrylonitrile to yield a product of addition and H_2S elimination. This reaction product may be formulated as **10** or regioisomeric **11** which is assumed to be formed *via* adduct **12**. Structure **11** has been confirmed as the correct one by its synthesis *via* reaction of pyridinethione **1** with paraformaldehyde and malononitrile in the presence of a base. We assumed that ethylidenemalononitrile is first formed and then adds to **1** to form an intermediate Michael adduct **13** that is spontaneously cyclized to intermediate **14** which undergoes aromatization with elimination of hydrogen cyanide to yield the isoquinoline **11** (Scheme 2). The structure of **11** is supported by its spectral data.

Scheme 2



Acylation of thieno[3,4-*c*]pyridine **8** with acetic anhydride afforded the diacetyl derivative **15**. The latter reacted with maleic anhydride to yield **16** *via* Diels-Alder addition to the thiophene fragment as diene and subsequent H_2S elimination.



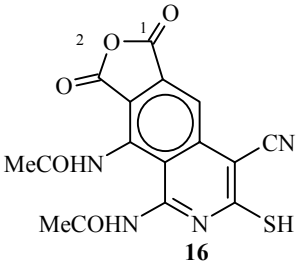


TABLE 1. *In Vitro* Batericidal and Fungicidal Activity of Some of the Newly Synthesized Compounds

Com-pound	*B. Cerceus*	*E. Coli*	*P. Aeruginosa*	*Staph. Aureus*	*A. Niger*	*C. Albicans*
1	+	+++	+	++	++	+++
4	++	+++	—	+++	+	++
5	—	++	—	++	—	+++
6	—	+++	—	—	++	++
8	—	—	—	++	—	+++
9	++	++	—	++	+	++
11	—	++	—	++	+++	+++
15	—	—	++	++	+++	+++
16	++	+	—	—	+++	+++

Slight effect = +, moderate effect = ++, severe effect = +++, complete effect = ++++. Rating percent control: no effect = 0; slight effect = 10, 20, 30; moderate effect = 40, 50, 60; severe effect = 70, 80, 90; complete effect = 100.

BIOLOGICAL ACTIVITY

The diverse biological activities of isoquinoline and its fused derivatives prompted us to test and study the biological activities of some of the newly synthesized products. The bactericidal and fungicidal activities were studied. The bactericidal effect was determined using the Gütter technique, while the antifungal effect was determined turbidimetrically [11, 12]. Table 1 shows that most of the tested compounds had high activity.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) with a Perkin-Elmer 1430 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-390 MHz (390 MHz) spectrometer in DMSO-d_6 using Me_4Si as internal standard, and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical data unit at Cairo University.

Compound **1** was prepared following literature procedure [13].

6-Amino-4-methyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (1). A solution of cyanothioacetamide (3 g, 0.03 mmol), malononitrile (1.9 g, 0.03 mmol), and acetaldehyde (1.4 g, 0.03 mmol) in ethanol (20 ml) with a few drops of piperidine was refluxed for 30 min. The mixture was diluted with water, and the solid product formed was collected by filtration and crystallized from ethanol as orange crystals (yield 1 g, 52%); mp 280°C. IR spectrum, ν, cm^{-1}: 3450-3330 (NH_2 and NH), 2222, 2220 (2CN). ^{1}H NMR spectrum, δ, ppm: 2.41 (s, 3H, CH_3); 3.50 (br, 2H, NH_2); 12.79 (s, 1H, NH). MS, *m/z*: 190 (M^+). Found, %: C 50.41; H 3.01; N 29.39; S 16.75. $C_8H_6N_4S$. Calculated, %: C 50.51; H 3.17; N 29.45; S 16.85.

1-Amino-8-imino-2,3,7,8-tetrahydro-3-thioxoisoquinolino-4,7,7-tricarbonitrile (4). To a solution of thione **1** (1.9 g, 0.01 mmol) in ethanol (30 ml), benzylidenemalononitrile (1.5 g, 0.01 mmol) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 3 h. The precipitate formed on dilution with water was collected by filtration and crystallized from dioxane as yellow crystals (yield 1 g, 32%); mp >300°C. IR spectrum, ν, cm^{-1}: 3400-3300 and 3220 (NH_2 and NH); 2220 (CN). ^{1}H NMR, spectrum, δ, ppm:

3.51 (br, 2H, NH_2); 7.15-7.67 (m, 7H, aromatic protons); 8.72 (s, 1H, NH); 10.10 (s, 1H, NH). MS, *m/z* 317 (M^+). Found, %: C 64.59; H 3.20; N 22.32; S 9.81. $C_{17}H_{11}N_5S$. Calculated, %: C 64.34; H 3.49; N 22.06; S 10.10.

1,5-Diamino-2-benzoyl-6-imino-5-phenyl-6,7-dihydrothieno[2,3-*c*]isoquinoline-7-carbonitrile (5). To a solution of **4** (3.42 g, 0.01 mmol) in dioxane (20 ml), phenacylbromide (1.89 g, 0.01 mmol) and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 3 h and poured into ice water. The solid product was crystallized from ethanol as yellow crystals (yield 2.9 g, 62%); mp 215°C. IR spectrum, ν, cm^{-1}: 3400-3300 (NH_2 and NH), 2220 (CN). Found, %: C 68.71; H 3.45; N 16.19; S 6.85. $C_{25}H_{17}N_5OS$. Calculated, %: C 68.95; H 3.94; N 16.09; S 7.35.

