THE USES OF ETHYL CYANOBROMOACETATE IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF THIOPHENE, PYRAZOLO-[3,4-*d*]THIAZOLE AND THIENO[2,3-*d*]PYRIDAZINE DERIVATIVES

Rafat Milad MOHAREB[a,*], Salah EL-KOUSY[b] and Abdel Monem EL-TORGOMAN[b]

[a] *Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt*

[b] *Chemistry Department, Faculty of Science, Menofia University, Shibin El-Kom, Egypt*

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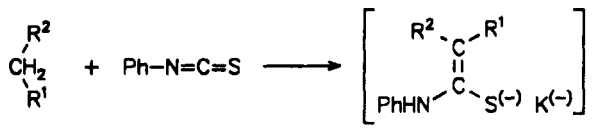
The reaction of active methylene reagents *Ia – Ie* with phenyl isothiocyanate in basic N,N-dimethylformamide solution followed by cyclization with ethyl cyanobromoacetate *II* affords the acyclic thioether derivatives *IVa – IVe*. The use of *IVa – IVe* in heterocyclic synthesis was described.

Various substituted thiophenes have received recently significant attention because of their diverse pharmacological properties. These include virucidal[1], anesthetic[2], anti-inflammatory[3], antihypertensive[4], antibacterial[5] and antiarthritic[6] activities. In the last few years we were involved in a program aimed at the development of convenient synthetic routs for polyfunctionally substituted heterocycles utilizing readily obtainable α-haloacetophenones[7], α-haloketoximes[8] and β-ketoanilides[9] as starting materials. In connection with our work, we expand our synthetic route via the use of such α-halocarbonyl compounds in reactions reported earlier by Hantzsch et al.[10 - 13] for the synthesis of thiophenes, thiazoles, 2,3-dihydrothiazoles[14 - 16] which are interesting as potential biodegradable agrochemicals[17,18].

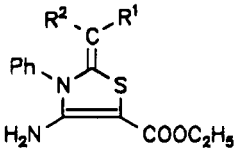
In this paper we report the use of ethyl cyanobromoacetate[19] (*II*) as the α-halocarbonyl reagent. Thus, the reaction of the active methylene reagents *Ia – Ie* with phenyl isothiocyanate in basic N,N-dimethylformamide affords intermediates *IIIa – IIIe* which cannot be isolated. Subsequent treatment of *IIIa – IIIe* with *II* affords the thioether derivatives *IVa – IVe*, not the thiazole derivatives *Va – Ve*. The determination of the structure of *IVa – IVe* was based on analytical and spectral data, e.g. for the reaction of *Ia*, a product with a molecular formula $C_{17}H_{17}N_3O_4S$ (M^+ 359) was obtained. Two possible isomeric structures *IVa* and *Va* were proposed. However, the structure *Va* was excluded on the basis of IR spectrum which revealed the presence of two C≡N groups

* The author to whom correspondence should be addressed.

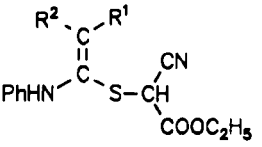


I *III*

II



V

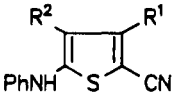


IV

In formulae *I*, *III* – *V*:

