Reaction of Thioglycolic Acid with *N*-Cyanoacetoarylsulphonylhydrazides: Novel Synthesis of 2-(*N*-Acetoarylsulfonylhydrazide)-2-thiazolin-4-ones and Their Corresponding Thiazolo[2,3-a]pyridines

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Abstract: The novel 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolin-4-ones **4** and their corresponding thiazolo[2,3-a]pyridine derivatives **10** were prepared by the reaction of arylsulphonylcyanoacetohydrazides **2** with thioglycolic acid followed by condensation with arylmethylidinemalononitriles **6**.

As a part of our program directed for development of an efficient procedure for the synthesis of azoles and fused azoles of potential biological activity [1-3], we have previously reported several new approaches for the synthesis of condensed heterocycles utilizing the 2-substituted methyl azolyl derivatives as starting materials[4,5]. In the present part we are reported the utility of reactions of arylsulphonylcyanoacetohydrazides with thioglycolic acid for the synthesis of 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolen-4-ones. Moreover, the scope and limitation of our procedure for the synthesis of thiazoles are also reported. Thus, it has been found that arylsulphonylcyanoacetohydrazides **2** react with thioglycolic acid in refluxing pyridine for 2h to give a condensation products **4** by water elimination. The analytical data for the product **4a** revealed a molecular formula $C_{11}H_{11}N_3S_2O_4$ (M^+ 313). Two tautomeric structures were considered in solutions. The structure of the 2-functionally substituted methyl-2-thiazoline-4-one form was readily rolled out based on ^{1}H NMR spectra, which revealed one proton signal at δ = 5.49 ppm. This signal can be only interpreted in terms of the 2-substituted methylidine form. The formation of **4** by the reaction of **2** with thioglycolic acid is assumed to proceed via the intermediacy of **3**, which formed by addition of thioglycolic acid to the cyano group in compounds **2**. Compounds **4** bearing latent functional substituents were found useful to synthesize its fused ring derivatives. Thus, compounds **4** readily reacted with aldehydes in refluxing ethanol containing a catalytic amount of piperidine in a 1 : 2 molar ratio to give the corresponding diarylidine derivatives **5**. Compounds **4** reacted with arylmethylidinemalononitriles **6** to yield products for which structures **8-10** were assigned. The possibility that the reaction products are the pyranothiazoles **8** resulting from the cyclization of **7** was eliminated based on the IR spectrum which revealed, in each case, two bands for two carbonyl groups. Also, structure **9** was rolled out based on ^{1}H NMR spectra, which revealed a pyridine H-4 signal at 4.8-5.1 ppm. This signal can only interpreted in terms of the structure **10**.

Moreover, the IR spectrum revealed the presence of two carbonyl groups. The formation of **10** by the reaction of **4** with **6** may be assumed to proceed via formation of 1 : 2 Micheal adduct intermediates **7**, which cyclize with loss of malononitrile to give compounds **10**. Analytical data for compound **10g** revealed a molecular formula $C_{29}H_{23}N_5S_2O_4$ (M^+ 569). ^1H NMR spectroscopy was used to confirm this structure for the product. Thus, ^1H NMR spectra for **10g** revealed the presence of a singlet band at δ = 4.89 ppm assigned to the pyridine H-4 proton and three broad bands at δ = 6.55, 10.82 and 12.2 ppm assignable to the NH_2 and two NH groups, respectively. Compounds **10** could also be obtained via direct reaction of **5** with malononitrile. In summary, we have achieved a regiospecific synthesis of novel 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolin-4-ones and their corresponding thiazolo[2,3-a]pyridine derivatives. The products obtained are currently under biological evaluation studies.

