Versatile 2-aminothiazoles, building blocks for highly functionalised heterocycles

Gerd Kaupp [a]*, Fathy A. Amer [b], Mohamed Abbas Metwally [b] and Ehab Abdel-latif [b]

[a] University of Oldenburg, Faculty 5, Organic Chemistry I, P.O. Box 2503, 26111 Oldenburg, Germany; Fax: +49 441 7983409
[b] University of Mansoura, Faculty of Sciences, Egypt; Fax: +20 502246781.

Received April 10, 2003

The reactions of quantitatively available 4-phenyl- and 4-(4-antipyrinyl)-2-aminothiazole ["4-antipyrinyl-" is used as a short-term for "4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1-*H*-pyrazol-4yl)-"] with chloroacetyl chloride, acetic anhydride, ethyl cyanoacetate and carbon disulphide are reported. The products are transformed further by Knoevenagel condensations and coupling reactions with aromatic diazonium salts. The latter occur both at the thiazole ring and at the active methylene sites. The tautomerism of these products is studied on the basis of density functional theory calculations at the B3LYP/6-31G* level.

J. Heterocyclic Chem., **40**, 963 (2003).

Introduction.

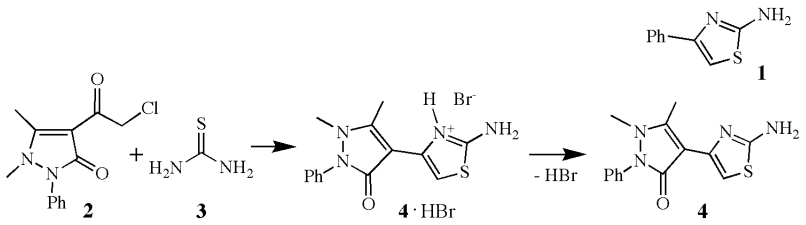
The 2-aminothiazole building block is of widespread use in chemistry [1], medicine [2-5] and pharmacology (for example antibacterial [6] or anti-inflammatory [7] applications). A large number of 2-aminothiazoles have been substituted with different groups for pharmaceutical purposes [8]. These syntheses are largely facilitated by the ease of access of 2-aminothiazoles when using the new waste-free solid-state synthesis techniques from thioureas and α–halogenoketones [9]. We explored the synthetic capabilities in view of varied and diverse reactions of 4-phenyl- and 4-(4-antipyrinyl)-2-aminothiazol in order to point out the versatility even in the presence of complicated functionality. Actually two pharmacophores are linked together in the latter system. The primary amino group of the 2-aminothiazoles can be substituted in various ways. Furthermore, secondary substitutions, cyclizations, Knoevenagel condensations and azo couplings, the latter to the thiazole ring and to the introduced cyanoacetamide substituent, will be performed in order to provide numerous highly functionalised heterocycles. The chromophores that were introduced might be useful as labels or for dying purposes of the model compounds.

Results.

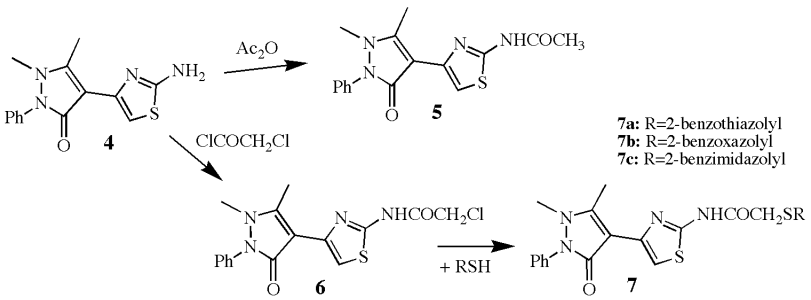
1. 2-Aminothiazoles.

4-Phenyl-2-aminothiazole (**1**) and related compounds have been prepared by waste-free solid-state reaction of α-halogenoketones and thioureas with 100% yield [9]. The same technique could be applied to 4-(chloroacetyl)-antipyrine (**2**) and thiourea (**3**). The product **4** (that had been previously obtained in 92% yield by conventional

Scheme 1



Scheme 2



synthesis [8]) could now be obtained with 100% yield from stoichiometric reactions by ball-milling followed by washings with Na_2CO_3 solutions (Scheme 1). This remarkable 3-cascade reaction of substitution, cyclization and dehydration proceeds again [9] in the solid state. The solid-state mechanism of such unusual processes has been amply demonstrated by nanoscopic techniques [9-10].

Numerous 2-aminothiazoles such as compound **1** have been reacted with aliphatic or aromatic aldehydes to form the corresponding imines (Schiff bases) and their antimicrobial and antifungal activities tested [11]. Numerous further reactions of the primary amino group of the reagents **1** and **4** appear useful.

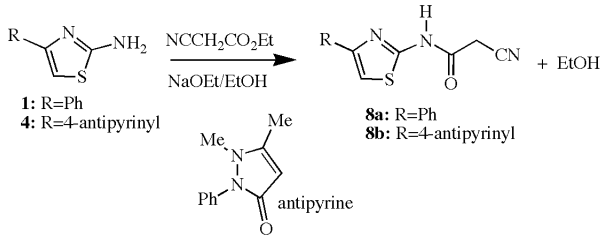
2. 2-Thiazolylamides and 2-Thiazolyl-cyanoacetamides.

2-(*N*-acetylamino)-4-phenyl-thiazole and many substituted derivatives have been described [12]. Similarly, treatment of compound **4** with acetic anhydride at 65° yielded the mono-acetylation product 2-(*N*-acetylamino)-4-(4-antipyrinyl)-thiazole (**5**) (Scheme 2).

Reaction of compound **4** with an equimolar amount of chloroacetylchloride in DMF containing some drops of triethylamine afforded the corresponding 4-(4-antipyrinyl)-2-(α-chloroacetamido)-thiazole (**6**) (Scheme 2). The spectral data of the amides **5** and **6** were consistent with their structures. Furthermore, compound **6** reacted with 2-mercapto-benzothiazole, -benzoxazol and -benzimidazol in ethanol solution containing a few drops of triethylamine to yield the thioethers **7a-c**. The structures of **7a-c** were established by spectral data (see Experimental). Interestingly, products of the type **7** (*e.g.* phenyl instead of the 4-antipyrinyl substituent) exhibited antimicrobial activity [13] and the present compounds may be tested accordingly.

The 2-aminothiazoles **1** and **4** reacted with ethyl cyanoacetate and sodium ethoxide in ethanol solution and afforded the corresponding cyanoacetamide derivatives **8** with an active methylene group for further derivatization (see Section 3). The molecular structures of compounds **8a** [14] and **8b** [15] are clearly indicated by the spectral data.

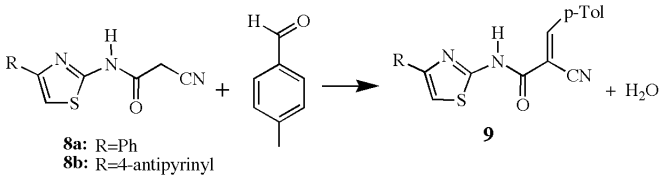
Scheme 3



3. N-(2-Thiazolyl)-2-propenamides.

The reactivity of the compounds **8** toward Knoevenagel condensation was tested with 4-methylbenzaldehyde and the corresponding derivatives **9a, b** were isolated (Scheme 4). The molecular structure of these products was confirmed on the basis of their spectral data.

