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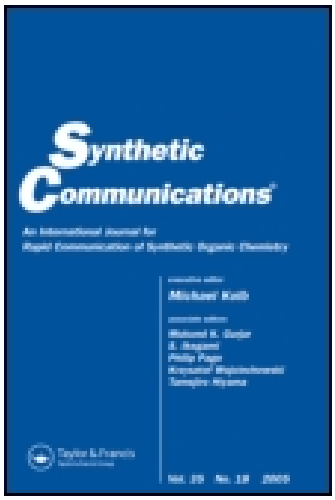

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A Novel Synthesis of Thiazoles and Thiazolopyridines Using N -Cyanoacetoarylsulfonylhydrazides

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A Novel Synthesis of Thiazoles and Thiazolopyridines Using *N*-Cyanoacetoarylsulfonylhydrazides

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ABSTRACT

A novel and efficient method for the synthesis of a new variety of 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolin-4-ones and their corresponding thiazolo[2,3-a]pyridines by the reaction of *N*-cyanoacetoarylsulphonylhydrazides with thioglycolic acid. The synthetic potential of the method is demonstrated.

We have previously reported several new approaches for the synthesis of azolopyridines and azolopyrimidines utilizing the 2-substituted methyl azolyl derivatives as starting materials.[1–7] In conjunction of this work we report here on the utility of reactions of *N*-cyanoacetoarylsulphonyl-

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hydrazides with thioglycolic acid for the synthesis of 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolin-4-ones. Moreover, the scope and limitation of our procedure for the synthesis of thiazoles are also reported. Thus, it has been found that *N*-cyanoacetoarylsulphonyl-hydrazides **2** react with thioglycolic acid in refluxing pyridine for 3 h to give the 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-thiazolin-4-one form was readily ruled out based on ^{1}H NMR spectra, which revealed one proton signal at $\delta = 5.49$ ppm. This signal can be only interpreted in terms of the 2-substituted methylidine form. The formation of **4** by the reaction of compound **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 compound **2**. Compound **4** bearing latent functional substituents were found useful to synthesize its fused ring derivatives. Thus, compound **4** readily reacted with furan-2-al or thiophen-2-al in refluxing ethanol containing a catalytic amount of piperidine in a 1:2 molar ratio to give the corresponding difuranylidene and dithiophenylidene derivatives **7a–d**. The structures of **7** were established on the basis of elemental analysis and spectral data (MS, IR, ^{1}H NMR). Compound **4** reacted with 2-β-cyanoethylenefuran derivatives **5a**,**b** and 2-β-cyanoethylene-thiophene derivatives **5c**,**d** to yield products for which the 5-amino-8-(*N*-formamidoarylsulfonylhydrazid)-7*H*-thiazolo[2,3-a]pyridine structure **8** were assigned. Each structure of **8** was confirmed on the basis of elemental analysis and spectral data (IR, MS, ^{1}H NMR). Thus, analytical data for compound **8a** revealed a molecular formula $C_{24}H_{17}N_5O_6S_2$ (M^+ 535). The ^{1}H NMR spectrum of **8a** revealed a signal at 5.00 ppm assignable to a pyridine H-4 and three broad signals at $\delta = 6.33$, 10.60 and 12.00 ppm assignable to the NH_2 group and two NH groups, respectively. Moreover, the IR spectrum revealed the presence of two carbonyl groups at 1710 and 1680 cm^{-1}. The formation of **8** by the reaction of **4** with **5** may be assumed to proceed via formation of 1:2 Michael adduct intermediates **6**, which cyclize with loss of malononitrile or ethyl cyanoacetate to give compounds **8**. Compounds **8** could also be obtained via direct reaction of **7** with malononitrile or ethyl cyanoacetate in refluxing ethanol containing catalytic amounts of piperidine.