EXPERIMENTAL

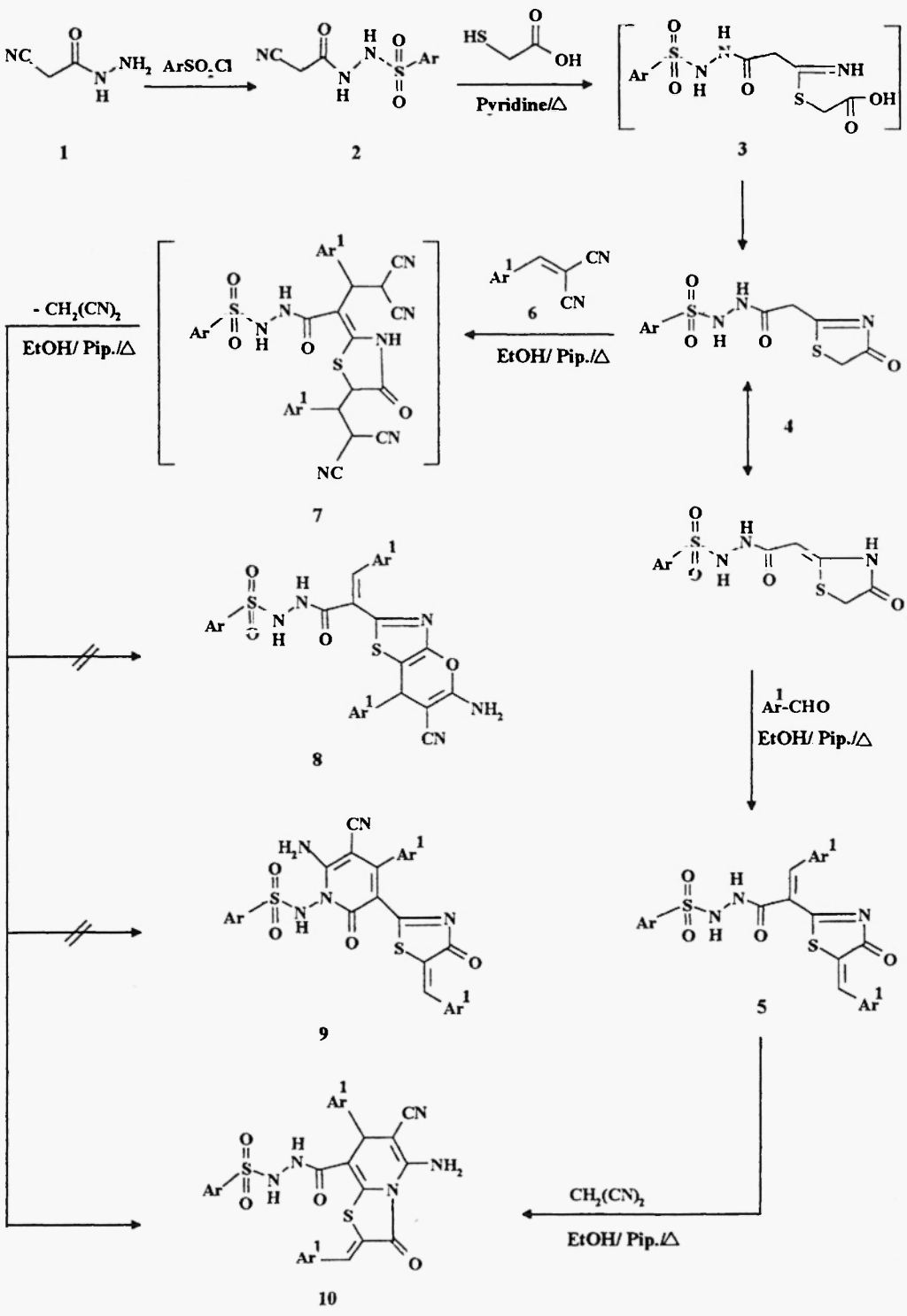
All melting points are uncorrected. IR spectra were obtained (KBr disk) on a Perkin Elmer 11650 FT-IR instrument. The ^1H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2$ SO using $Si(CH_3)_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo Univerisity.

2-Arylsulphonylhydrazidomethyl-2-thiazoline-4-ones (4a-b)

General procedure:

A mixture of an equimolar amounts of arylsulphonylhydrazides **2** and mercaptoacetic acid was refluxed in pyridine solution for 2 h. The reaction mixture was then cooled, poured over ice-water mixture and neutralized with dil. HCl solution. The formed solid product was filtered off and recrystallized from ethanol.