Scheme 4



4. Reactions of **1** and **4** with Carbon Disulphide.

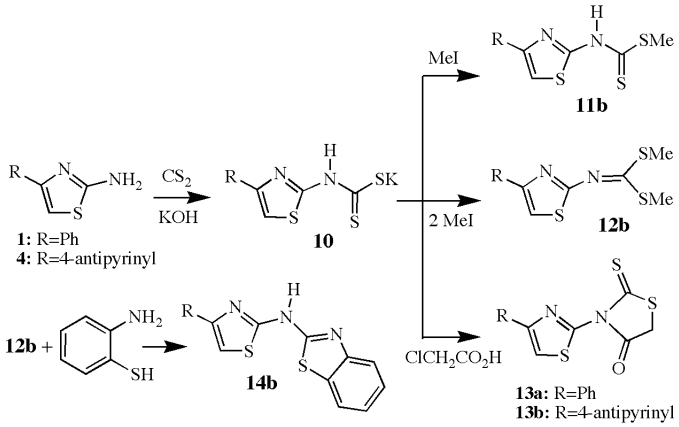
The base promoted nucleophilic addition of the 2-aminothiazoles **1** and **4** to an equimolar amount of carbon disulphide in DMF containing potassium hydroxide afforded the potassium sulphide salts **10** that were not isolated. Subsequent treatment of the salts **10** with an equimolar amount or an excess of methyl iodide and base furnished the mono- or di-methylated products **11b** and **12b**, respectively (Scheme 5). The compounds **11a** [16] and **12a** [17] are already known, the molecular structures of **11b** and **12b** were secured by spectral data.

Dimethyl dithiocarbonimidates are useful precursors for the synthesis of many important heterocyclic compounds *e.g.* arylamino- or heteroarylamino-1,3-heteroazoles [18], ß-lactams [19], 3-heteroaryl-tetrahydroquinazolin-2,4-diones [20], 8-arylamino- or heteroarylaminopurines [21] and they serve as dienes in Diels-Alder reactions [22]. We tried the reaction of **12b** with 2-aminothio-phenol in refluxing *N*,*N*-dimethylformamide (DMF) in the presence of one equivalent of sodium hydroxide and obtained a single product that was identified to be compound **14b**, based on analytical and spectral data. Heterocyclization of **10** was achieved by reaction with chloroacetic acid (after neutralization with sodium carbonate). The 3-substituted thiazolidinone-2-thione derivatives **13a, b** were obtained. The molecular structure of **13** was confirmed by analytical and spectral data. Thus, interesting heterocycles are easily accessible by these routes and extensions for further reactions can be predicted.

5. Coupling of **8**, **9** and **13** with Aryl Diazonium Salts.

The compounds **8** have two active sites for electrophilic substitution reactions with aromatic diazonium salts. The methylene group in compound **8a** proved to be more reactive toward the azo coupling reaction [23] with diazonium salts than the free C-5 position in the thiazole ring. Thus, an equimolar amount of aryl diazonium chlorides at 0-5 °C reacted with compound **8a** to yield the corresponding monohydrazone derivatives **15**. If two moles of aryl

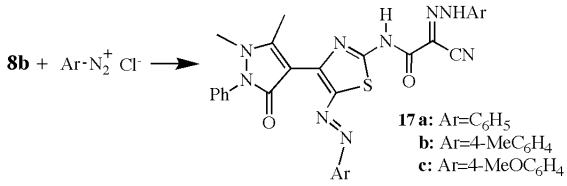
Scheme 5



diazonium chlorides and pyridine were applied at 0-5 °C the coupling at the thiazole ring occurred as well and the products **16** were obtained (Scheme 6). Compound **16** was also obtained by azo-coupling of the monohydrazone derivatives **15**. The molecular structure of the compounds **15** and **16** derives from the analytical and spectral data. The tautomeric structure of product **15** was elucidated by density functional calculations at the B3LYP/6-31G* level. The most stable tautomer found exhibits the hydrazone structure **15** with one intramolecular hydrogen bond. The alternative hydrazone structure **15'** was only 1.4 kcal mol^{-1} worse. Therefore, both should be in equilibrium. However, the best possible azo structure was found 13.7 kcal mol^{-1} higher in energy and that excludes their significant contribution to the equilibrium.

The azo couplings of compound **8b** could not avoid the reaction at the thiazole ring. If one mole or two moles of the diazonium salt were applied only the corresponding bis-azo derivatives **17** could be isolated (Scheme 7). This fact is explained by the 4-antipyrinyl group which donates electron density to the thiazole ring (the ^{13}C nmr shifts of the 5-C of **8a** and **8b** are 106.5 and 102.9 ppm, respectively). It appears that initial coupling to the imidazole ring enhances the reactivity of the remote methylene group by additionally withdrawing electron density from the 2-amide function. The couplings at C-5 to give **16** and **17** are unprecedented. Contrary to these results, no azo coupling at the thiazole ring of **8b** had previously been reported when heterocyclic diazonium salts reacted only at the active methylene group [15].

Scheme 7

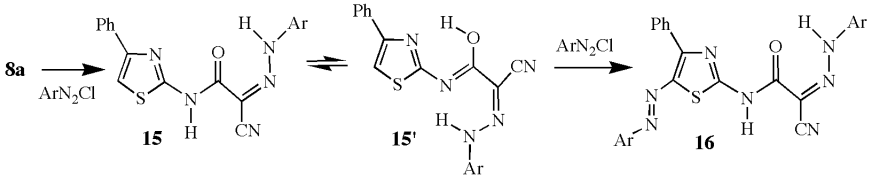


Interestingly, the compounds **16** and **17** have both a hydrazone and an azo moiety in the same molecule. Density functional model calculations at the B3LYP/6-31G* level (structure **16** but with the phenyl group and the cyanohydrazone carbon both replaced by H and Ar = Ph) excluded a double hydrazone structure for **16** or **17** by the estimated energy difference of 11.4 kcal mol^{-1}.

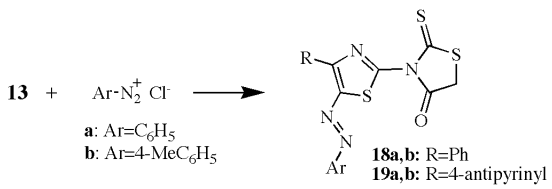
The methylene group in the compounds **13** was not active enough for the azo coupling. Thus, only electrophilic coupling at the thiazole site was observed with equimolar or excessive amounts of aryl diazonium chlorides at 0-5° (Scheme 8). The molecular structures of the monoazo derivatives **18** and **19** were established by analytical and spectroscopic data.

The azo coupling of compound **9** without a competing active methylene group occurred easily, as expected, to afford the products **20** and **21** (Scheme 9). The structure of the highly functionalized dyes **20** and **21** was assigned on the basis of spectral data.