	R^1	R^2
a	CN	$COOC_2H_5$
b	CN	CN
c	CN	COPh
d	$COCH_3$	$COCH_3$
e	$COOC_2H_5$	$COCH_3$

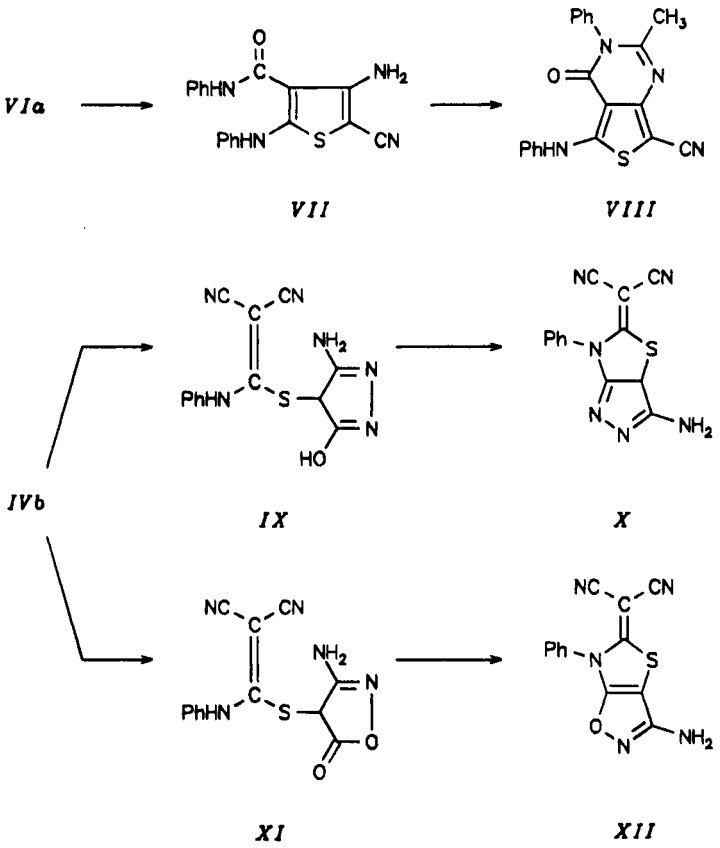
IVa–IVe ⟶

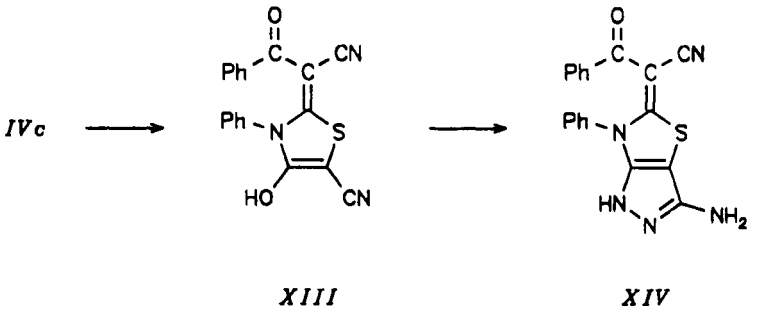


VI

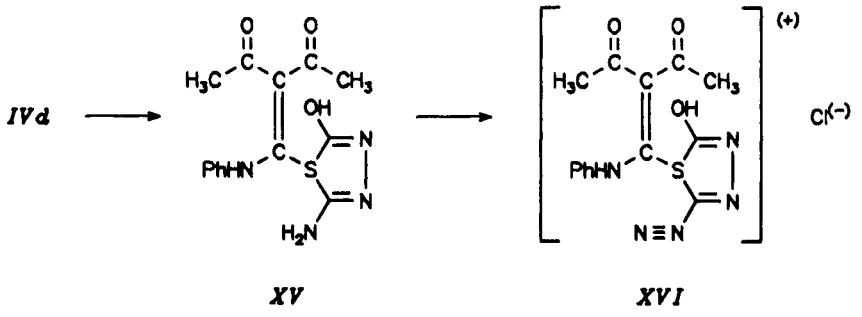
	R^1	R^2
a	NH_2	$COOC_2H_5$
b	NH_2	CN
c	NH_2	COPh
d	CH_3	$COCH_3$
e	OH	$COCH_3$

spreading at 2 220 and 2 215 cm^{-1}, together with the ^1H NMR spectrum which revealed the presence of two triplets at δ 1.38 and 1.43 ppm for two CH_3 groups, two quartets at δ 3.68 and 4.22 ppm for two CH_2 groups, a singlet at δ 5.66 ppm for CH, a multiplet at δ 7.33 – 7.38 ppm for C_6H_5 and a singlet at δ 8.89 ppm for NH. Boiling of *IVa – IVe* in ethanol/sodium hydroxide solution affords the thiophene derivatives *VIa – VIe*. Formation of these products is assumed to proceed via the hydrolysis of the ethyl ester group, followed by decarboxylation and in situ cyclization to afford *VIa – VIe*. Structures of *VIa – VIe* were established on the basis of analytical and spectral data (see Experimental).



