Pergamon

*Tetrahedron* Vol. 50, No. 19, pp. 5807-5820, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0237-N

# Heterocyclic Synthesis with Isothiocyanates: An Expeditious Synthetic Route for Polyfunctionally Substituted 3-(Thiazol-2`-ylidene)pyridines and Their Fused Derivatives

**Rafat M. Mohareb,* Hussein F. Zohdi, Sherif M. Sherif and Wagnat W. Wardkhan**

Department of Chemistry, Faculty of Science, University of Cairo, Giza, A.R.Egypt

**Abstract:** The reaction of phenyl isothiocyanate with the Knovenagel condensated active methylene compounds **1a-d** gave the non-isolable salts **3a-d**. The latter underwent in-situ heterocyclization on treatment with some halogenated compounds e.g. phenacyl bromide, ethyl bromoacetate, ɣ-bromoacetoacetanilide, ethyl ɣ-bromoacetoacetate and ɣ-bromo-ß-oxo-butyronitrile into the corresponding polyfunctionally substituted 3-(thiazol-2`-yliene)pyridine derivatives, which could also be annulated into fused heterocyclic ring systems. Chemical and spectroscopic evidences for the structure of the new compounds are described.

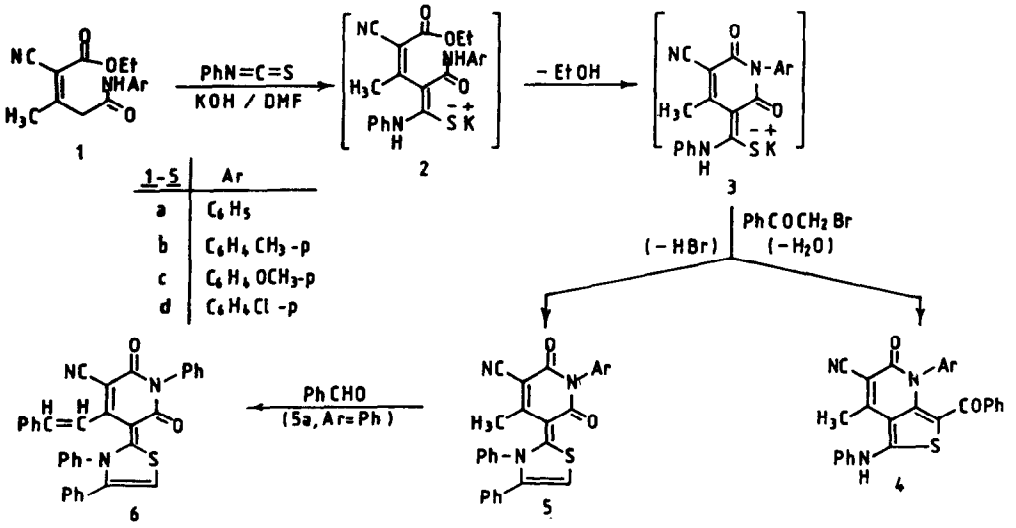
Previously, we have investigated the reaction of isothiocyanates with active methylenes followed by heterocyclization of the resulted adducts with α-halogenated compounds. Such synthetic route proved to be an easy, facile and sole approach for the synthesis of hitherto unreported derivatives of polyfunctionally substituted thiophenes, 2,3-dihydrothiazoles and thiazolidines.[1-6] The importance of such derivatives is due to their diverse biological and physiological potentialities as they are known to exhibit nematocidal,[7] antiprotozoal,[8] bactericidal[9] and hypoglycemic activity.[10] As an extension of such synthetic route, we wish to report herein on the scope and applicability of the Knovenagel condensated products **1a-d**, prepared by us,[11] for their heterocyclization with some α-halogenated compounds. The work has resulted in the formation of several new polyfunctionally substituted 3-(thiazol-2`-ylidene)pyridines. The latter could also be annulated into fused heterocyclic ring systems of expected wide spectrum of biological activities.

Thus, the base-promoted nucleophilic addition of the acidic Knovenagel condensated candidates **1a-d** to equimolecular amounts of phenyl isothiocyanate in dry dimethylformamide at room temperature afforded the non-isolable potassium sulphide salts **3a-d.** In-situ heterocyclization of the latter with phenacyl bromide yielded

products that could be formulated as the thieno[3,4-b]pyridine derivatives **4** or the isomeric 3-(thiazol-2`-ylidene)pyridine derivatives **5**. Structure **4** was ruled out based on IR and $^1$H NMR spectra which revealed the absence of the NH function. The 3-(thiazol-2`-ylidene)pyridine structure **5** was established for the reaction products on the basis of spectral data. Thus the $^1$H NMR spectrum of **5a**, as an example, revealed two singlet signals at δ 2.11 (3H) and 6.79 (1H) ppm assigned for the $CH_3$ and the thiazole H-5 protons, respectively, together with a multiplet signal at δ 7.32-7.58 (15H) corresponding to the aromatic protons.

The presence of the methyl group in the ortho-position to an electron withdrawing group showed an interesting activity towards electrophilic reagents.[12,13] Thus, compound **5a** was condensed with benzaldehyde on boiling, under reflux, in dimethylformamide in presence of a catalytic amount of piperidine to afford the corresponding benzal derivative **6**.

Unexpectdly, compound **5a** underwent regioselective electrophilic substitution upon coupling with benzenediazonium chloride at the active methyl group rather than the thiazole C-5 position[2,14,15] to afford the corresponding phenylhydrazone derivative **7** (cf. Scheme 2). Structure **7** was proved to be in the hydrazo form rather than the azo form on the basis of its $^1$H NMR spectrum which revealed the absence of any protons attached to $sp^3$ carbons and the presence of a singlet signal at δ 8.21 (1H, NH) which disappeared upon shaking the NMR sample with deuterium oxide. Compound **7** readily underwent intramolecular cyclization when boiled, under reflux, in ethanolic sodium ethoxide solution to afford the corresponding pyrido[4,3-d]pyridazine derivative **8**. The IR spectrum of **8** revealed the absence of CN function. When compound **8** was boiled in ethanolic sodium hydroxide solution, the imino group could be hydrolysed into an oxo group[16,17] to afford the corresponding 1-oxo-pyrido[4,3-d]pyridazine derivative **9**. Both elemental analyses and spectral data are in agreement with the proposed structure **9**. Thus, its IR and $^1$H NMR spectra revealed the absence of the NH function.