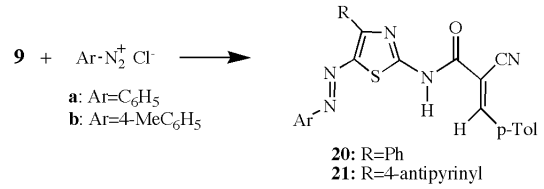
Scheme 6



Scheme 8



Scheme 9



Discussion.

A large number of substituted 2-aminothiazoles has been synthesized on useful paths. These highly functionalised derivatives may be of interest to pharmacy and for dyeing purposes, yet to be explored. Very high and complicated functionality is not only achieved by coupling to the antipyrine pharmacophore but also by further functionalization of the substituents at the 2-amino group. Thirty two 2-thiazolyl-amides, -cyanoacetamides, -sulfanylacetamides, -propenamides, -arylhydrazonoacetamides, -dithiocarbamates, -dithiocarbonimidates, -rhodanines, -aminobenzothiazoles and 5-arylazo-thiazolylamides were prepared and characterized. All of these products exhibit unusually high functionality with varied groups, which demonstrates the stability of the synthetic pathways that are opened by the waste-free access of the 2-aminothiazole building blocks. The azo couplings at the cyanoacetamide groups and at the thiazole ring are particularly versatile and show marked variations in reactivity. Interesting conjugated systems arise in compounds **15** - **21**. While the absorption maxima in the uv/visible spectra do not reach 500 nm, the dyeing properties may be favourable due to the high concentration of heteroatoms. These features will be explored in due time.

EXPERIMENTAL

General Aspects.

Melting points were determined with a Gallenkamp melting point apparatus (capillary method) and are uncorrected. Elemental analyses (C, H, N; Table 1) were carried out at the Microanalytical Unit of the Faculty of Science, Mansoura University, Egypt. Infrared spectra (ir) were recorded with a Perkin-Elmer 1720-X FT-IR spectrometer using potassium bromide pellets (not all frequencies are reported), uv/visible spectra with a Perkin-Elmer Lambda 551 S spectrometer. All nmr spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz (^{1}H) or 75.5 MHz (^{13}C; in broad band mode). Deuteriochloroform/dimethylsulfoxide-d_6 ($CDCl_3$/DMSO-d_6) mixtures contained up to 20% DMSO-d_6. All δ-values are given in ppm and refer to the internal standard tetramethylsilane (TMS), ψd in ^{1}H nmr stands for an apparent doublet of a higher order spin system. J-Values are given in Hertz (Hz). Mass spectra were obtained at a Finnigan MAT 212 instrument by electron impact at 70 eV. For known compounds spectral data were restricted to previously not available data. The ball-mill for 2 mmol runs was a Retsch MM 2000 swing mill with a 10 ml stainless steel double-walled beaker with fittings for a heating bath. Water of the appropriate temperature was circulated for heating or cooling. Two stainless steel balls with 12 mm diameter were used. Ball-milling was performed at 20–25 Hz frequency. Progress and completeness of the solid-state reactions was checked by ir spectroscopy in potassium bromide. The product yields were detected by weight, product purity by mp, thin layer chromatography (tlc, on Merck Silica Gel 60 F_{254} plates) and ^{1}H nmr spectroscopy. The short-term "4-antipyrinyl-" is used for the 4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1-*H*-pyrazol-4-yl)-substituent in order to improve the readability. B3LYP (basis set 6-31G*) density functional theory calculations with full geometry optimization were performed with the program TITAN, version 1.01, of Wavefunction, Inc., Irvine, USA.

2-Amino-4-(4-antipyrinyl)-thiazole (**4**).

A mixture of 4-(chloroacetyl)-antipyrine (**2**) [8] (497 mg, 2.00 mmol) and thiourea (**3**) (152 mg, 2.00 mmol) was ball-milled at 70° for 60 minutes. After drying at 0.01 bar at 80° a quantitative yield of **4** · HBr (615 mg, 100%) was obtained. The free base **4** was obtained by washing the fine powder of the hydrobromide with 5% aqueous Na_2CO_3 solution followed by water and drying at 80° in a vacuum. The yield was 530 mg (100%); mp 235-236° (Lit. [8] mp 235°); ir (KBr): 3327, 3151, 2956, 1636, 1593 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.70 (s, 3H), 3.15 (s, 3H), 6.55 (s, 2H), 7.15 (s, 1H, thiazol proton), 7.25 – 7.50 (m, 5H, phenyl protons); ^{13}C nmr (DMSO-d_6): δ 10.8, 33.9, 100.4, 102.7, 122.5 (2C), 124.8, 127.3 (2C), 133.6, 141.0, 150.6, 162.36, 165.6.

N-[4-(4-Antipyrinyl)-thiazol-2-yl]-acetamide (**5**).

A mixture of compound **4** (1.43 g, 5.0 mmol) and acetic anhydride (3.0 ml) was heated in an oil bath at 60 - 65° for 1 hour. The reaction mixture was allowed to cool at room temperature and then recrystallized from ethanol to afford 1.35 g (82%) colorless crystals**,** mp 227°; ir (KBr): 3185 (NH), 3094, 2964, 1689 (amide C=O), 1631 (pyrazole C=O), 1542, 1491, 1371, 1278 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.10 (s, 3H), 2.60 (s, 3H), 3.10 (s, 3H), 7.25-7.45 (m, 5H, phenyl protons), 7.70 (s, thiazol proton), 10.30 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 13.1, 23.7, 36.0, 105.2, 110.1, 125.7 (2C), 128.0, 129.9 (2C), 135.5, 142.1, 152.48, 157.9, 164.9, 168.8; ms: m/z (%) 328 (M^+,100), 313, 286, 271, 243, 226, 194, 166, 138, 93, 77, 56; hrms: calcd. for $C_{16}H_{16}N_4O_2S$ (M^+) 328.0994, found 328.0983.

N-[4-(4-Antipyrinyl)-thiazol-2-yl]-α-chloroacetamide (**6**).

Chloroacetyl chloride (1.2 ml, 15 mmol) was dropwise added with stirring to a solution of compound **4** (2.86 g, 10.0 mmol) in DMF (15 ml) containing triethyl amine (0.5 ml) at room temperature. Stirring was continued for 4 hours and the reaction mixture was poured to ice cooled water. The precipitate was collected by filtration, dried and recrystallized from ethanol to obtain 2.61 g (72%) colorless crystals, mp 208°; ir (KBr): 3282, 1700, 1615, 1590, 1549, 1487, 1455, 1410, 1322, 1260, 1155, 1082, 753 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.70 (s, 3H), 3.20 (s, 3H), 4.25 (s, 2H), 7.25-7.50 (m, 5H, phenyl protons), 7.85 (s, 1H, thiazol proton), 9.80 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 12.53, 35.40, 42.06, 104.42, 110.11, 124.60 (2C), 127.04, 129.21 (2C), 134.91, 142.12, 151.95, 155.50, 163.60, 164.21; ms: m/z (%) 364 (M^+), 362 (M^+,100), 328, 313, 286, 243, 213, 194, 138, 93, 77, 56; hrms: calcd. for $C_{16}H_{15}ClN_4O_2S$ 362.0604 (M^+), found 362.0605.

General Procedure for the Synthesis of 2-(Azol-sulfanyl)-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-acetamide Derivatives (**7a-c**).