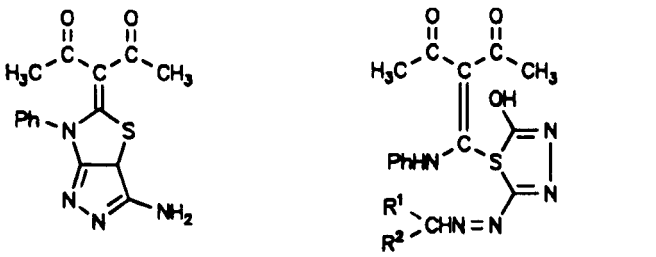


XIII *XIV*



XV *XVI*

Ia, Ib

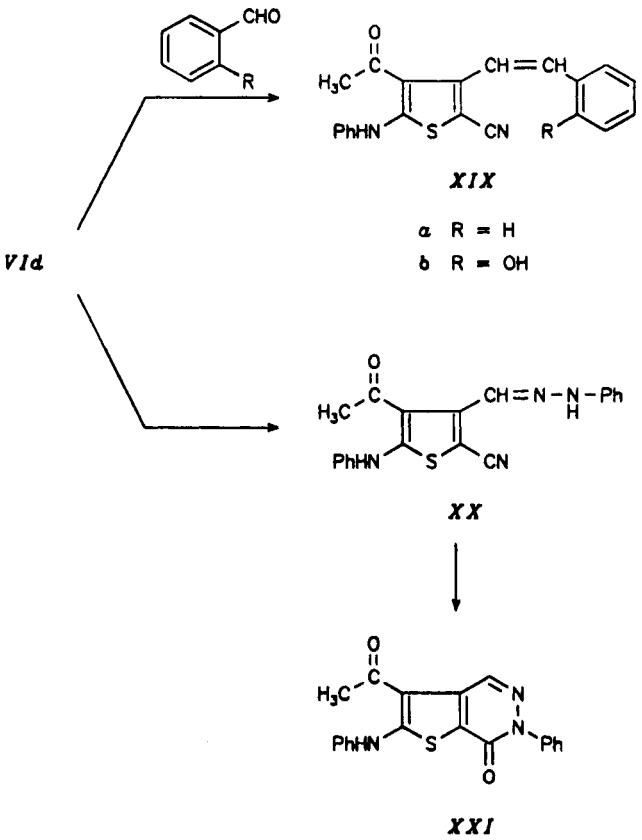


XVIII *XVII*

a R^1 = CN; R^2 = $COOC_2H_5$
b R^1 = R^2 = CN

Reaction of *VIa* with aniline at 160 °C affords the derivative *VII*. The latter product reacts with a mixture of acetic acid and anhydride to afford the thieno[3,4-*d*]pyrimidine derivatives *VIII*. The reaction of *IVb* with hydrazine hydrate affords the pyrazole derivative *IX*. This product undergoes further cyclization after heating in concentrated sulfuric acid to afford the pyrazolo[3,4-*d*]thiazole derivative *X*. Reaction of *IVb* with hydroxylamine hydrochloride affords the isoxazole derivative *XI*. The latter undergoes cyclization in concentrated sulfuric acid to afford the thiazolo[5,4-*d*]isoxazole derivative *XII*.

Compound *IVc* undergoes another type of cyclization when heated in ethanol/sodium ethoxide solution, to give *XIII* via ethanol elimination. The structure of *XIII* was confirmed on the basis of analytical and spectral data. The IR spectrum revealed the presence of OH group at 3 560 – 3 450 cm^{-1}. ^1H NMR spectrum revealed the presence of a multiplet at δ 7.32 – 7.38 ppm for two C_6H_5 and a singlet at δ 9.92 ppm for OH group. The reaction of hydrazine hydrate with *XIII* affords the pyrazolo[3,4-*d*]thiazole derivative *XIV* (M^+ 345).



The reaction of *IVd* with hydrazine hydrate affords the 3-amino-5-hydroxypyrazole derivative *XV*. The latter undergoes diazotation to afford the diazonium chloride salt *XVI* which, in turn couples with active methylene reagents to afford the corresponding coupling products. Thus, with *Ia*, *Ib* it affords the pyrazole derivatives *XVIIa*, *XVIIb*. Diazotation of aminopyrazole derivatives and their coupling with active methylene reagents was reported previously[20 - 22]. The pyrazole derivative *XV* undergoes further cyclization when heated with concentrated sulfuric acid to afford the pyrazolo[3,4-*d*]thiazole derivative *XVIII*.

Elnagdi et al.[23 - 26] have explored recently the synthetic potential of propene-1-carbonitriles. Our findings from studies of such a type of activity in π-excessive heterocycles as *VId* showed that it reacts with aromatic aldehydes like benzaldehyde and salicylaldehyde, to afford the benzyl derivatives *XIXa* and *XIXb*, respectively. Moreover, compound *VId* couples with benzene diazonium chloride to give the phenylhydrazo derivative *XX*. The latter undergoes readily cyclization when heated in ethanol/sodium hydroxide solution to afford the thieno[2,3-*d*]pyridazine derivative *XXI*. We believe that the extra activity of the methyl group in such a π-excessive heterocyclic system is a result of the high electron-withdraw effect of other groups attached to the thiophene ring.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer SP 177 spectrometer in KBr disc (wavenumbers in cm^{-1}). Proton NMR spectra were taken on a Varian A-300 (300 MHz) instrument at 25 °C in CD_3SOCD_3 with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

General Procedure for Preparation of Ethyl Cyano(2,2-disubstituted-1-phenylaminoethenylthio)acetate Derivatives *IVa – IVe*

To a cold suspension of finely ground potassium hydroxide (1.0 g, 0.025 mol) in N,N-dimethylformamide (30 ml) each of the active methylene reagent *Ia – Ie* (0.025 mol) was added and subsequently, phenyl isothiocyanate (3.25 g, 0.025 mol). The reaction mixture was stirred at room temperature for 24 h and treated with ethyl cyanobromoacetate *II* (4.8 g, 0.025 mol) and left at room temperature for additional 24 h. The reaction mixture was then triturated with cold water (100 ml) and neutralized with diluted hydrochloric acid. The resulting precipitated solid was collected by filtration.

Compound IVa: Crystallized from ethanol, m.p. 180 °C, yield 5.9 g (66%). IR spectrum: 3 460 – 3 360 (NH); 3 040 (CH aromatic); 2 970, 2 900 (CH_3, CH_2); 2 220, 2 215 (C≡N); 1 680 (C=O); 1 630 (C=C). ^{1}H NMR spectrum: 1.38 t and 1.43 t, 2 × 3 H, *J* = 7.77 (2 × CH_3); 3.68 q and 4.22 q, 2 × 2 H, *J* = 7.77 (2 × CH_2); 5.66 s, 1 H (CH); 7.33 – 7.36 m, 5 H (C_6H_5); 8.89 s, 1 H (NH). Mass spectrum, *m/z*: 359 (M^+). For $C_{17}H_{17}N_3O_4S$ (359.4) calculated: 56.81% C, 4.76% H, 11.69% N, 8.92% S; found: 56.55% C, 4.34% H, 11.56% N, 8.66% S.

