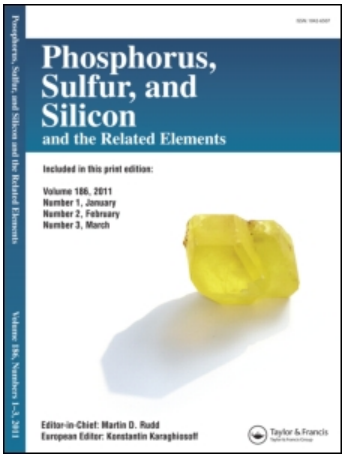

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HETEROCYCLIC SYNTHESIS WITH ISOTHIOCYANATES: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2,3-DIHYDROTHIAZOLE, 2-(PYRAZOL-4'-YL)-THIAZOLE, 5-(THIAZOL-2'-YL)PYRIMIDINE AND THIAZOLO[3,2-a]PYRIDINE DERIVATIVES

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HETEROCYCLIC SYNTHESIS WITH ISOTHIOCYANATES: A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2,3-DIHYDROTHIAZOLE, 2-(PYRAZOL-4′-YL)-THIAZOLE, 5-(THIAZOL-2′-YL)PYRIMIDINE AND THIAZOLO[3,2-a]PYRIDINE DERIVATIVES

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A facile convenient synthesis of the titled compounds, via cyclization of the non-isolable 1:1 adducts **1**, **9** and **13** with 4-bromo-2-phenylhydrazono-3-oxo-butyronitrile (**3**), is reported. Chemical and spectroscopic evidence of the newly synthesised compounds are described.

Key words: Isothiocyanates, thiazoles, β-enaminonitriles.