A mixture of 4-(4-antipyrinyl)-2-(α-chloroacetamido)thiazole **6** (1.08 g, 3.0 mmol) and the corresponding 2-mercaptobenzazole (3.0 mmol) was refluxed in ethanol (50 ml) containing 5 drops of triethyl amine for 4 hours. The precipitate upon cooling was collected by filtration and crystallized from ethanol.

2-(Benzothiazol-2-ylsulfanyl)-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-acetamide (**7a**).

This compound was obtained as colorless crystals, mp 120°; yield: 920 mg (62%); ir (KBr): 3174, 3057, 2963, 1695, 1641, 1591, 1562, 1488, 1455, 1424, 1299, 1238, 1120, 1080, 1006, 796, 755 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.60 (s, 3H), 3.10 (s, 3H), 4.15 (s, 2H), 7.20-7.50 (m, 7H, phenyl protons), 7.75 (ψd, 1H, phenyl proton), 7.85 (s, 1H, thiazol proton), 8.00 (ψd, 1H, phenyl proton), 11.90 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 12.4, 35.4, 36.1, 104.5, 109.4, 121.2, 121.4, 124.4 (2C), 125.1, 125.6, 126.3, 126.8, 129.1 (2C), 134.9, 135.4, 142.0, 151.9, 156.2, 164.2, 165.8, 167.1; ms: m/z (%) 493 (43, M^+), 419, 327, 313 (100), 286, 243, 208, 180, 108, 77, 56; hrms: calcd. for $C_{23}H_{19}N_5O_2S_3$ (M^+) 493.0701, found 493.0698.

2-(Benzoxazol-2-ylsulfanyl)-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-acetamide (**7b**).

This compound was obtained as colorless crystals, mp 182°; yield: 960 mg (67%); ir (KBr): 3194, 3100, 2969, 1702, 1645, 1592, 1562, 1510, 1455, 1413, 1370, 1318, 1264, 1239, 1216, 1134, 1098, 1049, 755 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.60 (s, 3H), 3.10 (s, 3H), 4.10 (s, 2H), 7.20-7.50 (m, 8H, phenyl protons), 7.60 (ψd, 1H, phenyl proton), 7.75 (s, 1H, thiazol proton), 11.60 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 12.3, 34.8, 35.2, 104.3, 109.4, 110.3, 118.1, 124.6 (3C), 124.7, 127.0, 129.1 (2C), 134.8, 140.8, 141.8, 151.8, 152.2, 156.1, 164.1, 164.9, 165.3; ms: m/z (%) 477 (M^+), 403, 313 (100), 286, 243, 192, 164, 151, 105, 78.

2-(1*H*-Benzimidazol-2-ylsulfanyl)-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-acetamide (**7c**).

This compound was obtained as colorless crystals, mp 161°; yield: 900 mg (63%); ir (KBr): 3385, 3171, 3082, 2991, 1683, 1627, 1590, 1562, 1497, 1441, 1416, 1348, 1310, 1268, 1133, 972, 836, 794, 746 cm^{-1}; ^1H nmr ($CDCl_3$/DMSO-d_6): δ 2.75 (s, 3H), 3.20 (s, 3H), 4.25 (s, 2H), 7.10-7.50 (m, 9H, phenyl protons), 7.65 (s, 1H, thiazol proton), 12.40 (br s, 2H, 2NH); ms: m/z (%) 476 (M^+), 442, 402, 388, 313, 286 (100), 243, 194, 118, 91, 77.

General Procedure for the Synthesis of *N*-(Thiazol-2-yl)-cyanoacetamides (**8**).

The 2-aminothiazole **1** or **4** (20 mmol) and ethyl cyanoacetate (2.13 ml, 20 mmol) were added to a solution of sodium ethoxide (from 0.46 g Na, 20 mmol) in absolute ethanol (30 ml). The reaction mixture was refluxed for 6 hours with stirring and the solvent was evaporated under reduced pressure. The residue was dissolved in water and neutralized by 1 *N* HCl. The separated solid was collected by filteration and recrystallized from ethanol.

N-(4-Phenyl-thiazol-2-yl)-cyanoacetamide (**8a**).

This compound was obtained as colorless crystals, mp 195° (Lit. [14] mp 192°); yield: 3.30 g (68%); ir (KBr): 3371, 3171, 3053, 2948, 2263 (CN), 1700, 1662, 1571, 1485, 1445, 1389, 1338, 1283, 1178 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.95 (s, 2H), 7.25-7.40 (m, 3H, 2 phenyl protons and thiazol proton), 7.85 (ψd, 2H, phenyl protons), 12.50 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 24.3, 106.5, 113.0, 124.2 (2C), 126.2, 127.0 (2C), 132.7, 147.9, 155.9, 159.8.

N-[4-(4-Antipyrinyl)-thiazol-2-yl]-cyanoacetamide (**8b**).

This compound was obtained as colorless crystals, mp 219-220° (Lit. [15] mp 225-226°); yield: 5.43g (77%); ir (KBr): 3391, 3166, 3062, 2969, 2260 (CN), 1697 (C=O), 1631, 1562, 1489, 1407, 1340, 1271, 1155, 1049, 942, 882, 837, 750, 695 cm^{-1}; ^1H nmr: δ 2.70 (s, 3H), 3.20 (s, 3H), 3.80 (s, 2H), 7.30-7.50 (m, 5H, phenyl protons), 7.70 (s, 1H, thiazol proton), 12.20 (br s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 11.4, 24. 9, 34.3, 102.9, 107.8, 113.3, 123.7 (2C), 126.0, 128.1 (2C), 133.9, 141.2, 150.8, 155.3, 159.7, 163.0; ms: m/z (%) 353 (M^+, 100), 313, 286, 243, 194, 143, 93, 77, 56; hrms: calcd. for $C_{17}H_{15}N_5O_2S$ (M^+) 353.0946, found 353.0946.

General Procedure for the Synthesis of 2-Cyano-*N*-[4-(hetero)aryl-2-thiazolyl)-3-(4-tolyl)-2-propenamides (**9**).

A mixture of **8** (10 mmol) and *p*-methylbenzaldehyde (1.2 ml, 10 mmol) in 20 ml ethanol and two drops of piperidine was refluxed for 2 hours. The solid products that separated on cooling were collected by filtration, dried and crystallized from ethanol.

2-Cyano-*N*-(4-phenyl-2-thiazolyl)-3-(4-tolyl)-2-propenamide (**9a**).

This compound was obtained as light yellow crystals, mp 202°; yield: 2.35 g (68%); ir (KBr): 3378, 3115, 2213 (CN), 1682, 1596, 1542, 1442, 1327, 1283, 1177, 816, 728 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.40 (s, 3H), 7.20 (s, 1H), 7.30-7.40 (m, 5H, phenyl protons), 7.85 (ψd, 2H, phenyl protons), 7.90 (ψd, 2H, phenyl protons), 8.40 (s, 1H, thiazol proton), 9.70 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 21.9, 100.8, 108.7, 116.2, 126.1 (2C), 128.2, 128.8 (2C), 128.8, 130.2 (2C), 131.3 (2C), 134.0, 145.3, 150.5, 155.0, 156.8, 158.6; hrms: calcd. for $C_{20}H_{15}N_3OS$ (M^+) 345.0936, found 328.0935.