Compound IVb: Crystallized from ethanol, m.p. 222 °C, yield 7.0 g (90%). IR spectrum: 3 460 – 3 360 (NH); 3 040 (CH aromatic); 2 220, 2 215, 2 210 (C≡N); 1 680 (C=O). ^{1}H NMR spectrum: 1.43 t, 3 H, *J* = 8.11 (CH_3); 8.89 q, 2 H, *J* = 8.11 (CH_2); 5.66 s, 1 H (CH); 7.33 – 7.35 m, 5 H (C_6H_5); 8.79 s, 1 H (NH). Mass spectrum, *m/z*: 312 (M^+). For $C_{15}H_{12}N_4O_2S$ (312.1) calculated: 57.67% C, 3.87% H, 17.95% N, 10.25% S; found: 57.34% C, 3.44% H, 18.14% N, 10.00% S.

Compound IVc: Crystallized from dioxane, m.p. 190 °C, yield 7.6 g (78%). IR spectrum: 3 340 – 3 380 (NH), 3 040 (CH aromatic), 2 980 (CH_3), 2 220, 2 215 (2 CN), 1 690, 1 680 (2 C=O). ^{1}H NMR spectrum: 1.48 t, 3 H (J = 7.67 (CH_3)); 3.94 q, 2 H (J = 7.67 (CH_2)); 5.99 s, 1 H (CH); 7.32 – 7.37 m, 10 H (2 × C_6H_5); 8.82 s, 1 H (NH). For $C_{21}H_{17}N_3O_3S$ (391.4) calculated: 64.43% C, 4.37% H, 10.73% N, 8.19% S; found: 64.01% C, 4.23% H, 10.59% N, 7.76% S.

Compound IVd: Crystallized from ethanol, m.p. 277 – 279 °C, yield 6.8 g (79%). IR spectrum: 3 460 – 3 445 (NH); 3 050 (CH aromatic); 2 980 (CH_3); 2 220 (C≡N); 1 700, 1 690 – 1 680 (C=O). ^{1}H NMR spectrum: 1.21 s and 1.32 s, 2 × 3 H, (2 × CH_3); 1.42 t, 3 H, J = 7.89 (CH_3); 3.96 q, 2 H, J = 7.89 (CH_2); 5.46 s, 1 H (CH); 7.32 – 7.36 m, 5 H (C_6H_5); 8.91 s, 1 H (NH). For $C_{17}H_{18}N_2O_4S$ (346.4) calculated: 58.94% C, 5.24% H, 8.08% N, 9.25% S; found: 58.43% C, 4.89% H, 8.38% N, 9.00% S.

Compound IVe: Crystallized from ethanol, m.p. 181 °C, yield 6.6 g (74%). IR spectrum: 3 460 – 3 420 (NH); 3 050 (CH aromatic); 2 980, 2 875 (CH_3, CH_2); 2 220 (C≡N); 1 700, 1 690 – 1 680 (C=O). ^{1}H NMR spectrum: 1.32 s, 3 H (CH_3); 1.42 t and 1.48 t, 2 × 3 H, J = 7.77 (2 × CH_3); 3.82 q and 3.91 q, 2 × 2 H, J = 7.77 (2 × CH_2); 5.48 s, 1 H (CH); 7.32 – 7.37 m, 5 H (C_6H_5); 8.82 s, 1 H (NH). For $C_{18}H_{20}N_2O_5S$ (376.4) calculated: 57.43% C, 5.35% H, 7.44% N, 8.52% S; found: 57.21% C, 5.62% H, 7.41% N, 8.52% S.

General Procedure for Preparation of 2-Cyano-3,4-disubstituted-5-phenylaminothiophene Derivatives *VIa – VIe*

A solution of each of *IVa – IVe* (0.01 mol) in ethanol/sodium hydroxide (0.01 mol) (prepared by adding sodium hydroxide (0.4 g, 0.01 mol) to ethanol (30 ml)) was heated in a boiling water bath for 6 h. The solid product formed in each case after dilution with cold water containing hydrochloric acid (till pH 6) was collected by filtration.

Compound VIa: Crystallized from dioxane, m.p. 149 °C, yield 2.0 g (71%). IR spectrum: 3 460 – 3 335 (NH_2, NH); 3 050 (CH aromatic); 2 980 (CH_3); 2 220 (C≡N); 1 690 (C=O). ^{1}H NMR spectrum: 1.42 t, 3 H, J = 7.81 (CH_3); 3.89 q, 2 H, J = 7.81 (CH_2); 5.21 s, 2 H (NH_2); 7.33 – 7.35 m, 5 H (C_6H_5); 8.89 s, 1 H (NH). Mass spectrum, *m/z*: 287 (M^+). For $C_{14}H_{13}N_3O_2S$ (287.3) calculated: 58.52% C, 4.56% H, 14.66% N, 11.23% S; found: 58.23% C, 4.23% H, 14.79% N, 11.41% S.