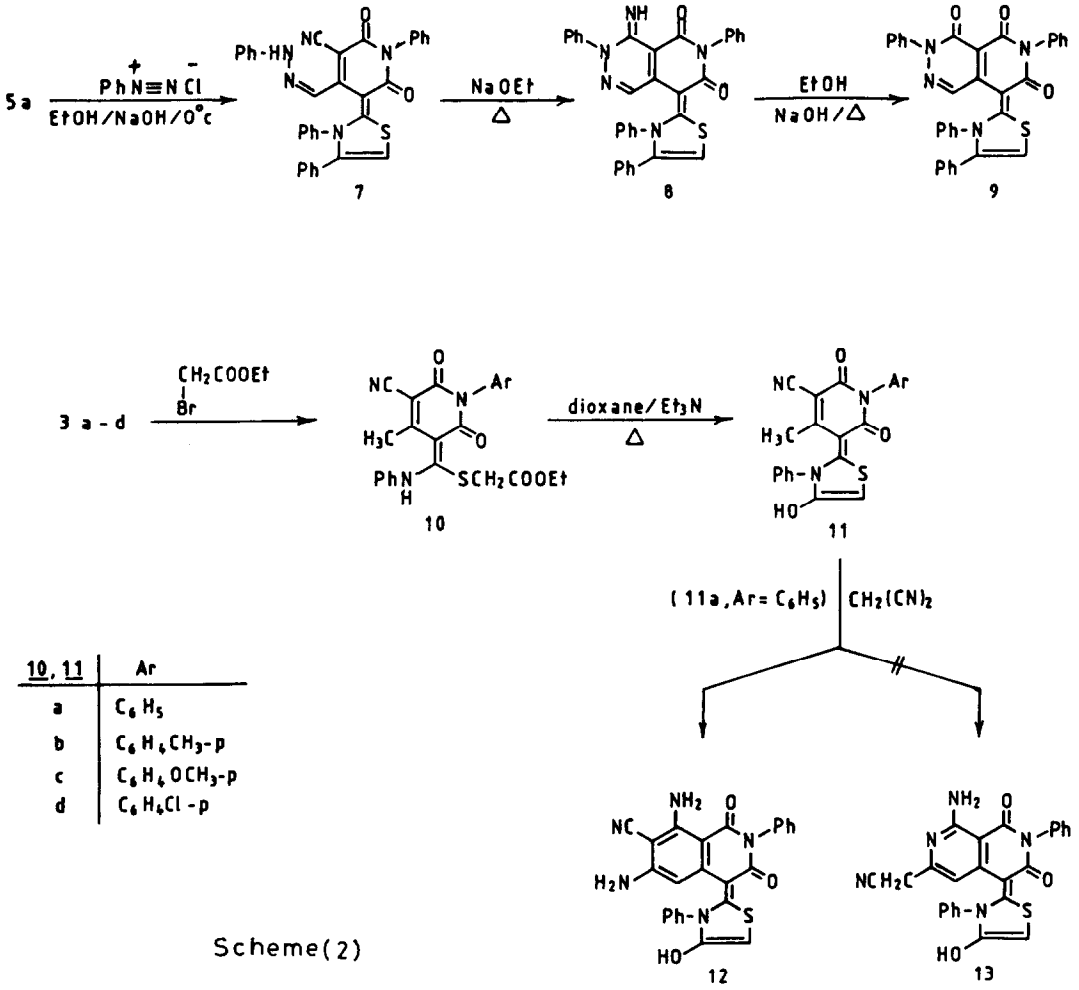

Scheme (1)

The applicability and generality of the non-isolable potassium sulphide salts **3a-d** for the synthesis of polyfunctionally substituted thiazole derivatives was further explored. Thus, treatment of **3a-d** with equimolecular amounts of ethyl bromoacetate at room temperature afforded the corresponding monocyclic S-alkylated products **10a-d**, respectively. Assignment of structure **10** was based on correct analytical data and compatible spectral data. Compounds **10a-d** could be cyclized, on boiling under reflux in dioxane containing a catalytic amount of triethylamine, into the corresponding 3-(4`-hydroxythiazol-2`-ylidene)pyridines **11a-d** via loss of ethanol. Compound **11a** reacted with malononitrile, upon reflux in dimethylformamide/piperidine solution, to afford a product that analyzed for $C_{25}H_{17}N_5O_3S$ ($M^+$/e = 467, 20%). Two possible isomeric structures **12** and **13** were considered (cf. Scheme 2). Structure **12** was established for the reaction product based on its $^1H$ NMR spectrum which revealed the absence of any protons attached to $sp^3$ carbons that would be expected to appear if we had structure **13.**

Similarly, the non-isolable salts **3a-d** reacted with ϑ-bromoacetoacetanilide (**14**)[18] to afford the 3-(3`-phenylcarbamidomethyleno-thiazol-2`-ylidene)pyridines **15a-d** in reasonablly good yields (cf. Scheme 3). Assignment of structure **15** for such products was based on analytical and spectroscopic data beside a chemical proof. Thus, treatment of the intermediate salts **3a-d** with ethyl ϑ-bromoacetoacetate(**16**)[19] afforded the expected cyclized products **17a-d**. Fusion of the latter with aniline at oil bath temperature (160°C) afforded products identical in all aspects (m.ps., mixed m.ps. and IR spectra) with **15a-d,** respectively.