3,6-Diamino-2-benzoyl-4-methylthieno[2,3-*b*]pyridine-5-carbonitrile (6). A solution of **1** (1.9 g, 0.01 mmol) in dioxane (20 ml) containing phenacyl bromide (1.8 g, 0.01 mmol) and several drops of triethylamine was refluxed for 3 h and poured into ice water. The solid product was collected by filtration and crystallized from ethanol as yellow crystals (yield 1.2 g, 63%); mp >300°C. IR spectrum, ν, cm^{-1}: 3400-3300 (NH_2 and NH); 2220 (CN); 1720 (CO). Found, %: C 62.22; H 3.82; N 18.10; S 10.30. $C_{16}H_{12}N_4OS$. Calculated, %: C 62.32; H 3.93; N 18.18; S 10.38.

3,4-Diamino-6-mercaptothieno[3,4-*c*]pyridine-7-carbonitrile (8). To a solution of thione **1** (1.9 g, 0.01 mmol) in dioxane (30 ml), elemental sulfur (0.3 g, 0.01 mmol) and a catalytic amount of triethylamine were added. The reaction mixture was refluxed for 3 h. The solid product formed on dilution with water was collected by filtration and crystallized from dioxane–ethanol as brown crystals (yield 1.6 g, 72%); mp >300°C. IR spectrum, ν, cm^{-1}: 3480-3330 (NH_2), 2221 (CN). ^{1}H NMR spectrum, δ, ppm: 3.8 (br, 4H, $2NH_2$); 6.25 (s, 1H, thiophene H); 8.21 (s, 1H, pyridinethione H). Found, %: C 43.20; H 2.62; N 25.19; S 28.79. $C_8H_6N_4S_2$. Calculated, %: C 43.24; H 2.72; N 25.23; S 28.80.

2-Benzoyldithieno[2,3-*b*:3,4-*d*]pyridine-1,5,6-triamine (9). To a solution of nitrile **8** (2.2 g, 0.01 mmol) in ethanol (30 ml), phenacyl bromide (1.9 g, 0.01 mmol) and several drops of triethylamine were added. The mixture was refluxed for 3 h and poured into ice water. The solid product was crystallized from ethanol as brown crystals (1.9 g, 55%); mp >300°C. IR spectrum, ν, cm^{-1}: 3400-3330 (NH_2), 1720 (CO). Found, %: C 56.33; H 3.41; N 16.32; S 18.71. $C_{16}H_{12}N_4OS_2$. Calculated, %: C 56.46; H 3.56; N 16.47; S 18.80.

1,8-Diamino-3-mercaptoisoquinoline-4,7-dicarbonitrile (11). A. To a solution of **8** (2.2 g, 0.01 mmol) in dioxane (20 ml) acrylonitrile (2 ml) and a few drops of acetic acid were added. The reaction mixture was refluxed for 3 h, then left to cool at room temperature. The solid product was filtered off and crystallized from ethanol.

B. To a solution of thione **1** (1.9 g, 0.01 mmol) in dioxane (10 ml), malononitrile (0.66 g, 0.01 mmol) and (1 g) of paraformaldehyde were added together with a catalytic amount of piperidine. The reaction mixture was refluxed for 3 h then poured into water (30 ml). The solid product was filtered off and crystallized from ethanol (yield 1.5 g, 78%); mp >300°C. IR spectrum, ν, cm^{-1}: 3400, 3300 (NH_2); 2220 (CN). ^{1}H NMR spectrum, δ, ppm: 3.01 (br, 2H, NH_2); 3.51 (br, 2H, NH_2); 6.30 (s, 1H, SH); 7.98-8.21 (m, 2H, aromatic protons). Found, %: C 54.61; H 2.81; N 29.01; S 13.21. $C_{11}H_7N_5S$. Calculated, %: C 54.76; H 2.93; N 29.05; S 13.26.

3,4-Diacetylamino-6-mercaptothieno[3,4-*c*]pyridine-7-carbonitrile (15). A solution of **8** (2.2 g, 0.01 mmol) in acetic anhydride (10 ml) was refluxed for 1 h. The solid product was collected by filtration and crystallized from acetic acid as brown crystals (yield 2 g, 67%); mp >300°C. IR spectrum, ν, cm^{-1}: 3200 (NH); 2221 (CN); 1710 (CO). Found, %: C 47.01; H 3.20; N 18.21; S 20.82. $C_{12}H_{10}N_4O_2S_2$. Calculated, %: C 47.06; H 3.29; N 18.30; S 20.90.

4,5-Diacetylamino-7-mercapto-1,3-dioxo-1,3-dihydrofuro[3,4-*f*]isoquinoline-8-carbonitrile (16). An equimolar amount (0.01 mmol) of **15** and maleic anhydride was heated at 160°C (oil bath) for 20 min. The resulting cold product was washed several times with water and crystallized from dioxane (yield 2g, 65%); mp >300°C. IR spectrum, ν, cm^{-1}: 3270 (NH); 2220 (CN); 1810 (CO). Found, %: C 51.88; H 2.52; N 15.10; S 8.50. $C_{16}H_{10}N_4O_5S$. Calculated, %: C 51.89; H 2.72; N 15.14; S 8.64.

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