Compound VIb: Crystallized from N,N-dimethylformamide, m.p. > 300 °C, yield 2.1 g (90%). IR spectrum: 3 460 – 3 380 (NH_2, NH); 3 050 (CH aromatic); 2 225, 2 220 (C≡N). ^{1}H NMR spectrum: 5.21 s, 2 H (NH_2); 7.33 – 7.35 m, 5 H (C_6H_5); 8.81 s, 1 H (NH). Mass spectrum, *m/z*: 240 (M^+). For $C_{12}H_8N_4S$ (240.3) calculated: 59.96% C, 3.35% H, 23.31% N, 13.34% S; found: 60.21% C, 3.01% H, 23.11% N, 13.31% S.

Compound VIc: Crystallized from N,N-dimethylformamide–ethanol mixture, m.p. 102 °C, yield 2.1 g (66%). IR spectrum: 3 460 – 3 300 (NH_2, NH); 3 050 (CH aromatic); 2 222 (C≡N); 1690 (C=O). ^{1}H NMR spectrum: 5.87 s, 2 H (NH_2); 7.32 – 7.36 m, 10 H (2 × C_6H_5); 9.92 s, 1 H (OH). Mass spectrum, *m/z*: 319 (M^+). For $C_{18}H_{13}N_3OS$ (319.4) calculated: 67.69% C, 4.10% H, 13.15% N, 10.04% S; found: 67.39% C, 3.79% H, 13.42% N, 9.75% S.

Compound VId: Crystallized from ethanol, m.p. 167 °C, yield 2.3 g (90%). IR spectrum: 3 450 (NH); 3 050 (CH aromatic); 2 975 (CH_3); 2 220 (C≡N); 1 700 (C=O). ^{1}H NMR spectrum: 1.38 s and 1.50 s, 2 × 3 H (2 × CH_3); 7.32 – 7.36 m, 5 H (C_6H_5); 8.72 s, 1 H (NH). For $C_{14}H_{12}N_2OS$ (256.3) calculated: 65.01% C, 4.72% H, 10.93% N, 12.51% S; found: 64.88% C, 4.82% H, 10.61% N, 12.01% S.

Compound VIe: Crystallized from ethanol, m.p. 217 °C, yield 2.2 g (84%). IR spectrum: 3 560 – 3 320 (OH, NH); 3 050 (CH aromatic); 2 980 (CH_3); 2 220 (C≡N); 1695 (C=O). ^{1}H NMR spectrum: 1.42 s, 3 H (CH_3); 7.32 – 7.36 m, 5 H (C_6H_5); 8.91 s, 1 H (NH); 9.99 brs, 1 H (OH). For $C_{13}H_{10}N_2O_2S$ (258.3) calculated: 60.45% C, 3.90% H, 10.84% N, 12.41% S; found: 60.21% C, 4.01% H, 10.74% N, 12.14% S.

3-Amino-2-cyano-5-phenylamino-4-phenylcarbamoylthiophene (*VII*)

To dry solid of *VIa* (2.83 g, 0.01 mol), aniline (0.93 g, 0.01 mol) was added and the mixture was heated at 160 °C for 2 h. The solid product formed after cooling was triturated with ethanol and collected by filtration. Crystallization from ethanol afforded 2.3 g (72%) of product *VII*, m.p. > 300 °C. IR spectrum: 3 660 – 3 300 (NH_2, NH); 3 050 (CH aromatic); 2 220 (C≡N); 1 690 (C=O). ^{1}H NMR spectrum: 5.23 s, 2 H (NH_2); 7.31 – 7.37 m, 10 H (2 × C_6H_5); 8.91 s and 9.99 s, 2 × 1 H (2 × NH). For $C_{18}H_{14}N_4OS$ (334.4) calculated: 64.65% C, 4.22% H, 16.75% N, 9.58% S; found: 64.35% C, 4.00% H, 16.47% N, 9.26% S.

4-Cyano-2-methyl-7-oxo-1-phenyl-6-phenylaminothieno[3,4-*d*]pyrimidine (*VIII*)

A solution of *VII* (3.3 g, 0.01 mol) in acetic acid (10 ml) and acetic anhydride (5 ml) was heated under reflux for 4.5 h, then evaporated in vacuo. The residue was triturated with ethanol and collected by filtration. Crystallization from N,N-dimethylformamide afforded 2.6 g (72%) of compound *VIII*, m.p. > 300 °C. IR spectrum: 3 450 – 3 400 (NH); 3 050 (CH aromatic); 2 980 (CH_3); 2 222 (C≡N); 1 695 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 1.33 s, 3 H (CH_3); 7.33 – 7.36 m, 10 H (2 × C_6H_5); 8.81 s, 1 H (NH). For $C_{20}H_{14}N_4OS$ (358.4) calculated: 67.02% C, 3.93% H, 15.63% N, 8.94% S; found: 66.73% C, 4.21% H, 15.58% N, 8.52% S.