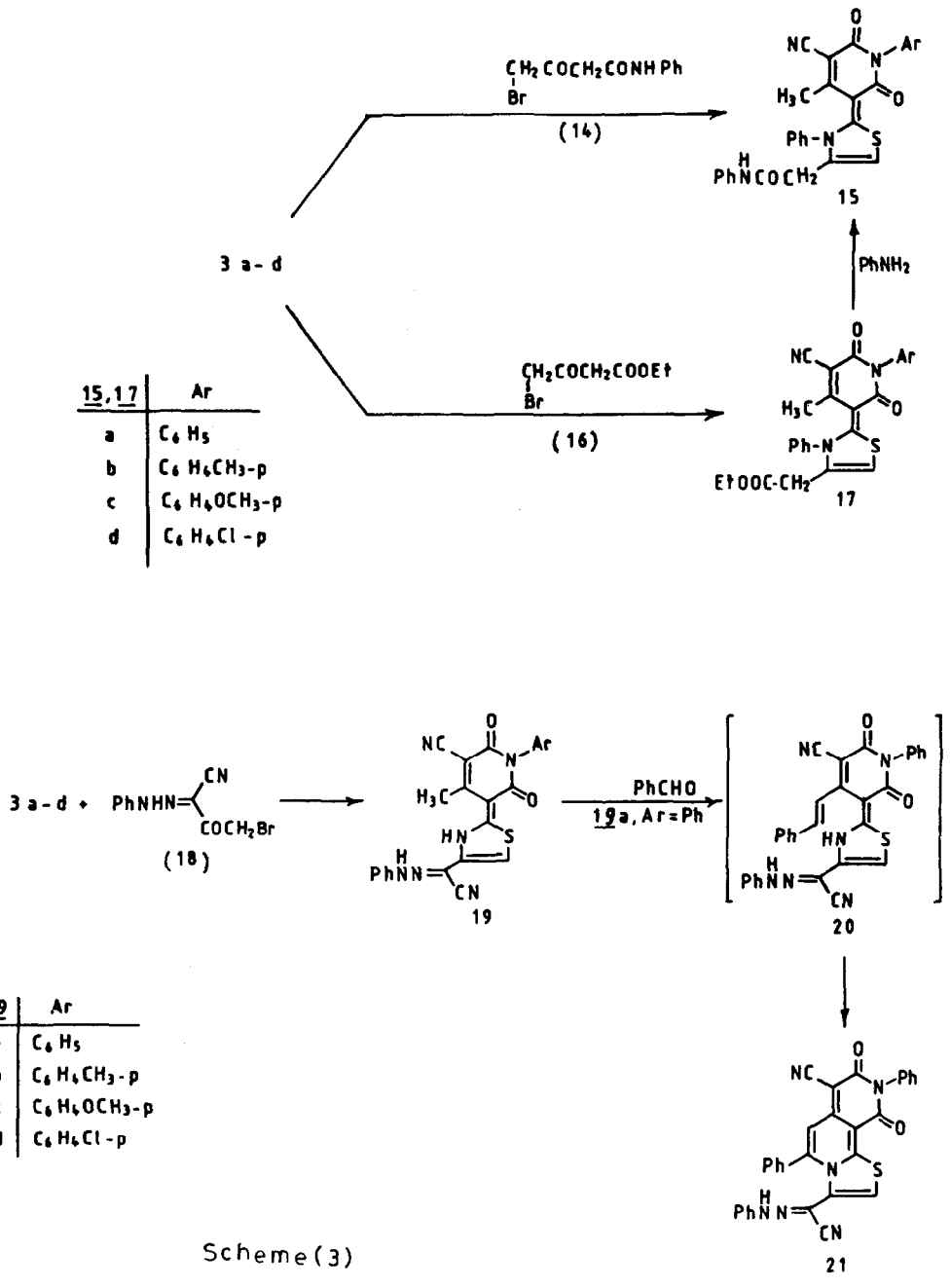
In contrast to the behaviour of the intermediate salts **3a-d** towards some halogenated compounds, treatment of **3a-d** with ϑ-bromo-ß-oxobutyronitrile (**18**)[20], under the same experimental conditions, furnished the corresponding dearylated products **19a-d,** respectively. Formation of **19** find parallelism to similar reported dearylation phenomena.[21,22] Structure **19** was established for the reaction products based on elemental analyses and compatible spectroscopic data. Thus, the mass spectrum of **19a,** as an example, revealed a molecular ion peak at m/e 452 (15%). Its $^1H$ NMR spectrum showed, in addition to the expected singlet signals attributed to the methyl and thiazole H-5 protons, a multiplet at δ 7.32-7.49 (10H) corresponding to two phenyl protons together with two $D_2O$-exchangeable singlets at δ 8.21 (1H) and 9.01 (1H) corresponding to two NH functions.

Again, the methyl group in compound **19** proved to be highly active. Thus, compound **19a** condensed with benzaldehyde, upon reflux in dimethylformamide in presence of a catalytic amount of piperidine, to yield the corresponding thiazolo[3,2-a]pyrido[3,4-c]pyridine derivative **21.** Formation of **21** was considered to proceed via intermediacy of the styryl derivative **20** followed by intramolecular cyclization and aromatization via autoxidation under the reaction conditions. Similar autoxidation have been previously reported.[23-25]




| 10, 11 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4CH_3$-p |
| c | $C_6H_4OCH_3$-p |
| d | $C_6H_4Cl$-p |

Scheme(2)


3 a-d
CH2COCH2CONHPh
Br
(14)
15
PhNH2
CH2COCH2COOEt
Br
(16)
17
15,17 | Ar
a | C6H5
b | C6H4CH3-p
c | C6H4OCH3-p
d | C6H4Cl-p
3 a-d + PhNHN=C(CN)COCH2Br
(18)
19
PhCHO
19a, Ar=Ph
20
21
19 | Ar
a | C6H5
b | C6H4CH3-p
c | C6H4OCH3-p
d | C6H4Cl-p

Scheme (3)

## EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. $^1$H NMR spectra were recorded on a Wilmad 270 MHz spectrometer and chemical shifts are expressed in δ (ppm) units using TMS as internal reference. Ms spectra were recorded on an AEI MS 30 mass spectrometer operating at 70 eV. Microanalytical data were obtained from the Microanalytical Data Center at Cairo University.

**1-Aryl-2,6-dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methylpyridine-5-carbonitriles 5a-d.** To a cold suspension of finally ground potassium hydroxide (0.57 g, 0.01 mol) in dimethylformamide (30 ml), the appropriate active methylene compound **1a-d** (0.01 mol) was added and subsequently phenyl isothiocyanate (1.3 g, 0.01 mol). The reaction mixture was then stirred at room temperature for 24 h then treated with phenacyl bromide (2.0 g, 0.01 mol) and left at room temperature for additional 24 h. The reaction mixture was then triturated with cold water (50 ml) and acidified slightly with dilute hydrochloric acid (pH = 6.5). The resulting precipitated solid was collected by filtration, washed with water, dried and crystallized from the proper solvent.

**2,6-Dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-1-phenylpyridine-5-carbonitrile (5a):** yield 3.6 g (79%), m.p. 226-7°C (dioxane). Ms ($M^+$/e) = 461. -IR : $\bar{\nu}$ = 3050 (CH arom.), 2220 (CN), 1705, 1695 (2 CO).-$^1$H-NMR (DMSO-$d_6$) : δ (ppm) = 2.11 (s, 3H, $CH_3$), 6.79 (s, 1H, thiazole H-5), 7.32-7.58 (m, 15H, aromatic protons). Found: C 72.6 H 4.0 N 9.3 S 6.8. Calcd. for $C_{28}H_{19}N_3O_2S$ (461.51) C 72.87 H 4.14 N 9.10 S 6.94.

**2,6-Dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-1-(p-tolyl)pyridine-5-carbonitrile (5b):** yield 3.5 g (74%), m.p. 268-9°C (dioxane). - IR: $\bar{\nu}$ = 3025 (CH arom.), 2215 (CN), 1705, 1695 (2 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.13 (s, 3H, $CH_3$), 2.82 (s, 3H, $CH_3$), 6.90 (s, 1H, thiazole H-5), 7.31-7.60 (m, 14H, aromatic protons). Found: C 73.4 H 4.3 N 8.6 S 6.6. Calcd. for $C_{29}H_{21}N_3O_2S$ (475.58) C 73.24 H 4.44 N 8.83 S 6.74.