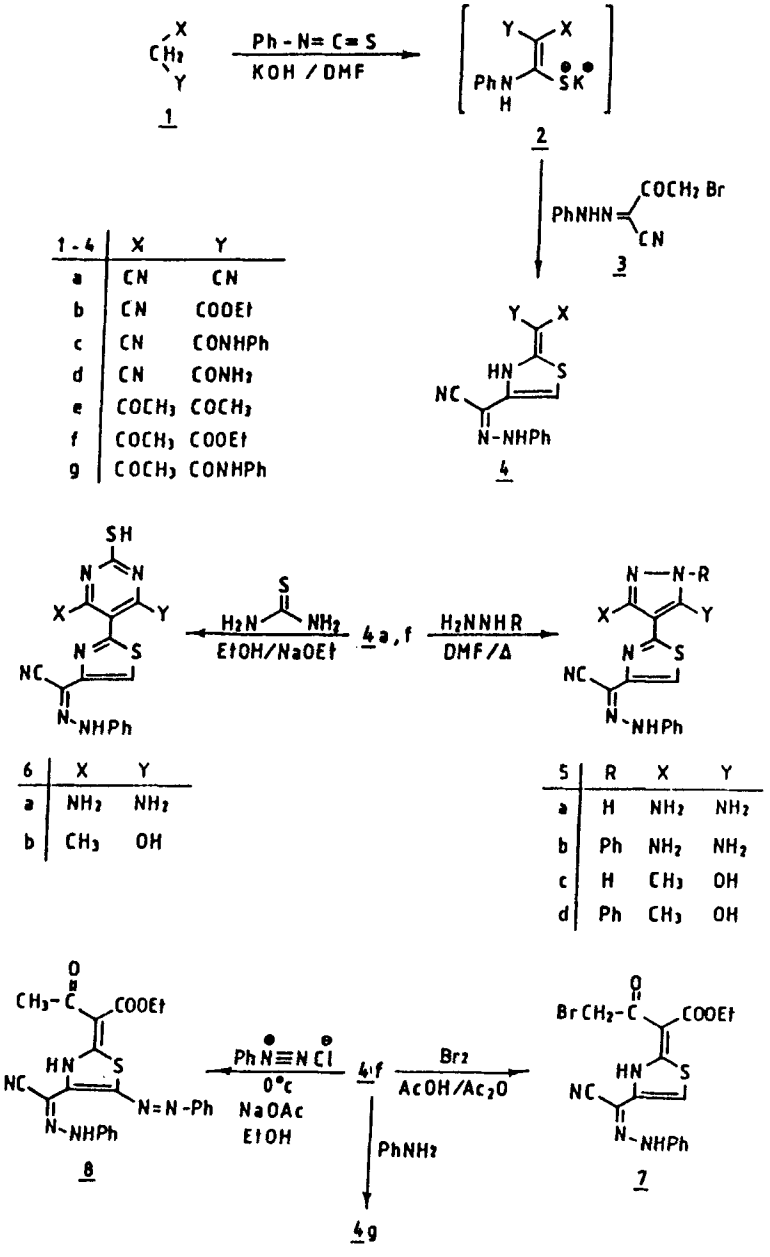
INTRODUCTION

During recent years, we have maintained a comprehensive program aimed at investigating the reaction of isothiocyanates with active methylenes followed by heterocyclization of the resultant adducts with halogenated compounds. Such synthetic route proved to be an easy, facile and sole approach for the synthesis of hitherto unreported derivatives of polyfunctionally substituted thiophenes, 2,3-dihydrothiazoles and thiazolidines.[1–5] The importance of such compounds is due to their diverse biological potential.[6–10] An extension of this synthetic route, the applicability of 4-bromo-2-phenylhydrazono-3-oxo-butyronitrile (**3**), is reported,[11] as a new reagent for the in-situ heterocyclization of such intermediate adducts. The work has resulted in the formation of several new polyfunctionally substituted 2,3-dihydrothiazoles, 2-(pyrazol-4′-yl)thiazoles, 5-(thiazol-2′-yl)pyrimidines and thiazolo[3,2-a]pyridines of expected wide spectrum biological activity. To our knowledge, a large number of heterocyclic thiazole derivatives were reported as antifungal, antibacterial and antileukemic agents.[12–17] Also, thiazolo[3,2-a]pyridinium salts were reported to have hypoglycemic activity.[18]

RESULTS AND DISCUSSION

Thus, it has been found that the base promoted nucleophilic addition of the active methylene candidates **1a–g** to equimolecular amounts of phenyl isothiocyanate in dry dimethylformamide yielded the corresponding non-isolable potassium sulfide salts **2a–g**. In-situ heterocyclization of the latter with **3** afforded products that could

be formulated as the 2,3-dihydrothiazoles **4a–g**, respectively, in reasonably good yields (cf. Scheme I). Assignment of structure **4** was established on the basis of elemental analyses, spectroscopic data and its behaviour towards some chemical reagents. Thus, the IR spectrum of **4a**, as an example, revealed the presence of NH stretching bands at 3420, 3400 cm^{-1} and three CN stretching bands at 2220, 2215 and 2210 cm^{-1}. Its ^{1}H-NMR spectrum (DMSO-d_6) revealed a singlet signal



SCHEME I

at δ 7.02 (1H) ppm characteristic for thiazole H-5, a multiplet at δ 7.33–7.48 (5H) ppm corresponding to one phenyl proton together with two D_2O-exchangeable singlets at δ 8.72 (1H) and δ 9.21 (1H) ppm corresponding to two NH functions. Formation of **4** find parallelism to similar previously reported dearylation phenomena.[19–21]

Compounds **4a–f** reacted with nitrogen nucleophiles, namely hydrazine hydrate and phenylhydrazine, in dimethylformamide solutions, under reflux, to afford the corresponding 2-(pyrazol-4′-yl)thiazole derivatives **5a–d**, respectively. Also, **4a,f** reacted with equimolecular proportions of thiourea in ethanolic sodium ethoxide solutions, on heating under reflux, to afford the corresponding 5-(thiazol-2′-yl)pyrimidine derivatives **6a,b**, respectively (cf. Scheme I). Both elemental analyses and spectral data of **5** and **6** were consistent with the assigned structures.