2-Cyano-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-3-(4-tolyl)-2-propenamide (**9b**).

This compound was obtained as brown shiny crystals, mp 232°; yield: 3.32 g (73%); ir (KBr): 3403, 3127, 2972, 2212 (CN), 1677, 1651, 1610, 1586, 1537, 1489, 1446, 1279, 1179, 1146 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.40 (s, 3H), 2.70 (s, 3H), 3.20 (s, 3H), 7.30-7.50 (m, 7H, phenyl protons), 7.80 (s, 1H, thiazol proton), 7.90 (ψd, 2H, phenyl protons), 8.45 (s, 1H), 9.75 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 12.7, 21.89, 35.3, 101.3, 103.2, 109.8, 116.5, 124.6 (2C), 127.0, 129.0, 129.2 (2C), 130.2 (2C), 131.3 (2C), 134.8, 141.6, 145.1, 152.0, 154.8, 156.5, 158.9, 164.1; ms: m/z (%) 455 (M^+, 100), 387, 353, 313, 243, 170, 115, 77; hrms: calcd. for $C_{25}H_{21}N_5O_2S$ (M^+) 455.1416, found 455.1426.

Methyl-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-dithiocarbamate (**11b**).

To a well stirred solution of **4** (2.86 g, 10.0 mmol) in DMF (20 ml) in an ice-bath were added dropwise and successively aqueous potassium hydroxide (0.56 g in 5 ml water), carbon disulphide (0.60 ml, 10 mmol) and methyl iodide (0.65 ml, 10 mmol). Stirring was continued for 3 hours and the mixture was poured into water. The solid thus obtained was collected by filtration, washed with water and recrystallized from ethanol to yield 1.96 g (52%) colorless crystals, mp 198°; ir (KBr): 3441, 3082, 2908, 1626, 1615, 1592, 1479, 1397, 1331, 1288, 1234, 1216, 1163, 1088, 1001, 949,

776, 693 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOD$): δ 2.60 (s, 3H), 2.80 (s, 3H), 3.50 (s, 3H), 7.00 (s, 1H, thiazol proton), 7.35 (s, 2H, phenyl protons), 7.60 (s, 3H, phenyl protons); ^{13}C nmr ($CDCl_3/CF_3COOD$): δ 11.5, 19.0, 33.3, 94.2, 104.6, 128.3 (2C), 129.9, 130.3, 130.8 (2C), 132.3, 146.7, 159.1, 162.1, 197.4; ms: m/z (%) 376 (M^+), 353, 328 (100), 253, 194, 165, 135, 76; hrms: calcd. for $C_{16}H_{16}N_4OS_3$ (M^+) 376.0486, found 376.0483.

Dimethyl-*N*-[4-(4-antipyrinyl)-thiazol-2-yl]-dithiocarbonimidate (**12b**).

To a well stirred solution of **4** (2.86 g, 10 mmol) in DMF (20 ml) in an ice-bath were dropwise and successively added aqueous potassium hydroxide (0.56 g in 5 ml water), carbon disulphide (0.60 ml; 10 mmol), aqueous potassium hydroxide (0.56 g in 5 ml water) and methyl iodide (1.3 ml; 21 mmol). Stirring was continued for 2-3 hours and the mixture was poured into water. The solid that separated was collected by filtration, washed with water and recrystallized from ethanol to yield 1.87g (48%) colorless crystals, mp 166°; ir (KBr): 3108, 2956, 1651, 1593, 1510, 1482, 1456, 1423, 1395, 1345, 1312, 1240, 1192, 1145, 1065, 1034, 977, 939, 922, 840, 787 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.60 (s, 6H), 2.80 (s, 3H), 3.15 (s, 3H), 7.25-7.45 (m, 5H, phenyl protons), 8.00 (s, 1H, thiazol proton); ^{13}C nmr ($CDCl_3$): δ 12.7, 15.9, 35.5, 104.8, 112.7, 124.3 (2C), 126.7, 129.1 (2C), 135.1, 144.1, 152.4, 164.4, 167.0, 169.9; ms: m/z (%) 390 (M^+, 100), 343, 329, 317, 296, 236, 171, 110, 77, 56; hrms: calcd. for $C_{17}H_{18}N_4OS_3$ (M^+) 390.0643, found 390.0647.

General Procedure for the Synthesis of 3-(Thiazol-2-yl)-rhodanines (**13**).

The reaction mixture of the 2-aminothiazole derivative **1** or **4** (10 mmol) and KOH (0.56 g in 4 ml water) and carbon disulphide (0.60 ml, 10 mmol) was stirred in DMF (20 ml) at 0-5° till a clear solution was obtained (about 2 hours). Simultaneously, chloroacetic acid (945 mg, 10 mmol that was neutralized by K_2CO_3 in 10 ml water) was added dropwise. The mixture was poured into water and acidified by 1 *M* HCl. The precipitate was collected by filtration, washed with water and recrystallized from DMF with addition of water.

3-(4-Phenyl-thiazol-2-yl)-rhodanine (**13a**).

This compound was obtained as colorless crystals, mp 202°; yield: 1.87 g (64%); ir (KBr): 3115, 2945, 1682, 1594, 1568, 1518, 1452, 1408, 1325, 1238, 1175, 1013 cm^{-1}; ^1H nmr (CF_3COOD): δ 4.25 (s, 2H), 7.15 (s, 1H, thiazol proton), 7.50-7.65 (m, 5H, phenyl protons); ^{13}C nmr (CF_3COOD): δ 37.4, 106.2, 126.6 (2C), 126.8, 129.9 (2C), 131.4, 141.4, 162.9, 174.1, 195.2; ms: m/z (%) 292 (M^+), 264, 250, 218 (100), 203, 186, 176, 134; hrms: calcd. for $C_{12}H_8N_2OS_3$ (M^+) 291.9799, found 291.9797.

3-[4-(4-Antipyrinyl)-thiazol-2-yl]-rhodanine (**13b**):

This compound was obtained as colorless crystals, mp 198°; yield: 2.21 g (55%); ir (KBr): 3131, 2932, 1722, 1616, 1573, 1480, 1397, 1304, 1214, 987, 776 cm^{-1}; ^1H nmr (CF_3COOD): δ 2.65 (s, 3H), 3.55 (s, 3H), 4.30 (s, 2H), 7.15 (s, 1H, thiazol proton), 7.35-7.70 (m, 5H, phenyl protons); ^{13}C nmr (CF_3COOD): δ 11.5, 33.3, 37.5, 94.3, 105.4, 128.5 (2C), 129.9, 131.0 (2C), 132.7, 146.9, 159.0, 160.7, 162.6, 173.5, 194.1; ms: m/z (%) 402 (M^+), 353, 290, 260, 265, 235 (100), 105, 78, 63, 44; hrms: calcd. for $C_{17}H_{14}N_4O_2S_3$ (M^+) 402.0279, found 402.0280.

2-[4-(4-Antipyrinyl)-thiazol-2-yl]-aminobenzothiazole (**14b**).