General Procedure for Preparation of Compounds *IX*, *XIV*, and *XV*

To a solution of each of *IVb* (3.1 g, 0.01 mol), *XIII* (3.4 g, 0.01 mol) or *IVd* (3.4 g, 0.01 mol) in dioxane (30 ml), hydrazine hydrate (1.25 g, 0.025 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed after dilution with cold water containing few drops of hydrochloric acid was collected by filtration.

2-Amino-5-hydroxy-4-(2,2-dicyano-1-phenylaminoethenylthio)pyrazole (IX): Crystallized from dioxane, m.p. 250 – 252 °C, yield 2.2 g (73%). IR spectrum: 3 540 – 3 360 (OH, NH_2, NH); 3 050 (CH aromatic); 2 220, 2 215 (C≡N); 1 660 (C=O). ^{1}H NMR spectrum: 4.99 s, 2 H (NH_2); 6.43 s, 1 H (pyrazole H-4); 7.32 – 7.36 m, 5 H (C_6H_5); 8.82 s, 1 H (NH): 9.97 brs, 1 H (OH). For $C_{13}H_{10}N_6OS$ (298.3) calculated: 52.34% C, 3.38% H, 28.18% N, 10.75% S; found: 52.24% C, 3.01% H, 28.24% N, 10.48% S.

6-Amino-2-(benzoylcyanomethylene)-3-phenyl-3H,4H-pyrazolo[3,4-d]thiazole (XIV): Crystallized from dioxane, m.p. 284 – 287 °C, yield 2.8 g (82%). IR spectrum: 3 460 – 3 340 (NH_2, NH); 3 050 (CH aromatic); 2 220 (C≡N); 1 695 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 4.48 s, 2 H (NH_2); 7.32 – 7.37 m, 10 H (2 × C_6H_5); 8.21 s, 1 H (NH). For $C_{19}H_{13}N_5OS$ (359.4) calculated: 63.49% C, 3.64% H, 19.48% N, 8.92% S; found: 63.37% C, 3.31% H, 19.12% N, 9.31% S.

3-Amino-5-hydroxy-4-(2,2-diacetyl-1-phenylaminoethenylthio)pyrazole (XV): Crystallized from N,N-dimethylformamide, m.p. > 300 °C, yield 2.9 g (90%). IR spectrum: 3 660 – 3 320 (OH, NH_2, NH); 3 050 (CH aromatic); 2 975 (CH_3); 1 700, 1 695 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 1.33 s and 1.46 s, 2 × 3 H (2 × CH_3); 5.48 s, 2 H (NH_2); 6.79 s, 1 H (pyrazole H-4); 7.32 – 7.36 m, 5 H (C_6H_5); 8.91 s, 1 H (NH); 10.0 s, 1H (OH). For $C_{15}H_{16}N_4O_3S$ (332.4) calculated: 54.21% C, 4.85% H, 16.85% N, 9.64% S; found: 54.37% C, 4.58% H, 16.49% N, 9.89% S.

3-Amino-4-(2,2-dicyano-1-phenylaminoethenylthio)-2-isoxazolin-5-one (*XI*)

To a solution of *IVb* (3.1 g, 0.01 mol) in ethanol (30 ml) containing sodium acetate (3.0 g), hydroxylamine hydrochloride (0.07 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h. The solid product formed after pouring into ice/water mixture was collected by filtration. Crystallization from N,N-dimethylformamide gave 2.1 g (72%) of compound *XI*, m.p. 267 °C. IR spectrum: 3 450 – 3 300 (NH_2, NH); 3 050 (CH aromatic); 2 225, 2 220 (C≡N); 1 690 (C=O); 1 650 (C=N). ^{1}H NMR spectrum:

5.20 s, 2 H (NH_2); 6.99 s, 1 H (isoxazole H-4); 7.30 – 7.35 m, 5 H (C_6H_5); 8.89 s, 1 H (NH). For $C_{13}H_9N_5O_2S$ (299.3) calculated: 52.16% C, 3.03% H, 23.29% N, 10.71% S; found: 51.75% C, 3.41% H, 23.05% N, 10.55% S.

General Procedure for Preparation of Compounds *X*, *XII*, and *XVIII*

To the dry solid of each of *IX* (2.9 g, 0.01 mol), *XI* (2.9 g, 0.01 mol) or *XV* (3.3 g, 0.01 mol), concentrated H_2SO_4 (5 ml) was added. The mixture was heated in a boiling water bath for 5 h, then left to cool. The solid product formed after the dilution with ice/water and neutralization with sodium hydroxide (till pH 7) was collected by filtration.

4-Amino-2-(dicyanomethylene)-1-phenylpyrazolo[3,4-d]thiazole (X): Crystallized from N,N-dimethylformamide, m.p. 269 – 273 °C, yield 2.0 g (74%). IR spectrum: 3 450 – 3 300 (NH_2); 3 050 (CH aromatic); 2 220, 2 215 (C≡N); 1 690 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 4.84 s, 2 H (NH_2); 6.69 s, 1 H (thiazole H-5); 7.32 – 7.34 m, 5 H (C_6H_5). For $C_{13}H_8N_6S$ (280.3) calculated: 55.74% C, 2.87% H, 29.98% N, 11.44% S; found: 55.29% C, 3.31% H, 29.58% N, 11.20% S.