The methyl group in **4f** proved to be highly reactive. Thus, bromination of **4f** with bromine in acetic acid/acetic anhydride mixture furnished the corresponding monobromomethyl derivative **7**. Its ^{1}H-NMR spectrum (DMSO-d_6) revealed beside the expected signals, a singlet signal at δ 3.48 (2H) ppm attributed to the CH_2 group.

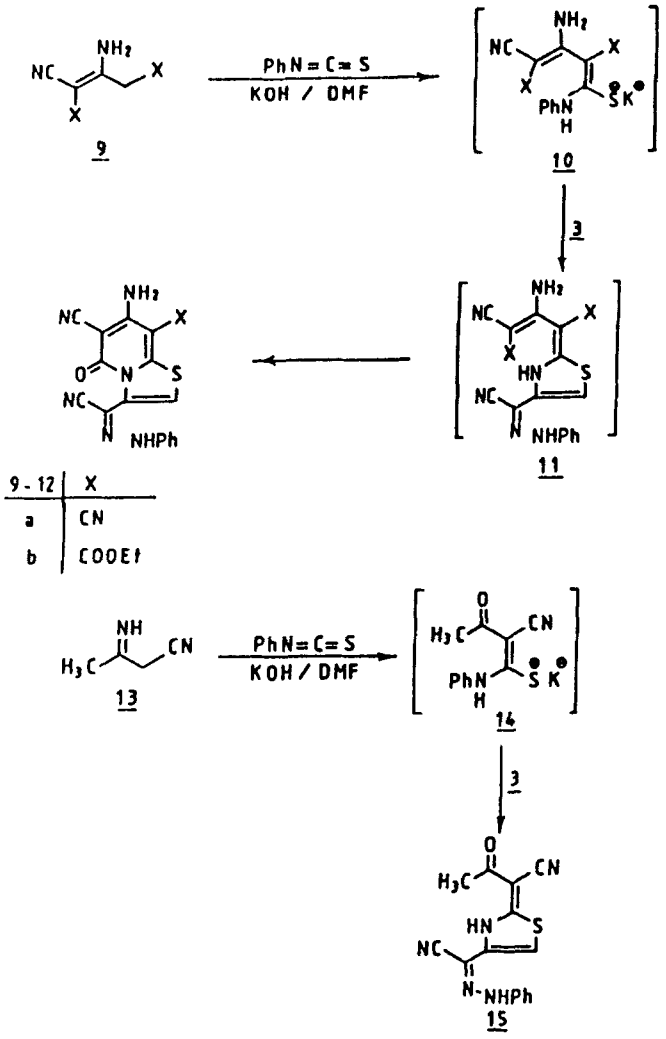
Compound **4f** underwent electrophilic substitution upon coupling with benzenediazonium chloride, at 0–5°C, to afford the corresponding 5-phenylazo derivative **8** (cf. Scheme I). The formation of 2,3-dihydro-5-(arylazo)thiazole derivatives has not been previously reported in the literature.[22–24]

Fusion of **4f** with equimolecular amount of aniline at oil bath temperature (140°C) afforded a product identical in all aspects (m.p., mixed m.p. and IR spectrum) with **4g**.

Although 3-amino-2,4-dicyanocrotononitrile (**9a**)[25] and diethyl 3-aminocrotononitrile-2,4-dicarboxylate (**9b**)[26] are interesting intermediates in heterocyclic synthesis, very little attention was paid to their potential utility for the synthesis of thiazoles and thiazolidines.[27,28] A facile and convenient applicability of **9** for the synthesis of such derivatives is reported here. Thus, the base-promoted nucleophilic addition of **9a,b** to equimolecular amounts of phenyl isothiocyanate in dry dimethylformamide at room temperature afforded the non-isolable 1:1 potassium sulfide adducts **10a,b**. In-situ heterocyclization of the latter with **3** yielded products that could be formulated as the thiazolo[3,2-a]pyridine derivatives **12a,b**, respectively. Formation of **12** was assumed to proceed via intermediate **11** (cf. Scheme II). Structure of **12** was established based on analytical and spectral data.