**2,6-Dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-(p-methoxyphenyl)-4-methylpyridine-5-carbonitrile (5c):** yield 3.6 g (73%), m.p. > 300°C (DMF). -IR : $\bar{\nu}$ = 3050 (CH arom.), 2220 (CN), 1710, 1685 (2 CO).- $^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.12 (s, 3H, $CH_3$), 4.13 (s, 3H, $OCH_3$), 6.73 (s, 1H, thiazole H-5), 7.33-7.65 (m, 14H, aromatic protons). Found: C 70.6 H 4.4 N 8.3 S 6.6 Calcd. for $C_{29}H_{21}N_3O_3S$ (491.5) C 70.86 H 4.30 N 8.54 S 6.52.

**1-(p-Chlorophenyl)-2,6-dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methylpyridine-5-carbonitrile (5d):** yield 3.6 g (74%), m.p. 201-2°C (DMF). -IR : $\bar{\nu}$ = 3040 (CH arom.), 2220 (CN), 1715, 1695 (2 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.17 (s, 3H, $CH_3$), 6.80 (s, 1H,

thiazole H-5), 7.33-7.69 (m, 14H, aromatic protons). Found: C 67.6 H 3.4 N 8.1 S 6.4. Calcd. for $C_{28}H_{18}ClN_3O_2S$ (495.96) C 67.81 H 3.65 N 8.47 S 6.46.

**4-Benzalmethino-2,6-dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-phenylpyridine-5-carbonitrile (6):** To a solution of **5a** (4.75 g, 0.01 mol) in dimethylformamide (30 ml) containing a catalytic amount of piperidine (0.5 ml), benzaldehye (0.9 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then evaporated in vacuo. The remaining product was triturated with ethanol, collected by filtration, dried and crystallized from DMF, yield 3.7 g (68%), m.p. 166°C. -IR :$\bar{\nu}$= 3050 (CH arom.), 2220 (CN), 1700, 1690 (2 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 6.79 (s, 1H, thiazole H-5), 6.99, 7.21 (2d, 2H, CH=CH), 7.32-7.61 (m, 20H, aromatic protons). Found: C 76.4 4.3 N 7.7 S 5.4. Calcd. for $C_{35}H_{23}N_3O_2S$ (549.62) C 76.48 H 4.21 N 7.64 S 5.83.

**2,6-Dioxo-3-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-phenyl-4-phenylhydrazonomethyl-pyridine-5-carbonitrile (7).** To a cold solution of **5a** (4.7 g, 0.01 mol) in ethanol (50 ml) containing sodium hydroxide (10 ml, 10%), benzenediazonium chloride (0.01 mol) [prepared by adding concentrated hydrochloric acid (3 ml) to aniline (0.9 g, 0.01 mol) at 0-5°C followed by treating the resulting hydrochloride salt with a cold solution of sodium nitrite (0.7 g, 0.01 mol) in water (6 ml)] was added dropwise with stirring at 0-5°C. The reaction mixture was stirred at room temperature for 3 h and the precipitated crude product was filtered off, dried and crystallized from ethanol, yield 3.8 g (69%), m.p. 172-3°C. -IR : $\bar{\nu}$= 3430 (NH), 3050 (CH arom.), 2220 (CN), 1715, 1690 (2 CO), 1665 (C=N). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 5.98 (s, 1H, CH=N), 6.82 (s, 1H, thiazole H-5), 7.32-7.68 (m, 20H, aromatic protons), 8.21 (s, 1H, NH, $D_2O$-exchangeable). Found: C 72.2 H 4.3 N 12.5 S 5.5. Calcd. for $C_{34}H_{23}N_5O_2S$ (565.63) C 72.19 H 4.10 N 12.38 S 5.66.

**6,8-Dioxo-2,7-diphenyl-5-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-imino-pyrido[4,3-d]pyridazine (8).** A solution of **7** (5.6 g, 0.01 mol) in ethanolic sodium ethoxide solution (0.01 mol) [prepared by adding sodium metal (0.23 g, 0.01 mol) to absolute ethanol (20 ml)] was heated on a boiling water bath for 7 h. The solid product, so formed on dilution the reaction mixture with water, was collected by filtration, dried and crystallized from DMF, yield 3.2 g (58%), m.p. >300°C. -IR : $\bar{\nu}$ = 3420 (NH), 3045 (CH arom.), 1700, 1690 (2 CO), 1680 (exocyclic C = N).- $^1$H-NMR (DMSO-$d_6$): δ (ppm) = 6.83 (s, 1H, thiazole H-5), 7.03 (s, 1H, pyridazine H-3), 7.32 - 7.73 (m, 20H, aromatic protons), 8.21 (s, 1H, NH, $D_2O$-exchangeable). Found: C 72.4 H 3.9 N 12.4 S 5.4. Calcd. for $C_{34}H_{23}N_5O_2S$ (565.63). C 72.19 H 4.10 N 12.38 S 5.66.

**2,7-Diphenyl-5-(3`,4`-diphenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1,6,8-trioxo-pyrido-[4,3-d]pyridazine (9).** A solution of **8** (5.6 g, 0.01 mol) in ethanol (40 ml) containing sodium hydroxide (0.5 g) was boiled under reflux for 8 h. The reaction mixture was then poured onto ice/water and slightly acidifed with dilute hydrochloric acid (pH = 6.5) whereby the solid product so formed was collected by filtration, dried and crystallized from dioxane, yield 3.8 g (71%), m.p. >300°C. -IR : $\bar{\nu}$ = 3050 (CH arom.) 1700, 1690, 1675 (3 CO), 1660 (C=N).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 6.80 (s, 1H, thiazole H-5), 7.19 (s, 1H, pyridazine H-3), 7.32-7.65 (m, 20H, aromatic prrotons). Found: C 72.0 H 4.1 N 9.6 S 5.7. Calcd. for $C_{34}H_{22}N_4O_3S$ (566.60) C 72.07 H 3.91 N 9.88 S 5.65.

**3-[Anilino-(ethoxycarbonylmethylthio)-carboylidene]-1-aryl-2,6-dioxo-4-methyl-pyridine-5-carbonitriles 10a-d.** The same experimental procedures described above for the synthesis of **5a-d** has been followed, except for adding ethyl bromoacetate (1.7 g, 0.01 mol) instead of phenacyl bromide. After leaving the reaction mixture at room temperature for 24 h, it was poured onto cold water (40 ml) and slightly acidified with dilute hydrochloric acid (pH = 6.5). The reaction product was then extracted from the aqueous layer by diethyl ether (3 x 50 ml). The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo whereby the solid product so formed was collected by filtration and crystallized from the proper solvent.