4-Amino-2-(dicyanomethylene)-1-phenylisoxazolo[5,4-d]thiazole (XII): Crystallized from N,N-dimethylformamide, m.p. 188 °C, yield 2.3 g (82%). IR spectrum: 3 450 (NH_2); 3 050 (CH aromatic); 2 220, 2 215 (C≡N); 1 650 (C=N). ^{1}H NMR spectrum: 5.21 s, 2 H (NH_2); 7.32 – 7.36 m, 5 H (C_6H_5). For $C_{13}H_7N_5OS$ (281.3) calculated: 55.50% C, 2.51% H, 24.89% N, 11.39% S; found: 55.21% C, 2.59% H, 25.11% N, 11.24% S.

4-Amino-2-(diacetylmethylene)-1-phenylpyrazolo[3,4-d]thiazole (XVIII): Crystallized from dioxane, m.p. > 300 °C, yield 2.4 g (79%). IR spectrum: 3 450 – 3 370 (NH_2); 3 050 (CH aromatic); 2 975 (CH_3); 1 700, 1 690 (C=O); 1 655 (C=N). ^{1}H NMR spectrum: 1.38 s and 1.45 s, 2 × 3 H (2 × CH_3); 5.28 s, 2 H (NH_2); 6.99 s, 1 H (thiazole H-5); 7.32 – 7.36 m, 5 H (C_6H_5). For $C_{15}H_{14}N_4O_2S$ (314.4) calculated: 57.31% C, 4.48% H, 17.82% N, 10.19% S; found: 57.11% C, 4.27% H, 17.82% N, 9.89% S.

5-Cyano-4-hydroxy-3-phenyl-2-benzoylcyanomethylene-4-thiazoline (*XIII*)

A solution of *IVc* (3.9 g, 0.01 mol) in sodium ethoxide solution (0.01 mol) (prepared from sodium metal (0.23 g, 0.01 mol) and ethanol (30 ml)) was heated in a boiling water bath for 7 h. The resulting product precipitated after the dilution with water containing few drops of hydrochloric acid (till pH 6) was collected by filtration. Crystallization from ether afforded 2.1 g (65%) of compound *XIII*, m.p. 166 °C. IR spectrum: 3 560 – 3 450 (OH); 3 045 (CH aromatic); 2 225, 2 215 (C≡N); 1 690 (C=O). ^{1}H NMR spectrum: 7.32 – 7.38 m, 10 H (2 × C_6H_5); 9.92 s, 1 H (OH). For $C_{19}H_{11}N_3O_2S$ (345.4) calculated: 66.07% C, 3.21% H, 12.16% N, 9.26% S; found: 66.41% C, 3.19% H, 11.79% N, 9.49% S.

General Procedure for Preparation of Compounds *XVIIa* and *XVIIb*

To a cold solution of each of *Ia* (1.1 g, 0.01 mol) or *Ib* (0.6 g, 0.01 mol) in ethanol (30 ml) containing sodium acetate (10 g), a suspension of diazonium salt of *XVI* (prepared by the addition of sodium nitrite (0.7 g, 0.01 mol) to a cold suspension of *XV* (3.3 g, 0.01 mol) in hydrochloric acid (30 ml) under stirring) was added. The solid product formed was collected by filtration.

4-(2,2-Diacetyl-1-phenylaminoethenylthio)-3-hydroxy-5-[cyano(ethoxycarbonyl)methylazo]pyrazole (XVIIa): Crystallized from ethanol, m.p. 114 °C, yield 3.8 g (85%). IR spectrum: 3 450 – 3 320 (OH, NH); 3 050 (CH aromatic); 2 985, 2 890 (CH_3, CH_2); 2 220 (C≡N); 1 700, 1 690 – 1 680 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 1.36 s and 1.40 s, 2 × 3 H (2 × CH_3); 1.48 t, 3 H, J = 7.75 (CH_3); 3.98 q, 2 H, J = 7.75 (CH_2); 5.98 s, 1 H (CH); 6.87 s, 1 H (pyrazole H-4); 7.32 – 7.37 m, 5 H (C_6H_5); 8.86 s, 1 H (NH); 10.0 s, 1 H (OH). For $C_{20}H_{20}N_6O_5S$ (456.5) calculated: 52.62% C, 4.41% H, 18.41% N, 7.02% S; found: 52.28% C, 4.02% H, 18.69% N, 7.26% S.