Although β-enaminonitriles have proven to be valuable tools in the synthesis of a wide variety of unique heterocyclic systems[29] including pyrazoles,[30] imidazoles,[31] pyridines[32] and pyrimidines,[33] no reports[4] describe its applicability for synthesis of thiazoles. Our method seems to be interesting for the preparation of such compounds with built in functional moieties for further exploitation.

The base-promoted reaction of 3-iminobutyronitrile (**13**)[34] with phenyl isothiocyanate in dry dimethylformamide at room temperature afforded the non-isolable 1:1 adduct (**14**). Treatment of the latter with an equimolecular portion of **3** furnished a single product in relatively good yield. The 2,3-dihydrothiazole structure **15** (cf. Scheme II) was assigned for the product on the basis of its correct elemental analyses and spectroscopic data. Its IR spectrum revealed the presence NH, 2 CN and CO functions at 3430, 2225, 2220 and 1690 cm^{-1}, respectively.



SCHEME II

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

5-Bromo-2-phenylhydrazono-3-oxo-butyronitrile (**3**),[11] 3-amino-2,4-dicyanocrotononitrile (**9a**),[25] diethyl 3-aminocrotononitrile-2,4-dicarboxylate (**9b**)[26] and 3-iminobutyronitrile (**13**)[34] were prepared following the literature procedures.

2,3-Dihydro-2-(disubstitutedmethylene)-4-(α-phenylhydrazonoacetonitrilo)-1,3-thiazoles **4a–g**: *General procedure*: To a solution of each of the active methylene reagents **1a–g** (0.01 mol) in dry dimethylformamide (30 ml) containing potassium hydroxide (0.01 mol) phenyl isothiocyanate (0.01 mol) was added portionwise. The reaction mixture was stirred at room temperature overnight and then **3** (0.01 mol) was added. The reaction mixture was stirred at room temperature for an additional 24 h. The solid product that formed, in each case, upon trituration with dilute hydrochloric acid (pH ≈ 7) was collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

TABLE I

Physical and analytical data of the newly prepared compounds

Compd. (Color)	Cryst. solvent	Yield %	M.p. [°C]	Mol. formula (mol. wt)	Analysis [%] Calcd./found C	H	N	S
4a (brown)	Dioxane	70	258	$C_{14}H_8N_6S$ (292.31)	57.52 57.3	2.75 3.0	28.75 28.5	10.96 10.7
4b (brown)	Dioxane	71	165	$C_{16}H_{13}N_5O_2S$ (339.36)	56.63 56.4	3.85 4.1	20.63 20.4	9.44 9.2
4c (brown)	DMF	74	268	$C_{20}H_{14}N_5OS$ (386.35)	62.17 62.0	3.64 3.4	21.75 21.8	8.30 8.0
4d (brown)	Dioxane	70	280-2	$C_{14}H_{10}N_6OS$ (310.32)	54.18 53.9	3.24 3.0	27.08 26.8	10.33 10.0
4e (yellow)	DMF	76	240	$C_{16}H_{14}N_4O_2S$ (326.36)	58.88 58.6	4.31 4.0	17.16 17.1	9.82 9.9
4f (orange)	EtOH	69	255-7	$C_{17}H_{16}N_4O_3S$ (356.38)	57.30 57.0	4.52 4.3	15.72 15.5	8.99 8.8
4g (red)	Dioxane	62	245	$C_{21}H_{17}N_5O_2S$ (403.44)	62.52 62.3	4.24 4.0	17.35 17.0	7.94 7.8
5a (orange)	EtOH	67	219	$C_{14}H_{12}N_8S$ (324.35)	51.84 51.6	3.72 3.5	34.54 34.4	9.88 9.9
5b (orange)	EtOH	65	145	$C_{20}H_{16}N_8S$ (400.44)	60.00 60.2	4.02 3.7	28.00 27.8	8.00 7.9
5c (yellow)	Dioxane	71	195	$C_{15}H_{12}N_6OS$ (324.35)	55.54 55.2	3.72 3.5	25.91 25.7	9.88 9.6
5d (orange)	Dioxane	58	245	$C_{21}H_{16}N_6OS$ (400.44)	63.00 63.2	4.02 3.8	21.00 21.3	8.00 7.9
6a (red)	Dioxane	70	260	$C_{15}H_{12}N_8S_2$ (368.43)	48.90 48.7	3.27 3.0	30.41 30.1	17.41 17.2
6b (brown)	DMF	64	240	$C_{16}H_{12}N_6OS_2$ (368.42)	52.16 52.0	3.27 3.3	22.81 22.9	17.40 17.2
7 (orange)	MeOH	73	215-7	$C_{17}H_{15}BrN_4O_3S$ (435.28)	46.91 46.7	3.47 3.6	12.87 12.6	7.36 7.1
8 (orange)	EtOH	72	220	$C_{23}H_{20}N_6O_3S$ (460.49)	60.00 60.2	4.37 4.2	18.25 18.0	6.96 6.7
12a (brown)	DMF	70	210	$C_{17}H_9N_7OS$ (359.35)	56.82 56.5	2.52 2.7	27.30 27.1	8.92 8.6
12b (yellow)	EtOH	69	190	$C_{19}H_{14}N_6O_3S$ (406.41)	56.15 56.0	3.46 3.6	20.67 20.5	7.90 7.6
15 (orange)	Dioxane	70	165	$C_{15}H_{11}N_5OS$ (309.33)	58.24 58.4	3.58 3.1	22.63 22.3	10.36 10.0