In summary, we have achieved a regiospecific synthesis of interesting 2-(*N*-acetoarylsulfonylhydrazide)-2-thiazolin-4-ones and their corresponding thiazolo[2,3-a]pyridine derivatives using the reaction of *N*-cyanoacetosulphonylhydrazides with thioglycolic acid.

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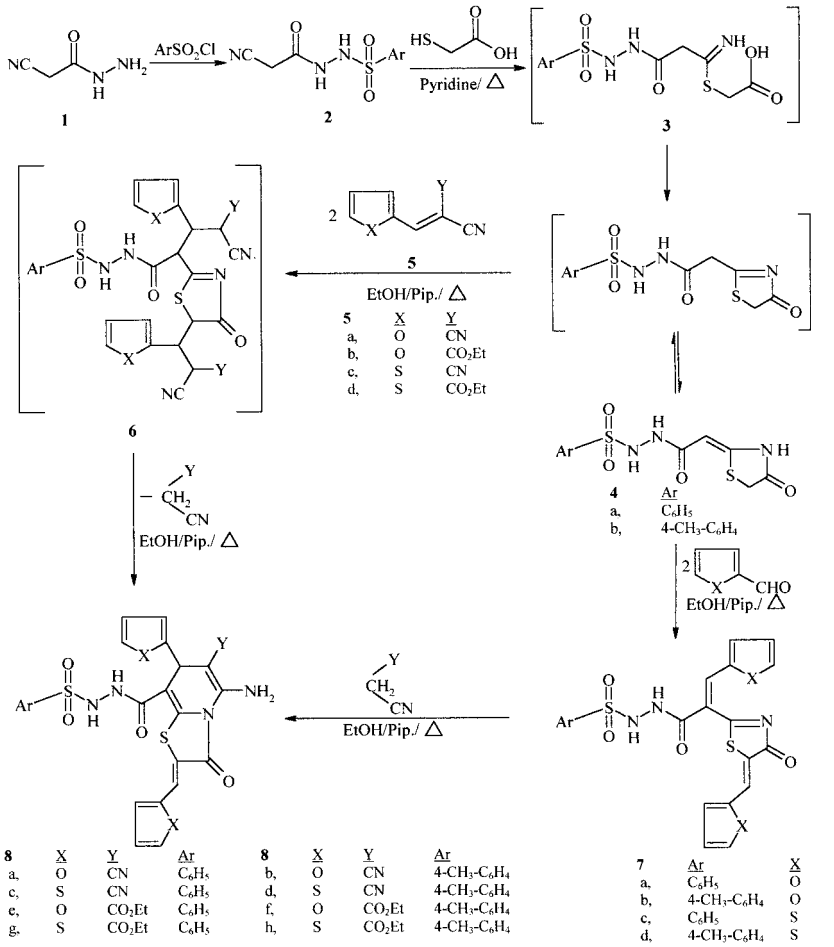

EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (KBr disk) on a Perkin Elmer 11650 FT-IR instrument. The ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2$ SO using $Si(CH_3\acute{y})_4$ 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.

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2-(*N*-Acetoarylsulphonylhydrazide)-2-thiazolin-4-ones (4a,b)

General procedure

A mixture of an equimolar amounts of *N*-cyanoacetoaryl-sulphonyl-hydrazides **2** and mercaptoacetic acid was refluxed in pyridine solution for 3 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: White (50%), m.p. 270°C, ν_{max}/cm^{-1} (KBr) 3454, 3055 (NH), 1736 (CO) and 1680 (CO); ^{1}H NMR (DMSO) $\delta = 3.62$ (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) $\delta = 31.98$ (CH_2), 89.07 (CH), 127.57–132.85 (C_6H_5), 140.00 (C-2), 165.51 (CO) and 174.07 (CO); *m/z* 313 (Calcd for $C_{11}H_{11}N_3S_2O_4$: C, 42.17; H, 3.51; N, 13.42; S, 20.45. Found: C, 41.7; H, 3.1; N, 13.6; S, 20.8%). **4b**: White (55%), m.p. 240°C, ν_{max}/cm^{-1} (KBr) 3564, 3228 (NH), 1707 (CO) and 1655 (CO); ^{1}H NMR (DMSO) $\delta = 2.38$ (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 5.49 (s, 1H, CH), 7.35–7.68 (m, 4H, 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) $\delta = 21.06$ (CH_3), 31.98 (CH_2), 89.16 (CH), 127.63–129.30 (C_6H_4), 142.55 (C-2), 165.52 (CO), 174.06 (CO); *m/z* 327 (Calcd for $C_{12}H_{13}N_3S_2O_4$: C, 44.04; H, 3.98; N, 12.84; S, 19.57. Found: C, 43.8; H, 3.5; N, 13.1; S, 20.0%).