**3-[Anilino-(ethoxycarbonylmethylthio)-carboylidene]-2,6-dioxo-4-methyl-1-phenyl-pyridine-5-carbonitrile (10a):** yield 3.1 g (72%), m.p. 145°C (EtOH). Ms ($M^+$/e = 447) -IR : $\bar{\nu}$ = 3430 (NH), 3050 (CH arom.), 2220 (CN), 1700, 1690, 1680 (3 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 1.16 (t, 3H, J = 7.99 Hz, $CH_3$), 2.12 (s, 3H, $CH_3$), 3.92 (s, 2H, $CH_2$), 4.45 (q, 2H, J = 7.95 Hz, $CH_2$), 7.33-7.59 (m, 10H, aromatic protons), 8.29 (s, 1H, NH, $D_2O$-exchangeable). Found: C 64.3 H 4.6 N 9.3 S 7.0. Calcd. for $C_{24}H_{21}N_3O_4S$ (447.48) C 64.42 H 4.72 N 9.38 S 7.16.

**3-[Anilino-(ethoxycarbonylmethylthio)-carboylidene]-2,6-dioxo-4-methyl-1-(p-tolyl)-pyridine-5-carbonitrile (10b):** yield 3.4 g (74%), m.p. 210°C (EtOH). - IR : $\bar{\nu}$ = 3430 (NH), 3050 (CH arom.), 2220 (CN), 1700, 1690, 1680 (3 CO).- $^1$H-NMR (DMSO-$d_6$) : δ (ppm) = 1.16 (s, 3H, J = 8.11 Hz, $CH_3$), 2.12 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 4.02 (s, 2H, $CH_2$), 4.44 (q, 2H, J = 8.11 Hz, $CH_2$), 7.32-7.69 (m, 9H, aromatic protons), 8.31 (s, 1H, NH, $D_2O$-exchangeable). Found: C 65.2 H 4.8 N 9.3 S 7.0. Calcd. for $C_{25}H_{23}N_3O_4S$ (461.51) C 65.06 H 5.02 N 9.10 S 6.94.

**3-[Anilino-(ethoxycarbonylmethylthio)-carboylidene]-2,6-dioxo-1-(p-methoxyphenyl)-4-methylpyridine-5-carbonitrile (10c):** yield 3.7 (79%), m.p. 193°C (dioxane). -IR : $\bar{\nu}$ = 3425 (NH), 3045 (CH arom.), 2220 (CN), 1705, 1690, 1680 (3 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 1.18 (t, 3H, J = 8.28 Hz, $CH_3$), 2.18 (s, 3H, $CH_3$), 3.98 (s, 3H, $OCH_3$), 4.08 (s, 2H, $CH_2$), 4.46 (q, 2H, J = 8.28 Hz, $CH_2$), 7.30-7.59 (m, 9H, aromatic protons), 8.39 (s, 1H, NH, $D_2O$-exchangeable). Found: C 63.0 H 4.7 N 8.6 S 6.9. Calcd. for $C_{25}H_{23}N_3O_5S$ (477.51) C 62.88 H 4.85 N 8.80 S 6.71.

**3-[Anilino-(ethoxycarbonylmethylthio)-carboylidene]-1-(p-chlorophenyl)-2,6-dioxo-4-methylpyridine-5-carbonitrile (10d):** yield 3.3 g (69%), m.p. 268-9°C (DMF). - IR : $\bar{\nu}$= 3450 (NH), 3050 (CH arom.), 2220 (CN), 1710, 1690, 1680 (3 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 1.18 (t, 3H, J = 7.89 Hz, $CH_3$), 2.16 (s, 3H, $CH_3$), 4.07 (s, 2H, $CH_2$), 4.49 (q, 2H, J = 7.89 Hz, $CH_2$), 7.30-7.57 (m, 9 H, aromatic protons), 8.36 (s, 1H, NH, $D_2O$-exchangeable). Found: C 59.7 H 4.3 N 8.9 S 6.6. Calcd. for $C_{24}H_{20}ClN_3O_4S$ (481.93) C 59.81 H 4.17 N 8.72 S 6.65.

**1-Aryl-2,6-dioxo-3-(4`-hydroxy-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-pyridine-5-carbonitriles 11a-d.** A solution of each of **10a-d** was boiled under reflux for 2 h then the solvent was evaporated in vacuo. The solid product, so formed, upon trituration with diethyl ether was collected by filtration, dried and crystallized from the proper solvent.

**2,6-Dioxo-3-(4`-hydroxy-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-1-phenyl-pyridine-5-carbonitrile (11a):** yield 2.8 g (70%), m.p. 205-6°C (DMF). Ms ($M^+$/e = 401).-IR : $\bar{\nu}$ = 3620-3430 (OH), 3050 (CH arom.), 2220 (CN), 1690, 1685 (2 CO). - $^1$H-NMR (DMSO-$d_6$) : δ (ppm) = 2.21 (s, 3H, $CH_3$), 6.98 (s, 1H, thiazole H-5), 7.32-7.55 (m, 10H, aromatic protons), 9.93 (s, 1H, OH, $D_2O$-exchangeable). Found: C 65.7 H 3.5 N 10.4 S 7.7. Calcd. for $C_{22}H_{15}N_3O_3S$ (401.42) C 65.82 H 3.76 N 10.46 S 7.98.

**2,6-Dioxo-3-(4`-hydroxy-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-1-(p-tolyl)-pyridine-5-carbonitrile (11b):** yield 3.0 g (72%), m.p. 199°C (dioxane).- IR: $\bar{\nu}$ = 3575 - 3325 (OH), 3045 (CH arom.), 2220 (CN), 1700, 1680 (2 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.22 (s, 3H, $CH_3$), 2.76 (s, 3H, $CH_3$), 6.89 (s, 1H, thiazole H-5), 7.30-7.60 (m, 9H, aromatic protons), 9.32 (s, 1H OH, $D_2O$-exchangeable). Found C 66.4 H 3.8 N 9.9 S 7.7. Calcd. for $C_{23}H_{17}N_3O_3S$ (415.45) C 66.49 H 4.12 N 10.11 S 7.72.

**2,6-Dioxo-3-(4`-hydroxy-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-(p-methoxy-phenyl)-4-methylpyridine-5-carbonitrile (11c):** yield 3.3 g (78%), m.p. 233-5°C (dioxane). -IR : $\bar{\nu}$ = 3620-3320 (OH), 3050 (CH arom.), 2220 (CN), 1700, 1680 (2 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.19 (s, 3H, $CH_3$), 3.99 (s, 3H, $OCH_3$), 6.81 (s, 1H, thiazole H-5), 7.30-7.49 (m, 9H, aromatic protons), 9.22 (s, 1H, OH, $D_2O$-exchangeable). Found: C 63.8 H 4.2 N 9.5 S 7.2. Calcd. for $C_{23}H_{17}N_3O_4S$ (431.45) C 64.03 H 4.00 N 9.74 S 7.43.