TABLE II

IR and ^{1}H NMR data for the newly prepared compounds

Compd. No.	IR (KBr) [cm^{-1}] (selected bands)	^{1}H-NMR [δ ppm]
4a	3420-3400(NH), 2220, 2215, 2210 (3 CN), 1630 (C=C)	7.02(s, 1H, thiazole H-5), 7.33-7.48(m, 5H, C_6H_5), 8.72(s, 1H, NH, D_2O-exchangeable), 9.21 (s, 1H, NH, D_2O-exchangeable)
4b	3440-3380(NH), 3050 (arom. CH), 2225, 2220 (2 CN), 1690(CO), 1660 (C=N)	1.32(t, 3H, CH_3), 4.22(q, 2H, CH_2), 7.02(s, 1H, thiazole H-5), 7.32-7.45(m, 5H, C_6H_5), 8.42, 9.39(2s, 2H, 2 NH), D_2O-exchangeable).
4c	3440-3370(NH), 3045 (arom. CH), 2220, 2215 2 CN), 1680(CO), 1640 (C=C)	7.09(s, 1H, thiazole H-5), 7.32-7.48(m, 10H, 2 C_6H_5), 8.29, 9.38, 9.45(3s, 3H, 3 NH, D_2O-exchangeable)
4d	3450-3370(NH_2, NH), 3050(arom. CH), 2225, 2220(2 CN), 1650(CO), 1640(C=C)	4.84(s, 2H, NH_2), 7.02(s, 1H, thiazole H-5), 7.30-7.45(m, 5H, C_6H_5), 8.32, 9.26(2s, 2H, 2 NH D_2O-exchaneable)
4e	3410-3365(NH), 3050 (arom. CH), 2220(CN), 1700, 1690 (2 CO), 1650 (C=N)	2.21(s, 3H, CH_3), 2.24(s, 3H, CH_3), 7.09(s, 1H, thiazole H-5), 7.32-7.56(m, 5H, C_6H_5), 8.27, 9.31(2s, 2H, 2 NH, D_2O-exchangeable)
4f	3420-3360(NH), 3040, (arom. CH), 2220(CN), 1700, 1680(2 CO), 1656 (C=N)	1.32(t, 3H, CH_3), 2.21(s, 3H, CH_3), 4.21(q, 2H, CH_2), 7.04 (s, 1H, thiazole H-5), 7.30-7.44 (m, 5H, C_6H_5), 8.22, 9.30(2s, 2H, 2 NH, D_2O-exchangeable)
4g	3440-3365(NH_2, NH), 3045(arom. CH), 2220(CN), 1700, 1685(2 CO), 1650 (C=N)	2.21(s, 3H, CH_3), 7.01(s, 1H, thiazole H-5), 7.31-7.52(m, 10H, 2 C_6H_5), 8.40, 9.25, 9.28 (3s, 3H, 3 NH, D_2O-exchangeable)
5a	3440-3360(NH_2, NH), 3045(arom. CH), 2220 (CN), 1630 (C=N)	4.71, 5.23(2s, 4H, 2 NH_2, D_2O-exchangeable), 7.05(s, 1H, thiazole H-5), 7.33-7.46(m, 5H, C_6H_5), 8.81, 9.20(2s, 2H, 2 NH, D_2O-exchangeable)
5b	3450-3320(NH_2, NH), 3050(arom. CH), 2220 (CN), 1655 (C=N)	4.82, 5.21(2s, 4H, 2 NH_2, D_2O-exchangeable), 7.08(s, 1H, thiazole H-5), 7.32-7.50(m, 10H, 2 C_6H_5), 9.21(s, 1H, NH, D_2O-exchangeable)