2,5-Difuranylidene- and Dithiophenylidene-thiazolin-4-ones (7a–d)

General procedure

A mixture of 2-(*N*-acetoarylsulphonylhydrazid)-2-thiazoline-4-ones **4** (0.01 mole) and furan-2-al or thiophen-2-al (0.02 mole) was refluxed for 1 h 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 the appropriate solvent.

7a: yellow, m.p. 160–162°C (from EtOH) yield (80%); IR (KBr disc) ν_{max}/cm^{-1} 3330, 3200 (NH), 1705 (CO) and 1670 (CO); ^{1}H NMR (DMSO) $\delta = 7.61$–8.52 (m, 13H, 2 ylidenic CH, 2 furan H-3,4,5 and C_6H_5), 9.68 (s, br, 1H, NH) and 10.60 (s, br, 1H, NH); $C_{21}H_{15}N_3O_6S_2$ (469), Calcd: C, 53.73; H, 3.20; N, 8.96; S, 13.65. Found: C, 53.6; H, 3.3; N, 9.1; S, 13.2%. **7b:** yellow, m.p. >290°C (from EtOH) yield (78%); IR (KBr disc) ν_{max}/cm^{-1} 3220, 3100 (NH), 1710 (CO) and 1670 (CO);

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^{1}H NMR (DMSO) $\delta = 2.38$ (s, 3H, CH_3), 7.65–8.42 (m, 12H, ylidenic CH, 2 furan H-3,4,5 and C_6H_4), 9.60 (s, br, 1H, NH) and 11.30 (s, br, 1H, NH); $C_{22}H_{17}N_3O_6S_2$ (483), Calcd: C, 54.66; H, 3.52; N, 8.70; S, 13.25. Found: C, 54.8; H, 3.4; N, 9.0; S, 13.0%. **7c:** yellow, m.p 150–152°C (from EtOH); yield (85%); IR (KBr disc) ν_{max}/cm^{-1} 3360, 3270 (NH), 1715 (CO) and 1690 (CO); ^{1}H NMR (DMSO) $\delta =$ 7.44–8.42 (m, 13H, 2 ylidenic CH, 2 thiophene H-3,4,5 and C_6H_5), 9.00 (s, br, 1H, NH), and 10.40 (s, br, 1H, NH); $C_{21}H_{15}N_3O_4S_4$ (437), Calcd: C, 57.67; H, 3.43; N, 9.61; S, 29.29. Found: C, 57.5; H, 3.4; N, 9.2; S, 29.0%. **7d:** yellow, m.p 164–166°C (from EtOH), yield (89%); IR (KBr disc) ν_{max}/cm^{-1} 3380, 2780 (NH), 1700 (CO) and 1660 (CO); ^{1}H NMR (DMSO) $\delta = 2.30$ (s, 3H, CH_3), 7.28–8.39 (m, 12H, 2 ylidenic CH, 2 thiophene H-3,4,5 and C_6H_4), 9.00 (s, br, 1H, NH), and 10.40 (s, br, 1H, NH); $C_{22}H_{17}N_3O_4S_4$ (515), Calcd: C, 51.26; H, 3.30; N, 8.16; S, 24.85. Found: C, 51.5; H, 3.7; N, 8.0; S, 24.6%.