**1-(p-Chlorophenyl)-2,6-dioxo-3-(4`-hydroxy-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methylpyridine-5-carbonitrile (11d):** yield 2.5 g (59 %), m.p. 233-4°C (DMF). -IR : $\bar{\nu}$ = 3580-3325 (OH), 3050 (CH arom.), 2220 (CN), 1710, 1685 (2 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.18 (s, 3H, $CH_3$), 6.87 (s, 1H, thiazole H-5), 7.29-7.65 (m, 9H, aromatic protons), 9.29 (s, 1H, OH, $D_2O$-

exchangeable). Found: C 60.4 H 3.0 N 9.6 S 7.1. Calcd. for $C_{22}H_{14}ClN_3O_3S$ (435.86) C 60.62 H 3.23 N 9.6 S 7.35.

**6,8-Diamino-1,3-dioxo-4-(4`-hydroxy-3`-phenylthiazol-2`-ylidene)-2-phenyl-isoquinoline-7-carbonitrile (12).** To a solution of **11a** (4.0 g, 0.01 mol) in dimethylformamide (30 ml) containing piperidine (0.5 ml), malononitrile (0.7 g, 0.01 mol) was added. The reaction mixture was boiled, under reflux, for 8 h then poured onto ice/water containing few drops of hydrochloric acid (pH = 6.5). The solid product so formed was filtered off, dried and crystallized from DMF, yield 2.4 g (52%), m.p. > 300°C. Ms ($M^+$/e = 467). - IR : $\bar{\nu}$= 3560-3360) (OH & $NH_2$), 3050 (CH arom.), 2220 (CN), 1690-1675 (2 CO).-$^1$H-NMR (DMSO-$d_6$) : δ (ppm) = 3.87 (s, 2H, $NH_2$, $D_2O$-exchangeable), 4.21 (s, 2H, $NH_2$, $D_2O$-exchangeable), 6.95 (s, 1H, thiazole H-5), 7.31-7.56 (m, 11H, aromatic protons), 9.34 (s, 1H, OH, $D_2O$-exchangeable). Found: C 64.0 H 3.8 N 15.0 S 6.7. Calcd. for $C_{25}H_{17}N_5O_3S$ (467.48) C 64.23 H 3.66 N 14.98 S 6.85.

**1-Aryl-2,6-dioxo-4-methyl-3-(3`-phenyl-4`-phenylcarbanilidomethyl-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitriles 15a-d.**

**Method A.** The same experimental procedures described above for the synthesis of **5a-d** has been followed except using ω-bromoacetoacetanilide (**14**) (2.5 g, 0.01 mol) instead of phenacyl bromide.

**2,6-Dioxo-4-methyl-1-phenyl-3-(3`-phenyl-4`-phenylcarbanilidomethyl-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (15a):** yield 3.2 g (65%), m.p. 213-4°C (dioxane). Ms ($M^+$/e = 518). -IR : $\bar{\nu}$ = 3420 (NH), 3050 (CH arom.), 2220 (CN), 1710, 1690, 1680 (3 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.13 (s, 3H, $CH_3$), 4.25 (s, 2H, $CH_2$), 6.91 (s, 1H, thiazole H-5), 7.30-7.61 (m, 15H, aromatic protons), 8.75 (s, 1H, NH, $D_2O$-exchangeable). Found: C 69.4 H 4.2 N 10.9 S 6.3. Calcd. for $C_{30}H_{22}N_4O_3S$ (518.56) C 69.50 H 4.27 N 10.80 S 6.18.

**2,6-Dioxo-4-methyl-3-(3`-phenyl-4`-phenylcarbanilidomethyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-(p-tolyl)pyridine-5-carbonitrile (15b):** yield 3.2 g (61%), m.p. 218-9°C (dioxane). -IR:$\bar{\nu}$= 3425 (NH), 3040 (CH arom.), 2220 (CN), 1710, 1695, 1680 (3 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) 2.22 (s, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 4.28 (s, 2H, $CH_2$), 6.94 (s, 1H, thiazole H-5), 7.30-7.63 (m, 14H, aromatic protons), 9.02 (s, 1H, NH, $D_2O$-exchangeable). Found: C 69.7 H 4.4 N 10.4 S 6.0. Calcd. for $C_{31}H_{24}N_4O_3S$ (532.60) C 69.91 H 4.53 N 10.52 S 6.02.

**2,6-Dioxo-1-(p-methoxyphenyl)-4-methyl-3-(3`-phenyl-4`-phenylcarbanilidomethyl-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (15c):** yield 3.3 g (60%), m.p. 160-1°C (dioxane). -IR : $\bar{\nu}$= 3450 (NH), 3050 (CH arom.), 2225 (CN), 1715, 1690, 1680 (3 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.29 (s, 3H, $CH_3$), 4.02 (s, 3H, $OCH_3$), 4.30 (s, 2H, $CH_2$), 6.96 (s, 1H, thiazole H-5), 7.29-7.58 (m, 14H, aromatic protons), 9.03 (s, 1H, NH, $D_2O$-exchangeable). Found: C 67.6 H 4.2 N 10.4 S 5.8.

Calcd. for $C_{31}H_{24}N_4O_4S$ (548.59) C 67.88 4.40 N 10.21 S 5.84.

**1-(p-Chlorophenyl)-2,6-dioxo-4-methyl-3-(3`-phenyl-4`-phenylcarbanilidomethyl-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (15d):** yield 2.7 g (50%), m.p. 213-4°C (DMF). -IR : $\bar{\nu}$ = 3440 (NH), 3050 (CH arom.), 2220 (CN), 1715, 1695, 1675 (3 CO). -$^1$H-NMR (DMSO-$d_6$) δ (ppm) = 2.23 (s, 3H, $CH_3$), 4.37 (s, 2H, $CH_2$), 6.92 (s, 1H, thiazole H-5), 7.30-7.53 (m, 14H, aromatic protons), 9.02 (s, 1H, NH, $D_2O$-exchangeable). Found: C 65.0 H 3.6 N 10.2 S 5.9. Calcd. for $C_{30}H_{21}ClN_4O_3S$ (553.01) C 65.15 H 3.82 N 10.13 S 5.83.

**Method B. 1-Aryl-2,6-dioxo-3-(4`-ethoxycarbonylmethyl-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methylpyridine-5-carbonitriles 17a-d.** To a cold suspension of finally ground potassium hydroxide (0.57 g, 0.01 mol) in dimethylformamide (30 ml), the appropriate active methylene compound **1a-d** (0.01 mol) was added and subsequently phenyl isothiocyanate (1.3 g, 0.01 mol). The reaction mixture was then stirred at room temperature for 24 h and then treated with ethyl ϰ-bromoacetoacetate (**16**) (2.1 g, 0.01 mol). The whole mixture was heated at 60°C for 4 h then stirred at room temperature overnight. The oily product, formed upon dilution with water (50 ml) containing few drops of hydrochloric acid (pH = 6.5), was extracted using diethyl ether (3x 50 ml). The organic layer was dried ($MgSO_4$), the solvent was evaporated in vacuo and the solid product formed upon trituration with ethanol was collected by filtration and crystallized from the proper solvent.