TABLE II (*Continued*)

Compd. No.	IR (KBr) [cm^{-1}] (selected bands)	^{1}H-NMR [δ ppm]
5c	3560-3320(OH, NH), 3050(arom. CH), 2220 (CN), 1650 (C=N)	1.98(s, 3H, CH_3), 7.12(s, 1H, thiazole H-5), 7.29-7.48(m, 5H, C_6H_5), 9.20, 9.25(2s, 2H, 2NH, D_2O-exchangeable),10.36 (s, 1H, OH, D_2O-exchangeable)
5d	3540-3300(OH, NH), 3040(arom. CH), 2220 (CN), 1650(C=N)	1.93(s, 3H, CH_3), 7.03(s, 1H, thiazole H-5), 7.33-7.49(m, 10H, 2 C_6H_5), 9.32(s, 1H, NH, D_2O- exchangeable), 10.21(s, 1H, OH, D_2O-exchangeable)
6a	3460-3320(NH_2, NH), 3050(arom. CH), 2220 (CN), 1650 (C=N)	4.92, 5.36(2s, 4H, 2 NH_2, D_2O-exchangeable), 7.02(s, 1H, thiazole H-5), 7.33-7.49(m, 5H, C_6H_5), 8.35(s, 1H, SH, D_2O-exchangeable), 9.25(s, 1H, NH, D_2O-exchangeable)
6b	3450-3320(OH, NH), 3045(arom. CH), 2220 (CN), 1650(C=N)	2.11(s, 3H, CH_3), 7.08(s, 1H, thiazole H-5), 7.30-7.48(m, 5H, C_6H_5), 9.28(s, 1H, SH, D_2O-exchangeable), 9.92(s, 1H, NH, D_2O-exchangeable), 10.28(s, 1H, OH, D_2O-exchangeable)
7	3450-3420(NH), 3050 (arom. CH), 2220(CN), 1695, 1685(2 CO)	1.33(t, 3H, CH_3), 3.48(s, 2H, CH_2), 4.21(q, 2H, CH_2), 7.05 (s, 1H, thiazole H-5), 7.32-7.47 (m, 5H, C_6H_5), 8.36, 9.21(2s, 2H, 2NH, D_2O-exchangeable)
8	3450-3380(NH), 3045 (arom. CH), 2220(CN), 1690, 1680(2 CO), 1655 (C=N)	1.36(t, 3H, CH_3), 2.21(s, 3H, CH_3), 4.21(q, 2H, CH_2), 7.31-7.47(m, 10H, 2 C_6H_5), 8.41, 9.22(2s, 2H, 2 NH, D_2O-exchangeable)
12a	3420-3400(NH_2, NH), 3045(arom. CH), 2225, 2220, 2215(3 CN), 1695 (CO).	5.38(s, 2H, NH_2), 7.04(s, 1H, thiazole H-5), 7.33-7.48(m, 5H, C_6H_5), 9.32(s, 1H, NH)
12b	3460-3420(NH_2, NH), 3045(arom. CH), 2220, 2215(2 CN), 1695(CO)	1.31(t, 3H, CH_3), 4.24(q, 2H, CH_2), 5.23(s, 2H, NH_2, D_2O-exchangeable), 7.02(s, 1H, thiazole H-5), 7.30-7.45(m, 5H, C_6H_5), 8.91(s, 1H, NH, D_2O-exchangeable)
15	3430(NH), 3050(arom. CH), 2225, 2220(2 CN), 1690(CO), 1655(C=N)	2.11(s, 3H, CH_3), 7.04(s, 1H, thiazole H-5), 7.32-7.48(m, 5H, C_6H_5), 8.22, 9.30(2s, 2H, 2NH, D_2O-exchangeable)