A solution of 2-aminothiophenol (250 mg, 2.0 mmol) in DMF (10 ml) was heated with aqueous sodium hydroxide (0.40 g in 3 ml water) and the mixture was stirred at room temperature for 30 minutes. A solution of **12b** (780 mg, 2.0 mmol) in DMF was then added dropwise and the reaction mixture heated under reflux for 4 hours. After cooling, the mixture was poured into water and neutralized with 1 *M* HCl. The precipitate thus obtained was collected by filtration, washed with water, dried and recrystallized from an ethanol-DMF mixture (1:1) to yield 470 mg (56%) colorless crystals, mp 231°; ir (KBr): 3196, 3048, 2945, 1637, 1618, 1592, 1521, 1476, 1452, 1301, 1278, 1211, 1066, 1019, 912, 875, 753, 725, 700, 640 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOD$): δ 2.65 (s, 3H), 3.70 (s, 3H), 7.40 (ψd, 2H, phenyl protons), 7.50 (s, 1H, thiazol proton), 7.60-7.75 (m, 6H, phenyl protons), 7.85 (ψd, 1H, phenyl proton); ^{13}C nmr ($CDCl_3/CF_3COOD$): δ 11.4, 33.4, 96.3, 115.0, 123.1, 124.3, 126.7, 128.7 (2C), 129.5, 129.9, 131.1 (2C), 132.2, 133.1, 135.6, 146.9, 157.8, 162.4, 166.2, 167.0; ms: m/z (%) 419 (M^+, 100), 387, 335, 321, 286, 243, 215, 176, 135, 108, 91, 77; hrms: calcd. for $C_{21}H_{17}N_5OS_2$ (M^+) 419.0875, found 419.0871.

General Procedure for the Synthesis of *N*-(4-Phenyl-thiazol-2-yl)-2-arylhydrazono-2-cyanoacetamides (**15**).

A solution of sodium nitrite (0.70 g, 10.0 mmol in 10 ml water) was gradually added to a well cooled solution of the aromatic amine (10.0 mmol) in concentrated HCl (3 mL). The diazonium salt solution was added with constant stirring to a cold solution of compound **8** (10.0 mmol) in ethanol (50 ml) and sodium acetate (4.0 g). The reaction mixture was allowed to rest at 0° for 2 hours and the solid was collected by filtration. The monoarylazo derivatives **15** thus obtained, were dried and recrystallized from an ethanol-DMF mixture (1:1).

N-(4-Phenyl-thiazol-2-yl)-2-phenylhydrazono-2-cyanoacetamide (**15a**).

This compound was obtained as yellow crystals, mp 247°; yield: 2.64 g (76%); uv/visible (CH_3OH): λ max 382 nm; ir (KBr): 3387, 3213, 3102, 3068, 2222 (CN), 1672, 1605, 1537, 1482, 1444, 1330, 1270, 1204, 1063, 1028, 888, 745, 691 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 7.20 (s, 1H, thiazol proton), 7.30-7.65 (m, 10H, phenyl protons), 10.35 (s, 1H, NH); ^{13}C nmr ($CDCl_3/CF_3COOH$): δ 104.3, 108.6, 109.2, 117.0 (2C), 126.6 (2C), 126.8, 127.9, 129.8 (2C), 130.0 (2C), 131.3, 139.6, 142.0, 160.3, 162.4; hrms: calcd. for $C_{18}H_{13}N_5OS$ (M^+) 347.0840, found 347.0843.

N-(4-Phenyl-thiazol-2-yl)-2-(*p*-tolylhydrazono)-2-cyanoacetamide (**15b**).

This compound was obtained as yellow crystals, mp 230°; yield: 2.64 g (73%); uv/visible (CH_3OH): λ max 387 nm; ir (KBr): 3392, 3225, 3104, 3062, 2221 (CN), 1674, 1604, 1537, 1482, 1444, 1329, 1274, 1206, 1061, 1028, 887, 814, 746 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 2.35 (s, 3H), 7.20 (ψd, 2H, phenyl protons), 7.25 (s, 1H, thiazol proton), 7.45-7.65 (m, 7H, phenyl protons), 10.35 (s, 1H, NH); ^{13}C nmr ($CDCl_3/CF_3COOH$): δ 20.9, 103.7, 108.5, 109.4, 116.9 (2C), 126.6 (2C), 126.9, 129.5, 129.8 (2C), 130.6 (2C), 131.3, 137.4, 138.4, 142.0, 162.0; hrms: calcd. for $C_{19}H_{15}N_5OS$ (M^+) 361.0997, found 361.0999.

N-(4-Phenyl-thiazol-2-yl)-2-(*p*-methoxyphenylhydrazono)-2-cyanoacetamide (**15c**).

This compound was obtained as yellow crystals, mp 251°; yield: 3.24 g (86%); uv/visible (CH_3OH): λ max 399 nm; ir (KBr): 3395, 3192, 3107, 2222 (CN),, 1670, 1611, 1537, 1482, 1441, 1328, 1274, 1251, 1206, 1165, 1059, 1025, 887, 826, 747 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 3.90 (s, 3H), 7.00 (ψd, 2H, phenyl protons), 7.25 (s, 1H, thiazol proton), 7.45-7.60 (m, 7H, phenyl protons), 10.45 (s, 1H, NH); ^{13}C nmr ($CDCl_3$/ CF_3COOH): δ 56.0, 103.1, 108.5, 109.7, 115.6 (2C), 118.8 (2C), 126.6 (2C), 126.8, 129.8 (2C), 131.4, 133.9, 142.0, 158.8, 160.6, 162.4; ms: m/z (%) 377 (M^+,100), 242, 203, 176, 134, 122, 107, 77; hrms: calcd. for $C_{19}H_{15}N_5O_2S$ (M^+) 377.0946, found 377.0946.

General Procedure for the Synthesis of *N*-(5-Arylazo-thiazol-2-yl)-2-arylhydrazono-2-cyanoacetamides (**16** and **17**).

A solution of sodium nitrite (0.70 g, 10.0 mmol in 10 ml water) was gradually added to a well cooled solution of the aromatic amine (10.0 mmol) in concentrated HCl (3 ml). The diazonium salt solution was added with constant stirring to a cold solution of the compounds **8a** or **8b** (5.0 mmol) in pyridine (30 ml). The reaction mixture was allowed to rest at 0° for 2 hours, was diluted with water and then the solid was collected by filtration. The arylazo derivatives **16** or **17** thus obtained, were dried and recrystallized from an ethanol/*N*,*N*-dimethylformamide mixture (1:1).

N-(4-Phenyl-5-phenylazo-thiazol-2-yl)-2-phenylhydrazono-2-cyanoacetamide (**16a**).

This compound was obtained as brown crystals, mp 260-261°; yield: 1.26 g (56%); uv/visible (CH_3OH): λ max 446 nm; IR (KBr): 3401, 3228, 3062, 2222 (CN), 1675, 1604, 1554, 1521, 1480, 1446, ,1327, 1272, 1073, 891, 763, 691 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 7.30-7.80 (m, 15H, phenyl protons), 10.40 (s, 1H, NH); ms: m/z (%) 451 (M^+), 416, 347, 307, 279, 242, 203 (100), 176, 134, 106, 92, 77; hrms: calcd. for $C_{24}H_{17}N_7OS$ (M^+) 451.1215, found 451.1214.

N-[4-Phenyl-5-(*p*-methylphenylazo)-thiazol-2-yl]-2-(*p*-methylphenylhydrazono)-2-cyanoacetamide (**16b**).