4a: Buff (50 %), m. p. 270 °C, ν_{max} / cm^{-1} (KBr) 3454 and 3055 (NH), 1736 (CO) and 1680 (CO) ^1H NMR (DMSO): δ = 3.62 (s, 2H, CH_2), 5.49 (s, 1H, CH), 7.55-7.80 (m, 5H, C_6H_5), 9.70 (s, br, 1H, NH), 9.80 (s, br, 1H, NH) and 11.37 (s, br, 1H, NH); ^{13}C NMR (DMSO): δ = 31.98 (CH_2), 89.07 (CH), 127.57-132.85 (C_6H_5); 165.51 (C-2), 174.07 (2CO), m/z 313 (Calcd for $C_{11}H_{11}N_3S_2O_4$: C, 42.2, H, 3.5, N, 13.4; S, 20.4. Found: C, 41.7; H, 3.1; N, 13.6, S, 20.8 %). **4b**: Buff (55 %), m. p. 240 °C, ν_{max} / cm^{-1} (KBr) 3564 and 3228 (NH), 1707 (CO) and 1655 (CO); ^1H NMR (DMSO): δ = 2.38 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 5.49 (s, 1H, CH), 7.35-7.68 (m, 5H, C_6H_4), 9.60 (s, br, 1H, NH), 9.70 (s, br, 1H, NH) and 11.35 (s, br, 1H, NH); ^{13}C NMR (DMSO): δ = 21.06 (CH_3), 31.98 (CH_2), 89.16 (CH), 127.63-129.30 (C_6H_4), 165.52 (C-2), 174.06 (2CO); m/z 327 (Calcd for $C_{12}H_{13}N_3S_2O_4$: C, 44.0; H, 4.0; N, 12.8; S, 19.6. Found: C, 43.8; H, 3.5; N, 13.1; S, 20.0 %).


ArSO2Cl
Pyridine/△
- CH2(CN)2
EtOH/ Pip./△
EtOH/ Pip./△
Ar1-CHO
EtOH/ Pip./△
CH2(CN)2
EtOH/ Pip./△
1
2
3
4
5
6
7
8
9
10

5, 10	Ar	Ar^1	5, 10	Ar	Ar^1
a	C_6H_5	C_6H_5	g	4-H_3C-C_6H_4	C_6H_5
b	C_6H_5	4-Cl-C_6H_4	h	4-H_3C-C_6H_4	4-Cl-C_6H_4
c	C_6H_5	2-Cl-C_6H_4	i	4-H_3C-C_6H_4	2-Cl-C_6H_4
d	C_6H_5	4-H_3C-C_6H_4	j	4-H_3C-C_6H_4	4-H_3C-C_6H_4
e	C_6H_5	4-H_3CO-C_6H_4	k	4-H_3C-C_6H_4	4-H_3CO-C_6H_4
f	C_6H_5	4-NO_2-C_6H_4	l	4-H_3C-C_6H_4	4-NO_2-C_6H_4

2, 4	Ar
a	C_6H_5
b	4-H_3C-C_6H_4

2,5-Disubistituted Thiazolidine-4-ones (5a-l)

General procedure:

A mixture of 2-arylsulphonylhydrazidomethyl-2-thiazoline-4-ones 4 (0.01 mole) and the aldehyde derivative (0.02 mole) was refluxed for 1h in ethanol solution containing the catalytic amount of pipridine. The reaction mixture was cooled and the formed solid product was filtered off and recrystallized from ethanol.