4-(2,2-Diacetyl-1-phenylaminoethenylthio)-3-hydroxy-5-(dicyanomethylazo)pyrazole (XVIIb): Crystallized from dioxane, m.p. 189 °C, yield 3.5 g (87%). IR spectrum: 3 520 – 3 330 (OH, NH); 3 050 (CH aromatic); 2 975 (CH_3); 2 220, 2 215 (C≡N); 1 700, 1 680 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 1.38 s and 1.49 s, 2 × 3 H (2 × CH_3); 5.82 s, 1 H (CH); 6.89 s, 1 H (pyrazole H-4); 7.33 – 7.38 m, 5 H (C_6H_5); 8.21 s, 1 H (NH); 9.89 s, 1 H (OH). For $C_{18}H_{15}N_7O_3S$ (409.4) calculated: 52.81% C, 3.70% H, 23.95% N, 7.83% S; found: 52.66% C, 3.67% H, 23.58% N, 7.53% S.

General Procedure for Preparation of Compounds *XIXa* and *XIXb*

To a solution of *VId* (2.5 g, 0.01 mol) in N,N-dimethylformamide (30 ml) containing piperidine (0.5 ml), benzaldehyde (0.9 g, 0.01 mol) or salicylaldehyde (1.1 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 1 h and then evaporated in vacuo. The remaining product was triturated with ethanol and collected by filtration.

4-Acetyl-3-styryl-2-cyano-5-phenylaminothiophene (XIXa): Crystallized from ethanol, m.p. 285 – 288 °C, yield 2.5 g (75%). IR spectrum: 3 440 – 3 390 (NH); 3 050 (CH aromatic); 2 980 (CH_3); 2 220 (C≡N); 1 695 (C=O). ^{1}H NMR spectrum: 1.39 s, 3 H (CH_3); 6.32 d and 6.98 d, 2 × 1 H (CH=CH); 7.30 – 7.36 m, 10 H (2 × C_6H_5); 8.79 s, 1 H (NH). For $C_{21}H_{16}N_2OS$ (344.4) calculated: 73.23% C, 4.68% H, 8.13% N, 9.31% S; found: 72.87% C, 4.38% H, 8.19% N, 9.64% S.

4-Acetyl-3-(2'-hydroxystyryl)-2-cyano-5-phenylaminothiophene (XIXb): Crystallized from ethanol, m.p. > 300 °C, yield 2.9 g (82%). IR spectrum: 3 530 – 3 390 (OH, NH); 3 050 (CH aromatic); 2 970 (CH_3); 2 220 (C≡N); 1 685 (C=O). ^{1}H NMR spectrum: 1.38 s, 3 H (CH_3); 6.32 d and 6.98 d, 2 × 1 H (CH=CH); 7.32 – 7.38 m, 9 H (C_6H_5, C_6H_4); 8.57 s, 1 H (NH); 10.21 brs, 1 H (OH). For $C_{21}H_{16}N_2O_2S$ (360.4) calculated: 69.98% C, 4.47% H, 7.77% N, 8.89% S; found: 69.67% C, 4.62% H, 7.39% N, 8.82% S.

4-Acetyl-2-cyano-5-phenylamino-3-phenylhydrazonomethylthiophene (*XX*)

To a cold solution of *VId* (2.5 g, 0.01 mol) in ethanol (40 ml) containing sodium acetate (10 g), benzenediazonium chloride (prepared by the addition of a cold solution of sodium nitrite (0.7 g, 0.01 mol) to aniline (0.9 g, 0.01 mol) in concentrated hydrochloric acid (9 ml) under stirring) was added under continuous stirring for 3 h. The solid product formed was collected by filtration. Crystallization from ethanol gave 2.8 g (79%) of compound *XX*, m.p. 179 °C. IR spectrum: 3 450 – 3 370 (NH); 3 050 (CH aromatic); 2 965 (CH_3); 2 220 (C≡N); 1 660 (C=N). ^{1}H NMR spectrum: 1.39 s, 3 H (CH_3); 6.21 s, 1 H (CH=N); 7.31 – 7.36 m, 10 H (2 × C_6H_5); 8.81 s and 9.21 s, 2 × 1 H (2 × NH). For $C_{20}H_{16}N_4OS$ (360.4) calculated: 66.64% C, 4.47% H, 15.55% N, 8.89% S; found: 66.59% C, 4.06% H, 15.55% N, 8.71% S.

4-Acetyl-1-phenyl-5-phenylaminothieno[2,3-*d*]pyridazin-7-one (*XXI*)

A solution of *XX* (3.6 g, 0.01 mol) in ethanol (30 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 8 h. The solid product formed after the addition of ice/water containing few drops of hydrochloric acid (till pH 6) was collected by filtration. Crystallization from N,N-dimethylformamide afforded 2.4 g (67%) of compound *XXI*, m.p. > 300 °C. IR spectrum: 3 450 – 3 390 (NH); 3 040 (CH aromatic); 2 975 (CH_3); 1 690 (C=O); 1 660 (C=N). ^{1}H NMR spectrum: 1.39 s, 3 H (CH_3); 7.0 s, 1 H (pyridine H-3); 7.32 – 7.40 m, 10 H (2 × C_6H_5); 8.89 s, 1 H (NH). For $C_{20}H_{15}N_3O_2S$ (361.4) calculated: 66.46% C, 4.18% H, 11.62% N, 8.87% S; found: 66.37% C, 4.06% H, 11.21% N, 8.93% S.

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