5-Amino-8-(*N*-formamidoarylsulfonylhydrazid)-3-oxo-2,3-dihydro-7*H*-thiazolo[2,3-a]pyridines (8a–h)

General Procedure

Method (A): A mixture of 2-(*N*-acetoarylsulphonylhydrazid)-2-thiazolin-4-ones **4** (0.01 mol) and 2-β-cyanoethylenefuran derivatives **5a**,**b** or 2-β-cyanoethylenethiophen derivatives **5c**,**d** (0.02 mol) 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 the appropriate solvent.

Method (B): A mixture of 2,5-difuranylidene- or dithiophenylidene-thiazolin-4-ones **7** (0.01 mol) and malononitril or ethyl cyanoacetate (0.01 mol) 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 the appropriate solvent.

8a: yellow, m.p. 228–230°C (from EtOH) yield (73%); IR (KBr disc) ν_{max}/cm^{-1} 3320 (NH_2), 2210 (CN), 1680 (CO), 1710 (CO); ^{1}H NMR (DMSO) $\delta = 5.00$ (s, 1H, pyridine H-4), 6.33 (s, br, 2H, NH_2), 7.19–7.62 (m, 12H, ylidenic CH, 2 furan H-3,4,5 and C_6H_5), 10.60 (s, br, 1H, NH) and 12.00 (s, br, 1H, NH); $C_{24}H_{17}N_5O_6S_2$ (535), Calcd: C, 53.83; H, 3.24; N, 13.08; S, 11.96. Found: C, 54.0; H, 3.5; N, 13.3; S, 11.5%. **8b:** yellow, m.p. 186–188°C (from EtOH) yield