5a: Yellow (80 %), m. p. 200 °C, ν_{max} / cm^{-1} (KBr) 3220 and 3180 (NH), 1710 (CO) and 1655 (CO); m/z 489 (Calcd for $C_{25}H_{19}N_3S_2O_4$: C, 61.3; H, 3.9; N, 8.6; S, 13.1. Found: C, 60.1; H, 3.5; N, 9.1; S, 13.5 %). **5b**: Brown (80 %), m. p. 270 °C, ν_{max} / cm^{-1} (KBr) 3208 and 3100 (NH), 1700 (CO) and 1664 (CO); m/z 558 (Calcd for $C_{25}H_{17}N_3S_2O_4Cl_2$: C, 53.8; H, 3.0; N, 7.5; S, 11.5. Found: C, 53.5; H, 3.5; N, 7.2; S, 11.1 %). **5c**: Yellow (85 %), m. p. 250 °C, m/z 558 (Calcd for $C_{25}H_{17}N_3S_2O_4Cl_2$: C, 53.8; H, 3.0; N, 7.5; S, 11.5. Found: C, 53.3; H, 3.5; N, 7.1; S, 11.2 %). **5d**: Brown (85 %), m. p. 240 °C, ν_{max} / cm^{-1} (KBr) 3240 and 3195 (NH), 1705 (CO) and 1655 (CO); m/z 517 (Calcd $C_{27}H_{23}N_3S_2O_4$: C, 62.7; H, 4.4; N, 8.1; S, 12.4. Found: C, 62.5; H, 4.0; N, 8.5; S, 13.0 %). **5e**: Brown (80 %), m. p. 270 °C, m/z 549 (Calcd for $C_{27}H_{23}N_3S_2O_6$: C, 59.0; H, 4.2; N, 7.7; S, 11.7 %. Found: C, 58.7; H, 4.4; N, 8.1; S, 11.3 %). **5f**: Yellow (75 %), m. p. 220 °C, ν_{max} / cm^{-1} (KBr) 3400 and 3075 (NH), 1697 (CO) and 1664 (CO); m/z 579 (Calcd for $C_{25}H_{17}N_5S_2O_8$: C, 51.8; H, 2.9; N, 12.1; S, 11.1. Found: C, 51.4; H, 2.4; N, 12.5; S, 11.5 %). **5g**: Yellow (70 %), m. p. 210 °C, ν_{max} / cm^{-1} (KBr) 3217 and 3068 (NH), 1706 (CO) and 1650 (CO) m/z 503 (Calcd for $C_{26}H_{21}N_3S_2O_4$: C, 62.0; H, 4.2; N, 8.3; S, 12.7 %. Found: C, 61.6; H, 4.6; N, 8.5; S, 13.1 %). **5h**: Yellow (70 %), m. p. 240 °C, ν_{max} / cm^{-1} (KBr) 3208 and 3050 (NH), 1719 (CO) and 1664 (CO); m/z (Calcd for $C_{26}H_{19}N_3S_2O_4Cl_2$: C, 54.4; H, 3.3; N, 7.3; S, 11.2. Found: C, 54.0; H, 2.8, N, 7.8; S, 11.1 %). **5i**: Yellow (70 %), m. p. 240 °C, m/z 572 (Calcd for $C_{26}H_{19}N_3S_2O_4Cl_2$: C, 54.4; H, 3.3; N, 7.3; S, 11.2. Found: C, 54.2; H, 3.6; N, 7.1; S, 11.4 %). **5j**: Yellow (70 %), m. p. 235 °C, ν_{max} / cm^{-1}

(KBr) 3208 and 3050 (NH), 1719 (CO) and 1664 (CO); m/z 531 (Calcd for $C_{28}H_{25}N_3S_2O_4$: C, 63.3; H, 4.7; N, 7.9; S, 12.1. Found: C, 62.8; H, 4.3; N, 8.3; S, 12.5 %). **5k**: Yellow (80 %), m. p. > 300 °C, ν_{max} / cm^{-1} (KBr) 3400 and 3054 (NH), 1706 (CO) and 1665 (CO); m/z 563 (Calcd for $C_{28}H_{25}N_3S_2O_6$: C, 59.7; H, 4.4; N, 7.5; S, 11.4. Found: C, 59.3; H, 4.5; N, 8.0; S, 11.2 %). **5l**: Yellow (85 %), m. p. 230 °C, ν_{max} / cm^{-1} (KBr) 3410 and 3074 (NH), 1697 (CO) and 1650 (CO); ^1H NMR (DMSO): δ = 2.38 (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 7.65-8.42 (m, 12H, $3C_6H_4$), 9.60 (s, br, 1H, NH), 9.70 (s, br, 1H, NH), 10.24 (s, 1H, Yledinic CH) and 11.40 (s, br, 1H, NH) ^{13}C NMR (DMSO): δ = 21.95 (CH_3), 31.98 (CH_2), 124.29-130.29 ($3C_6H_4$), 140.0 (CH Yledinic), 174.05 (C-2) and 192.35 (2CO); m/z 593 (Calcd for $C_{26}H_{19}N_5S_2O_8$: C, 53.5; H, 3.3; N, 12.5; S, 11.4. Found: C, 53.0; H, 3.0; N, 12.6; S, 11.0 %).