**2,6-Dioxo-3-(4`-ethoxycarbonylmethyl-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methyl-1-phenylpyridine-5-carbonitrile (17a):** yield 2.8g (60%), m.p. 280-1°C (EtOH). Ms ($M^+$/e = 471). -IR : $\bar{\nu}$ = 3050 (CH arom.), 2220 (CN), 1690, 1680, 1670 (3 CO). -$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 1.31 (t, 3H, J = 8.25 Hz, $CH_3$), 2.25 (s, 3H, $CH_3$), 4.20 (s, 2H, $CH_2$), 4.45 (q, 2H, J = 8.45 Hz, $CH_2$), 6.89 (s, 1H, thiazole H-5), 7.32-7.48 (m, 10H, aromatic protons). Found C 66.3 H 4.3 N 9.0 S 6.7. Calcd. for $C_{26}H_{21}N_3O_4S$ (471.51) C 66.23 4.48 N 8.91 S 6.80.

**2.6-Dioxo-3-(4`-ethoxycarbonylmethyl-3`-phenyl-2`,3`-dihydro-thiazol-2`-yliene)-4-methyl-1-( p-tolyl)pyridine-5-carbonitrile (17b):** yield 3.4 g ( 72 %), m.p. > 300°C ( dioxane). - IR : $\bar{\nu}$ $\bar{\nu}$ =3050 (CH aram.), 2220 (CN) , 1695, 1680, 1670 (3 CO).- $^1$H-NMR (DMSO-$d_6$) : δ (ppm) =1.30 (t, 3H, J = 8.01 Hz, $CH_3$), 2.20 (s, 3H, $CH_3$), 2.70 (s, 3H, $CH_3$), 4.29 (s, 2H, $CH_2$), 4.45 (q, 2H, J = 7.01 Hz, $CH_2$), 6.87 (s, 1H, thiazole H- 5), 7.30 - 7.74 (m, 9H, aromatic protons). Found C 66.7 H 5.O N 8.4 S 6.8 Calcd. for $C_{27}H_{23}N_3O_4S$ (485.53) C 66,79 H 4.77 N 8.65 S 6.60.

**2,6-Dioxo-3-(4`-ethoxycarbonylmethyl-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-1-(p-methoxyphenyl)-4-methylpyridine-5-carbonitrile (17c):** yield 3.1 g (62%), m.p. 188°C (DMF). - IR : $\bar{\nu}$ = 3045 (CH arom.), 2225 ( CN), 1700, 1690, 1680 (3 CO). - $^1$H-NMR (DMSO-$d_6$) : δ (ppm) = 1.32 (t, 3H, J = 7.91 Hz, $CH_3$), 2.89 (s, 3H, $CH_3$), 3.98 ( s, 3H, $OCH_3$), 4.30 (s, 2H, $CH_2$), 4.51 (q, 2H, J = 7.91 Hz, $CH_2$), 6.86 (s, 1H, thiazole H-5), 7.32 -7.50 (m, 9H, aromatic protons). Found C 64.8 H 4.4 N

8.2 S 6.0. Calcd. for $C_{27}H_{23}N_3O_5S$ ( 501.53) C 64.66 H 4.59 N 8.37 S 6.39.

**1-(p-Chlorophenyl)-2,6-dioxo-3-(4`-ethoxycarbonylmethyl-3`-phenyl-2`,3`-dihydro-thiazol-2`-ylidene)-4-methylpyridine-5-carbonitrile (17d)**: yield 5.3 g ( 71%), m.p. 245-6°C (dioxane).- IR : $\bar{\nu}$ = 3020 (CH arom.), 2220 (CN), 1690, 1680, 1670 (3 CO).-$^1$H-NMR ( DMSO -$d_6$) : δ (ppm) = 1.3 (t, 3H, J = 7.88 Hz, $CH_3$), 2.98 (s, 3H, $CH_3$), 4.32 (s, 2H, $CH_2$), 4.53 (q, 2H, J = 7.88 Hz, $CH_2$) , 6.91 (s, 1H, thiazole H-5), 7-35-7.52 (m, 9H, aromatic protons). Found: C 61.7 H 4.0 N 8.4 S 6.6. Calcd. for $C_{26}H_{20}Cl\ N_3O_4S$ (505.95) C 61.75 H 4.00 N 8.30 S 6.33.

**Conversion of 17a-d into 15a-d.** Equimolecular amounts (0.05 mol) of each of the appropriate **17a-d** and aniline was heated on an oil bath at 160°C for 3 h. The reaction mixture was triturated with ethanol, whereby the solid product so formed, in each case, was filtered off and crystallized from the proper solvent. The products, were found to be identical in all aspects (m.ps, m.m.ps and IR spectra) with **15a-d**, respectively prepared according to method A.

**1-Aryl-2,6-dioxo-4-methyl-3-(4`-phenylhydrozonoacetonitrilo-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbanitriles 19a-d.** The same experimental procedures described above for the synthesis of **5a-d** has been followed up except for using ɣ-bromo-β-oxobutyronitrile (**18**) instead of phenacyl bromide.

**2,6-Dioxo-4-methyl-1-phenyl-3-(4`-phenylhydrozonoacetonitrilo-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (19a)**: yield 2.3 g (52%), m.p. 220-1°C (EtOH). Ms ( $M^+$/e = 452).- IR : $\bar{\nu}$ = 3420, 3415 (NH), 3050 (CH arom), 2220 (CN), 1690, 1675 (2 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.22 (s, 3H, $CH_3$), 6.66 (s, 1H, thiazole H-5), 7.32-7.49 (m, 10H, aromatic protons), 8.21 (s, 1H, NH, $D_2O$-exchangeable), 9.01 (S,1H, NH, $D_2O$-exchangeable). Found: C 63.5 H 4.0 N 18.6 S 7.0. Calcd. for $C_{24}H_{16}N_6O_2S$ ( 452 .49) C 63.71 H 3.56 N 18.75 S 7.08.

**2,6-Dioxo-4-methyl-3-(4`-phenylhydrazonoacetonitrilo-2`,3`-dihydro-thiazol-2`-ylidene)-1-(p-tolyl)pyridine-5-carbonitrile (19b)**: yield 3.6 g (80%), m.p. 288-9°C (EtOH).-IR: $\bar{\nu}$ = 3430, 3420 (NH), 3050 (CH arom.), 2220 (CN), 1700, 1685 (2 CO).-$^1$H-NMR (DMSO-$d_6$): δ (ppm) = 2.23 (s, 3H, $CH_3$), 2.77 (s, 3H, $CH_3$), 6.99 (s, 1H, thiazole H-5), 7.31 - 7.47 (m, 9H, aromatic protons), 8.20 (s, 1H, NH, $D_2O$-exchangeable), 9.01 (s, 1H, NH, $D_2O$-exchangeable). Found C 64.7 H 4.1 N 17.7 S 6.6 Calcd. for $C_{25}H_{18}N_6O_2S$ (466.53) C 64.36 H 3.90 N 18.01 S 6.87.