This compound was obtained as brown crystals, mp 241-242°; yield: 1.51 g (63%); uv/visible (CH_3OH): λ max 450 nm; ir (KBr): 3392, 3225, 3033, 2921, 2218 (CN), 1677, 1603, 1520, 1481, 1445, 1327, 1277, 1211, 1073, 1030, 891, 816, 744, 693 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 2.35 (s, 3H), 2.40 (s, 3H), 7.20-7.85 (m, 13H, phenyl protons), 10.10 (s, 1H, NH); ms: m/z (%) 479(M^+, 100), 446, 361, 321, 293, 266, 203 (100), 176, 134, 106, 92, 77; hrms: calcd. for $C_{26}H_{21}N_7OS$ (M^+) 479.1528, found 479.1531.

N-[4-Phenyl-5-(*p*-methoxyphenylazo)-thiazol-2-yl]-2-(*p*-methoxyphenylhydrazono)-2-cyanoacetamide (**16c**).

This compound was obtained as red-brown crystals, mp 248°; yield: 1.38 g (54%); uv/visible (CH_3OH): λ max 468 nm; ir (KBr): 3402, 3202, 3067, 2938, 2217 (CN), 1676, 1599, 1578, 1521, 1479, 1327, 1279, 1250, 1081, 1030, 892, 827 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.80 (s, 3H), 3.85 (s, 3H), 6.95 (ψd, 2H, phenyl protons), 7.05 (ψd, 2H, phenyl protons), 7.35-7.50 (m, 3H, phenyl protons), 7.75 (m, 4H, phenyl protons), 8.25 (ψd, 2H, phenyl protons), 12.10 (s, 1H, NH), 12.45 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 53.6, 53.8, 102.9, 109.2, 112.5 (2C), 112.9 (2C), 116.8 (2C), 122.5 (2C), 126.5 (2C), 127.2, 128.0 (2C), 132.0, 133.7, 142.7, 144.8, 147.4, 155.5, 156.4, 158.9, 159.,8; ms: m/z (%) 511 (M^+), 481, 416, 377, 335, 310 (100), 279, 229, 214, 176, 133, 107, 77.

N-[4-(4-Antipyrinyl)-5-phenylazo-thiazol-2-yl)-2-(phenylhydrazono)-2-cyanoacetamide (**17a**).

This compound was obtained as orange crystals, mp 276-277°; yield: 1.77 g (63%); uv/visible (CH_3OH): λ max 456 nm; ir (KBr): 3393, 2925, 2211 (CN), 1687, 1646, 1608, 1515, 1484, 1346, 1271, 1206, 1143 cm^{-1}; ^1H nmr (CF_3COOD): δ 2.90 (s, 3H), 3.65 (s, 3H), 7.25-7.80 (m, 15H, phenyl protons); ^{13}C nmr (CF_3COOD): δ 13.0, 33.7, 97.5, 104.4, 109.2, 117.1 (2C), 123.4 (2C), 128.2, 128.6 (2C), 129.5, 130.1 (2C), 130.1 (2C), 131.1 (2C), 133.1, 133.8, 136.4, 139.5, 143.4, 148.9, 150.9, 157.8, 160.1, 160.5; ms: m/z (%) 561 (M^+), 534, 506, 457, 430, 362, 312, 286, 269, 234, 221, 169, 161, 145 (100), 91, 77, 56; hrms: calcd. for $C_{29}H_{23}N_9O_2S$ (M^+) 561.1695, found 561.1693.

N-[4-(4-Antipyrinyl)-5-(*p*-methyl-phenylazo)-thiazol-2-yl]-2-(*p*-methyl-phenylhydrazono)-2-cyanoacetamide (**17b**).

This compound was obtained as orange crystals, mp 283-284°; yield: 2.00g (68%); uv/visible (CH_3OH): λ max 461 nm; ir (KBr): 3393, 2918, 2210 (CN), 1682, 1651, 1610, 1515, 1484, 1413, 1273, 1212, 1070 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 2.35 (s, 3H), 2.40 (s, 3H), 2.85 (s, 3H), 3.60 (s, 3H), 7.15-7.75 (m, 13H, phenyl protons), 10.10 (s, 1H, NH); ^{13}C nmr ($CDCl_3$/ CF_3COOH): δ 12.9, 20.8, 21.6, 33.7, 97.7, 104.5, 109.4, 116.6 (2C), 123.3 (2C), 128.5 (2C), 129.6, 130.5 (2C); 130.6 (2C), 130.8 (2C), 132.6, 136.7, 137.3, 137.9, 143.1, 144.9, 148.8, 157.8, 159.4, 159.6, 160.0.

N-[4-(4-Antipyrinyl)-5-(*p*-methoxyphenylazo)-thiazol-2-yl]-2-(*p*-methoxy-phenylhydrazono)-2-cyanoacetamide (**17c**).

This compound was obtained as orange crystals, mp 277-278°; yield: 2.27 g (73%); uv/visible (CH_3OH): λ max 471 nm; ir (KBr): 3392, 2939, 2210 (CN), 1678, 1646, 1597, 1510, 1478, 1436, 1246, 1146, 1068 cm^{-1}; ^1H nmr ($CDCl_3/CF_3COOH$): δ 2.85 (s, 3H), 3.60 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 6.90-7.70 (m, 13H, phenyl protons); ^{13}C nmr ($CDCl_3/CF_3COOH$): δ 12.8, 33.7, 55.8, 55.9, 97.7, 103.6, 109.6, 115.5 (4C), 118.5 (2C), 126.1 (2C), 128.5 (2C), 129.5, 130.9 (2C), 132.8, 133.7, 134.6, 143.3, 145.0, 148.5, 157.7, 158.8, 159.7, 160.0, 164.1.

General Procedure for the Synthesis of 3-(5-Arylazo-thiazol-2-yl)-rhodanines (**18** and **19**).

A solution of sodium nitrite (0.35 g, 5.0 mmol in 5 ml water) was gradually added to a well cooled and stirred suspension of the aromatic amine (5.0 mmol) in concentrated HCl (1.5 ml). The diazonium salt solution was added with constant stirring to a cold solution (0-5°) of compound **13** (5.0 mmol) in pyridine (30 ml). The reaction mixture was allowed to rest at 0° for 2 hours, it was diluted with water and then the solid was collected by filtration. The solid arylazo derivatives **18** or **19** thus obtained, were dried and recrystallized from DMF with addition of water.

3-(4-Phenyl-5-phenylazo-thiazol-2-yl)-rhodanine (**18a**).

This compound was obtained as brown crystals, mp 212-213°; yield: 1.33 g (67%); uv/visible (CH_3OH): λ max 433 nm; ir (KBr): 2918, 1694, 1592, 1567, 1516, 1458,1415, 1393, 1283,

1242, 1016, 913 cm^{-1}; ^{1}H nmr ($CDCl_3$/CF_3COOD): δ 4.25 (s, 2H), 7.45-7.60 (m, 6H, phenyl protons), 7.80 (ψd, 2H, phenyl protons), 7.90 (ψd, 2H, phenyl protons); ^{13}C nmr ($CDCl_3$/CF_3COOD): δ 37.4, 123.6 (2C), 126.3, 129.5 (2C), 129.7 (4C), 132.1, 133.2, 138.8, 140.3, 151.3, 162.6, 173.8, 195.5; ms: m/z (%) 396 (M^+), 321 (100), 279, 173, 133, 102, 89, 77; hrms: calcd. for $C_{18}H_{12}N_4OS_3$ (M^+) 396.0173, found 396.0176.