2,3-Dihydro-4-(α-phenylhydrazonoacetonitrilo)-2-(1',3',5'-trisubstituted-pyrazol-4'-yl)-1,3-thiazoles **5a–d**: *General procedure*: To a solution of each of **4a,f** (0.01 mol) in dimethylformamide (40 ml), hydrazine hydrate or phenylhydrazine (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h. The solid product that precipitated upon trituration the reaction mixture with dilute hydrochloric acid was filtered off and crystallized from the proper solvent (cf. Tables I and II).

4, 6-(Disubstitued)-5-[4'-(α-phenylhydrazonoacetonitrilo)-2', 3'-dihydrothiazol-2'-yl]pyrimidine-2-thiones **6a,b**: *General procedure*: To a solution of each of **4a,f** (0.01 mol) in ethanolic sodium ethoxide solution [prepared by dissolving sodium metal (0.01 mol) in absolute ethanol (50 ml)], thiourea (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, cooled at room temperature, poured onto cold water and then acidified with dilute HCl (pH ≈ 6). The solid product that precipitated in each case was collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

2-(α-Bromoacetyl-ethoxycarbonylmethylene)-2,3-dihydro-4-(α-phenylhydrazonoacetonitrilo)-1,3-thiazole (**7**): To a solution of **4f** (0.01 mol) in glacial acetic acid (20 ml) and acetic anhydride (20 ml), bromine (0.01 mol) was added dropwise with stirring at room temperature. The reaction mixture was then heated for 5 min, left to cool at room temperature and then poured onto ice/water mixture. The solid product so formed was collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

2-[Acetyl(ethoxycarbonyl)methylene]-2,3-dihydro-5-phenylazo-4-(α-phenylhydrazonoacetonitrilo)-1,3-thiazole (**8**): To a solution of **4f** (0.01 mol) in ethanol (50 ml) containing sodium acetate (3 g), benzenediazonium chloride (0.01 mol) [prepared by adding $NaNO_2$ (0.01 mol) to the appropriate quantity of cold aniline in hydrochloric acid] was added dropwise with stirring while cooling at 0–5°C. The reaction mixture was left at room temperature for 4 h while stirring whereby the solid product, so formed, was collected by filtration and crystallized from the proper solvent.

Conversion of **4f** *into* **4g**: In a dry test tube, a mixture of **4f** (0.01 mol) and aniline (0.01 mol) was heated in an oil bath (140°C) for 3 h. The reaction mixture was triturated with ethanol, whereby the solid product so formed was collected by filtration and crystallized from dioxane, yield 61%, identical in all aspects (m.p., mixed m.p. and IR spectrum) with an authentic sample of **4g** prepared as previously described.

Thiazolo[3,2-a]pyridines **12a,b**: The same experimental procedures described above for the synthesis of **4** has been followed except for using **9a,b** (0.01 mol) instead of **1**. The oily product formed after acidification with dilute HCl (pH ≈ 6) was triturated with diethyl ether, whereby the solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

2-[Acetyl(cyano)methylene]-2,3-dihydro-4(α-phenylhydrazonoacetonitrilo)-1,3-thiazole (**15**): The same experimental procedure described above for the synthesis of **12** has been followed except for using **13** (0.01 mol) instead of **9** (cf. Tables I and II).

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