**2,6-Dioxo-1-(p-methoxyphenyl)-4-methyl-3-(4`-phenylhydrazonoacetonitrilo-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (19c)**: yield 3.7 g (77%), m.p. 170-2°C (dioxane/EtOH).-IR: $\bar{\nu}$ = 3425, 3415 (NH), 3040 (CH arom.), 2225 (CN), 1700, 1680 (2 CO).- $^1$H-NMR ( DMSO-$d_6$) : δ (ppm) = 2.93 (s, 3H, $CH_3$), 4.11 (s, 3H, $OCH_3$), 6.97 (s, 1H, thiazole H-5), 7.32-7.52 (m, 9H, aromatic protons), 8.22 (s, 1H, NH, $D_2O$-exchangeable), 8.98 (s, 1H, NH, $D_2O$-exchangeable). Found C 62.0

H 3.8 N 17.9 S 6.4. Calcd. for $C_{25}H_{18}N_6O_3S$ (482.48) C 62.23 H 3.75 N 7.42 S 6.64.

**1-(p-Chlorophenyl)-2,6-dioxo-4-methyl-3-(4`-phenylhydrazonoacetonitrilo-2`,3`-dihydro-thiazol-2`-ylidene)pyridine-5-carbonitrile (19d):** yield 4.1 g (8%), m.p. 152°C (DMF). -IR: $\bar{\nu}$= 3430, 3405 (NH), 3045 (CH arom.), 2225 (CN), 1690, 1680 (3 CO).-$^1$H-NMR (DMSO-$d_6$) : δ (ppm)= 2.93 (s, 3H, $CH_3$), 6.69 (s, 1H, thiazole H-5), 7.33 -7.53 (m, 9H, aromatic protons), 8.22 (s, 1H, NH, $D_2O$-exchangeable), 9.05 (s, 1H, NH, $D_2O$-exchangeable). Found: C 59.5 H 3.1 N 17.5 S 6.4. Calcd. for $C_{24}H_{15}ClN_6O_2S$ (486. 91) C 59.20 H 3.10 N 17.25 S 6.58.

**Thiazolo[3,2-a]pyrido[3,4-c]pyridine derivative (21)** . To a solution of **19a** (4.5 g, 0.01 mol) in dimethylformamide (50 ml) containing piperidine (0.5 ml), benzaldehyde (1.1 g, 0.01mol) was added. The reaction mixture was heated under reflux for 6 h then evaporated in vacuo. The solid product so formed upon trituration with diethyl ether was collected by filtration, dried and crystallized from dioxane. yield 3.7 g (69%), m.p.> 300°C. -IR: $\bar{\nu}$ = 3450 (NH), 3050 (CH arom.), 2225, 2220 (2 CN) , 1690, 1680 (2 CO).-$^1$H-NMR ( DMSO-$d_6$): δ (ppm) = 6.93 (s, 1H, thiazole H-5), 7.30 - 7.53 (m, 16H, aromatic protons+ pyridine H-3), 8.59 (s, 1H, NH, $D_2O$-exchangeable). Found : C 69.0 H.3.6 N 15.4 S 5.5.90 Calcd. for $C_{30}H_{18}N_6O_2S$ (538.56) C 69.13 H 3.36 N 15.60 S 5.95.

**ACKNOWLEDGEMENTS**. R. M. Mohareb is greatly indebted for his fellowship support by the Alexander von Humboldt Foundation in Erlangen, Germany.

## REFERENCES

1. Mohareb, R. M.; Sherif, S. M. Arch. Pharm. (Weinheim), **1991**, 324, 469.
2. Mohareb, R. M.; Sherif, S. M.; Abdel-Aal, F. A.; Sayed, N.I.A. Liebigs Ann. Chem., **1991**, 1143.
3. Mohareb, R. M.; Sherif, S. M.; Zohdi, H. F. J. Chin. Chem. Soc., **1993**, 40, 181.
4. Mohareb, R. M.; Sherif, S. M. Sulfur Lett., **1992**, 15, 91.
5. Mohareb, R. M., Monat. Chem., **1992**, 123, 341.
6. El-Kousy, S. M.; Mohareb, R. M.; Sherif, S. M. J. Chem. Res. (S), **1993**, 312; (M), **1993**, 1981.
7. Rao, R. P.; Singh, S. R. J. Indian Chem. Soc., **1973**, 50, 492.
8. Mallick, S. K.; Martin, A. R.; Lingard, R. G. J. Med. Chem., **1971**, 14, 528.
9. Dhal, P. N.; Achary, T. E.; Nayak, A. Indian J. Chem., **1975**, 13, 753.
10. Burton, W. H., Budde, W.L., Cheng, C. C. J. Med. Chem., **1970**, 13, 1009.
11. Habashi, A.; Ibrahim, N.S.; Sherif, S. M.; Shams, H. Z.; Mohareb, R. M. Heterocycles, **1986**, 24, 2463.
12. Abdel-Galil, F. M.; Elnagdi, M. H. Liebigs Ann. Chem., **1987**, 477.
13. Elnagdi, M. H.; Ibrahim, N. S.; Sadek, K. U.; Mohamed, M. H. Liebigs Ann. Chem., **1988**, 1005.
14. Newkome, G. R.; Nayak, A. Adv. Heterocycl. Chem., **1979**, 25, 84.
15. Raasch, M. S. J. Heterocycl. Chem., **1974**, 11, 587.
16. Sato, K.; Amakasu, T. J. Org. Chem., **1968**, 33, 2446.
17. Methcohn, O.; Tarnowski, B. Synthesis, **1978**, 56.
18. Ali, M. I.; Abou-State, M. A.; Hassan N. M. Indian J. Chem., **1973**, 4.

19. Momose, T.; Toyooka, N.; Takeuchi, Y. Heterocycles, **1986**, 24, 1429.
20. Mohareb, R. M.; Abdel-Sayed, N. I. Collect. Czech. Chem. Commun., **1992**, 57, 1758.
21. Harb, A. A.; Hussein, A. M.; Metwally, S. A.; Elnagdi, M. H. Liebigs Ann. Chem., **1989**, 585.
22. Mohareb, R. M.; Shams, H. Z.; Aziz, S. I. J. Chem. Res. (S), **1992**, 154; (M), **1992**, 1132.
23. Soto, J. L.; Seoane, C.; Zammorano, P.; Javier, F. Synthesis, **1981**, 529.
24. Yamanaka, H.; Ohba, S.; Konno, S. Heterocycles, **1987**, 26. 2853.
25. Figueras, J. J. Org. Chem., **1966**, 31, 803.

(*Received in UK* 14 *February* 1994; *accepted* 11 *March* 1994)