4-Amino-2,5,6,7-tetrasubistituted-3-oxo-2,3-dihydro-*6H*-thiazolo-[2,3-a]pyridine (10a-l)

General procedures: Method (A):

A mixture of 2-arylsulphonylhydrazidomethyl-2-thiazoline-4-ones **4** (0.01 mole) and arylmethylidine malononitril **5** (0.02 mole) was refluxed in ethanol solution containing a catalytic amount of pipridine for 1 h. The reaction mixture was cooled and the solid product was filtered off and recrystallized from ethanol.

Method (B):

A mixture of 2,5-disubistituted thiazolidine-4-ones **5** (0.01 mole) and malononitril (0.01 mole) was refluxed in ethanol solution containing the catalytic amount of pipridine for 1 h. The reaction mixture was cooled and the solid product was filtered off and recrystallized from ethanol.

10a: Yellow (90 %), m. p. 250 °C, ν_{max} / cm^{-1} (KBr) 3420, 3210 and 3050 (NH_2), 2195 (CN), 1720 (CO) and 1670 (CO); m/z 555 (Calcd for $C_{28}H_{21}N_5S_2O_4$: C, 60.5; H, 3.8, N, 12.6; S, 11.5. Found: C, 59.0; H, 3.4; N, 13.0; S, 11.1 %). **10b**: Yellow (85 %), m. p. 280 °C, ν_{max} / cm^{-1} (KBr) 3420, 3250 and 3050 (NH_2), 2100 (CN), 1780 (CO) and 1690 (CO); m/z 624 (Calcd for $C_{28}H_{19}N_5S_2O_4Cl_2$: C, 53.8; H, 3.0; N, 11.2; S, 10.3. Found: C, 53.5, H, 3.4, N, 11.6, S, 9.8 %). **10c**: Yellow (90 %), m. p. 265 °C, ν_{max} / cm^{-1} (KBr) 3410, 3250 and 3040 (NH_2), 2150 (CN), 1760 (CO) and 1680 (CO); m/z 624 (Calcd for $C_{28}H_{19}N_5S_2O_4Cl_2$: C, 53.8; H, 3.0; N, 11.2; S, 10.3. Found: C, 53.3; H, 3.4; N, 11.7, S, 9.9 %). **10d**: Yellow (85 %), m. p. 245 °C, ν_{max} / cm^{-1} (KBr) 3520, 3210 and 3005 (NH_2), 2200 (CN), 1710 (CO) and 1650 (CO); m/z 583 (Calcd for $C_{30}H_{25}N_5S_2O_4$: C, 61.7; H, 4.3; N, 12.0; S, 11.0. Found: C, 62.1; H, 4.7; N, 11.6; S, 10.5 %). **10e**: Yellow (91 %), m. p. 230 °C, ν_{max} / cm^{-1} (KBr) 3450, 3250 and 3100 (NH_2), 2150 (CN), 1720 (CO) and 1675 (CO); m/z 615 (Calcd for $C_{30}H_{25}N_5S_2O_6$: C, 58.5, H, 4.1; N, 11.4, S, 10.4. Found: C, 58.1; H, 4.4; N, 11.8; S, 10.9 %). **10f**: Yellow (93 %), m. p. 275 °C, ν_{max} / cm^{-1} (KBr) 3400, 3250 and 3000 (NH_2), 2150 (CN), 1720 (CO) and 1670 (CO); m/z 645 (Calcd for $C_{28}H_{19}N_7S_2O_8$: C, 52.1; H, 3.9; N, 15.2; S, 9.9. Found: C, 52.4;