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(81%); IR (KBr disc) ν_{max}/cm^{-1} 3400, 3300 and 3200 (NH_2), 2210 (CN), 1720 (CO) and 1680 (CO); ^1H NMR (DMSO) $\delta = 3.32$ (s, 3H, CH_3), 4.89 (s, 1H, pyridine H-4), 6.55 (s, br, 2H, NH_2), 7.19–7.62 (m, 11H, ylidenic CH, 2 furan H-3,4,5 and C_6H_4), 10.82 (s, br, 1H, NH) and 12.2 (s, br, 1H, NH); $C_{25}H_{19}N_5O_6S_2$ (549), Calcd: C, 54.64; H, 3.46; N, 12.75. Found: C, 54.2; H, 3.4; N, 15.1%. **8c:** yellow, m.p. >300°C (from EtOH) yield (75%); IR (KBr disc) ν_{max}/cm^{-1} 3400, 3320 and 3210 (NH_2), 2205 (CN), 1730 (CO) and 1680 (CO); ^1H NMR (DMSO) $\delta = 5.10$ (s, 1H, pyridine H-4), 6.45 (s, br, 2H, NH_2), 7.39–7.49 (m, 12H, ylidenic CH, 2 thiophene H-3,4,5 and C_6H_5), 8.06 (m, 1H, NH), 10.87 (s, 1H, NH); $C_{24}H_{17}N_5O_4S_4$ (567), Calcd: C, 50.79; H, 3.00; N, 12.35; S, 22.57. Found: C, 50.9; H, 2.9; N, 12.5; S, 22.4%. **8d:** yellow, m.p. 180°C (from EtOH) yield (70%); IR (KBr disc) ν_{max}/cm^{-1} 3390, 3300 and 3200 (NH_2), 2195 (CN), 1730 (CO) and 1650 (CO); ^1H NMR (DMSO) $\delta = 2.30$ (s, 3H, CH_3), 5.00 (s, 1H, pyridine H-4), 6.53 (s, br, 2H, NH_2), 7.00–8.11 (m, 11H, ylidenic CH, 2 thiophene H-3,4,5 and C_6H_4), 8.88 (m, 1H, NH), 9.87 (s, 1H, NH); $C_{25}H_{19}N_5O_4S_4$ (581), Calcd: C, 51.64; H, 3.27; N, 12.05; S, 22.03. Found: C, 51.5; H, 3.7; N, 12.2; S, 22.0%. **8e:** yellow, m.p. >300°C (from EtOH) yield (85%); IR (KBr disc) ν_{max}/cm^{-1} 3410, 3320–3200 (NH_2), 2195 (CN), 1730 (CO) and 1650 (CO); ^1H NMR (DMSO) $\delta = 1.09$ (t, 3H, CH_3), 3.48 (q, 2H, CH_2), 5.20 (s, 1H, pyridine H-4), 6.77 (s, br, 2H, NH_2), 7.26-8.36 (m, 12H, ylidenic CH, 2 furan H-3,4,5 and C_6H_5), 10.79 (s, br, 1H, NH) and 12.45 (s, br, 1H, NH); $C_{26}H_{22}N_4O_8S_2$ (582), Calcd: C, 53.61; H, 3.78; N, 9.62; S, 11.00. Found: C, 53.9; H, 4.1; N, 10.0; S, 11.0%. **8f:** yellow, m.p 198–200°C (from EtOH) yield (88%); IR (KBr disc) ν_{max}/cm^{-1} 3410, 3320 and 3200 (NH_2), 2195 (CN), 1730 (CO) and 1650 (CO); ^1H NMR (DMSO) $\delta = 1.09$ (t, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.48 (q, 2H, CH_2), 5.18 (s, 1H, pyridine H-4), 6.80 (s, br, 2H, NH_2), 7.11–8.08 (m, 11H, ylidenic CH, 2 furan H-3,4,5 and C_6H_4), 10.50 (s, br, 1H, NH) and 11.00 (s, br, 1H, NH); $C_{27}H_{24}N_4O_8S_2$ (596), Calcd: C, 54.36; H, 4.03; N, 9.40; S, 10.74. Found: C, 53.9; H, 4.0; N, 9.5; S, 10.5%. **8g:** yellow, m.p. 148°C (from EtOH) yield (66%); IR (KBr disc) ν_{max}/cm^{-1}3370, 3300 and 3200 (NH_2), 2210 (CN), 1720 (CO) and 1670 (CO); ^1H NMR (DMSO) $\delta = 0.99$ (t, 3H, CH_3), 3.88 (q, 2H, CH_2), 4.99 (s, 1H, pyridine H-4), 6.78 (s, br, 2H, NH_2), 7.07–8.00 (m, 12H, ylidenic CH, 2 thiophene H-3,4,5 and C_6H_5), 10.77 (s, br, 1H, NH) and 11.08 (s, br, 1H, NH); $C_{26}H_{22}N_4O_6S_4$ (614), Calcd: C, 50.81; H, 3.58; N, 9.12; S, 20.85. Found: C, 50.9; H, 4.0; N, 9.4; S, 20.5%. **8h:** yellow, m.p 190–192°C (from EtOH) yield (72%); IR (KBr disc) ν_{max}/cm^{-1} 3380, 3310 and 3260 (NH_2), 2195 (CN), 1730 (CO) and 1650 (CO); ^1H NMR (DMSO) $\delta = 1.11$ (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.69 (q, 2H, CH_2), 5.00 (s, 1H, pyridine H-4), 6.48 (s, br, 2H, NH_2),

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7.00–8.22 (m, 11H, ylidenic CH, 2 thiophene H-3,4,5 and C_6H_4), 10.98 (s, br, 1H, NH) and 11.34 (s, br, 1H, NH); $C_{27}H_{24}N_4O_6S_4$ (628), Calcd: C, 51.59; H, 3.82; N, 8.91; S, 20.38. Found: C, 51.6; H, 3.9; N, 8.5; S, 20.0%.

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