H, 3.5; N, 15.1; S, 10.4 %). **10g**: Yellow (90 %), m. p. 270 °C, ν_{max} / cm^{-1} (KBr) 3458, 3319 and 3211 (NH_2), 2183 (CN), 1693 (CO) and 1647 (CO); ^1H NMR (DMSO): δ = 3.32 (s, 3H, CH_3), 4.89 (s, 1H, pyridine H-4), 6.55 (s, br, 2H, NH_2), 7.0 (s, 1H, yledinic CH), 7.19-7.62 (m, 14H, $2C_6H_5$, C_6H_4), 10.82 (s, br, 1H, NH) and 12.2 (s, br, 1H, NH); m/z 569 (Calcd for $C_{29}H_{23}N_5S_2O_4$: C, 61.2; H, 4.0; N, 12.3; S, 11.2. Found: C, 60.9; H, 4.5; N, 12.1; S, 12.0 %). **10h**: Yellow (92 %), m. p. 280 °C, ν_{max} / cm^{-1} (KBr) 3430, 3230 and 3030 (NH_2), 2185 (CN), 1710 (CO) and 1650 (CO), m/z 638 (Calcd for $C_{29}H_{21}N_5S_2O_4Cl_2$: C, 54.5; H, 3.3; N, 11.0; S, 10.0. Found: C, 54.9; H, 3.7; N, 10.5; S, 9.6 %). **10i**: Yellow (85 %), m. p. 240 °C, ν_{max} / cm^{-1} (KBr) 3410, 3200 and 3000 (NH_2), 2195 (CN), 1730 (CO) and 1680 (CO); m/z 638 (Calcd for $C_{29}H_{21}N_5S_2O_4Cl_2$: C, 54.5; H, 3.3; N, 11.0; S, 10.0. Found: C, 54.0, H, 3.5; N, 11.3; S, 9.5 %). **10j**: Yellow (85 %), m. p. 245 °C, ν_{max} / cm^{-1} (KBr) 3460, 3330 and 3220 (NH_2), 2150 (CN), 1710 (CO) and 1660 (CO); ^1H NMR (DMSO): δ = 2.30 (s, 6H, $2CH_3$), 3.49 (s, 3H, CH_3), 4.84 (s, 1H, pyridine H-4), 6.48, 6.52 (s, br, 2H, NH_2), 7.16 (s, 1H, yledinic CH), 7.21-7.68 (m, 12H, $3C_6H_4$), 10.79 (s, br, 1H, NH) and 12.15 (s, br, 1H, NH); m/z 597 (Calcd for $C_{31}H_{27}N_5S_2O_4$: C, 62.3; H, 4.5; N, 11.7; S, 10.7. Found: C, 62.8; H, 4.1; N, 12.0; S, 10.3 %). **10k**: Yellow (90 %), m. p. 253 °C, ν_{max} / cm^{-1} (KBr) 3400, 3320 and 3210 (NH_2), 2200 (CN), 1720 (CO) and 1650 (CO); ^1H NMR (DMSO): δ = 2.30 (s, 3H, CH_3), 3.78-3.82 (s, 6H, $2OCH_3$), 4.87 (s, 1H, pyridine H-4), 6.47-6.49 (s, br, 2H, NH_2), 6.97 (s, 1H, yledinic CH), 6.98-7.63 (m, 12H, $3C_6H_4$), 10.09 (s, br, 1H, NH) and 12.05 (s, br, 1H, NH); m/z 629 (Calcd for $C_{31}H_{27}N_5S_2O_6$: C, 59.1; H, 4.3; N, 11.1; S, 10.2. Found: C, 58.8; H, 4.8; N, 10.7; S, 10.7 %). **10l**: Yellow (93 %), m. p. 260 °C, ν_{max} / cm^{-1} (KBr) 3410, 3320 and 3200 (NH_2), 2195 (CN), 1730 (CO) and 1650 (CO); ^1H NMR (DMSO): δ = 2.30 (s, 3H, CH_3), 5.1 (s, 1H, pyridine H-4), 6.72 (s, br, 2H, NH_2), 6.8 (s, 1H, yledinic CH), 70.2-8.41 (m, 12H, $3C_6H_4$), 10.82 (s, br, 1H, NH), 12.15 (s, br, 1H, NH); m/z 659 (Calcd for $C_{29}H_{21}N_7S_2O_8$: C, 52.8; H, 3.2; N, 14.9; S, 9.7. Found: C, 52.5; H, 3.7; N, 15.3; S, 9.3 %).

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