3-[4-Phenyl-5-(*p*-tolylazo)-thiazol-2-yl]-rhodanine (**18b**).

This compound was obtained as red-brown crystals, mp 222-223°; yield: 1.46 g (71%); uv/visible (CH_3OH): λ max 430 nm; ir (KBr): 2920, 1700, 1598, 1563, 1516, 1451, 1411, 1386, 1282, 1240, 1208, 1014 cm^{-1}; ^{1}H nmr ($CDCl_3$/CF_3COOD): δ 2.40 (s, 3H), 4.25 (s, 2H), 7.35 (ψd, 2H, phenyl protons), 7.55 (s, 3H, phenyl protons), 7.75 (ψd, 2H, phenyl protons), 7.90 (ψd, 2H, phenyl protons); ^{13}C nmr ($CDCl_3$/CF_3COOD): δ 21.5, 37.4, 123.6 (2C), 126.5, 129.6 (2C), 129.7 (2C), 130.5 (2C), 132.2, 140.7, 144.7, 145.0, 149.1, 162.7, 173.9, 195.4; ms: m/z (%) 410 (M^+), 393, 335 (100), 293, 173, 133, 102, 91, 65.

3-[4-(4-Antipyrinyl)-5-phenylazo-thiazol-2-yl]-rhodanine (**19a**).

This compound was obtained as violet-brown crystals, mp 160-161°; yield: 1.85 g (73%); uv/visible (CH_3OH): λ max 440 nm; ir (KBr): 2970, 1727, 1617, 1578, 1478, 1419, 1284, 1247, 1191, 1146, 1048, 992 cm^{-1}; ^{1}H nmr ($CDCl_3$/CF_3COOD): δ 2.85 (s, 3H), 3.60 (s, 3H), 4.20 (s, 2H), 7.30-7.70 (m, 10H, phenyl protons); ^{13}C nmr ($CDCl_3$/CF_3COOD): δ 12.9, 33.7, 37.3, 98.7, 122.8 (2C), 128.5 (2C), 129.4, 129.8 (2C), 130.8 (2C), 132.7 (2C), 139.9, 140.8, 149.3, 150.5, 156.8, 161.6, 172.5, 194.3; ms: m/z (%) 506 (M^+), 430 (100), 390, 362, 338, 298, 282, 242, 240, 169, 119, 93, 77, 56.

3-[4-(4-Antipyrinyl)-5-(*p*-tolylazo)-thiazol-2-yl]-rhodanine (**19b**).

This compound was obtained as violet-brown crystals, mp 175-176°; yield: 1.51 g (58%); uv/visible (CH_3OH): λ max 443 nm; ir (KBr): 2925, 1723, 1616, 1583, 1476, 1420, 1328, 1281, 1247, 1144, 988, 751 cm^{-1}; ^{1}H nmr ($CDCl_3$/CF_3COOD): δ 2.40 (s, 3H), 2.9 (s, 3H), 3.7 (s, 3H), 4.3 (s, 2H), 7.3-7.8 (m, 9H, phenyl protons); ^{13}C nmr ($CDCl_3$/CF_3COOD): δ 12.9, 21.6, 33.7, 37.2, 98.2, 123.3 (2C), 128.5 (2C), 129.3, 130.8 (2C), 131.0 (2C), 133.0 (2C), 138.1, 140.1, 148.6, 148.8, 157.1, 162.1, 174.0, 193.4; ms: m/z (%) 520 (M^+), 466, 434, 404, 393, 328, 317, 286 (100), 213, 188, 149, 124, 106, 77, 56.

General Procedure for the Synthesis of 2-Cyano-3-(*p*-tolyl)-*N*-(5-arylazo-thiazol-2-yl)-2-propeneamides (**20** and **21**).

A solution of sodium nitrite (0.35 g, 5.0 mmol in 5 ml water) was gradually added to a well cooled solution of the aromatic amine (5.0 mmol) in concentrated HCl (1.5 ml). The diazonium salt solution was added with constant stirring to a cold solution of compound **9** (5.0 mmol) in pyridine (50 ml). The reaction mixture was stirred at 0° for 3 hours and the solid product was collected by filtration. The arylazo derivatives **20** or **21** were dried and recrystallized from DMF.

2-Cyano-3-(*p*-tolyl)-*N*-(4-phenyl-5-phenylazo-thiazol-2-yl)-2-propeneamide (**20a**).

This compound was obtained as orange crystals, mp 241-242°; yield: 2.04 g (91%); uv/visible (CH_3OH): λ max 424 nm; ir (KBr): 3058, 2899, 2227(CN), 1646, 1605, 1580, 1479, 1443, 1381, 1322, 1302, 1282 cm^{-1}; ^{1}H nmr (CF_3COOD): δ 2.45 (s, 3H), 7.35 (ψd, 2H, phenyl protons), 7.50-8.00 (m, 12H, phenyl protons), 8.55 (s, 1H); ^{13}C nmr (CF_3COOD): δ 22.0, 99.6, 123.8 (2C), 126.4, 128.3, 129.5 (4C), 129.6 (2C), 130.6 (2C), 132.0, 132.3 (2C), 133.3, 140.6, 142.8, 147.7, 151.6, 158.4, 161.5, 161.7 (together with a signal of the solvent), 162.7; hrms: calcd. for $C_{26}H_{19}N_5OS$ (M^+) 449.1310, found 449.1309.

2-Cyano-3-(*p*-tolyl)-*N*-[4-phenyl-5-(*p*-tolylazo)-thiazol-2-yl]-2-propeneamide (**20b**).

This compound was obtained as orange crystals, mp 263-264°; yield: 2.04 g (88%); uv/visible (CH_3OH): λ max 429 nm; ir (KBr): 3063, 2919, 2227 (CN), 1646, 1604, 1561, 1484, 1444, 1380, 1321, 1302, 1282 cm^{-1}; ^{1}H nmr (CF_3COOD): δ 2.45 (s, 6H), 7.30-7.40 (m, 4H, phenyl protons), 7.60 (br s, 3H, phenyl protons), 7.80 (ψd, 2H, phenyl protons), 7.95 (ψd, 4H, phenyl protons), 8.55 (s, 1H).

2-Cyano-3-(*p*-tolyl)-*N*-[4-(4-antipyrinyl)-5-phenylazo-thiazol-2-yl)-2-propeneamide (**21a**).

This compound was obtained as orange-yellow crystals, mp 261-262°; yield: 2.12 g (76%); uv/visible (CH_3OH): λ_{max} = 455 nm; ir (KBr): 3056, 2953, 2218 (CN), 1669, 1618, 1586, 1538, 1495, 1424, 1370, 1320, 1301 cm^{-1}; ^{1}H nmr (CF_3COOD): δ 2.50 (s, 3H), 3.05 (s, 3H), 3.75 (s, 3H), 7.40-7.85 (m, 12H, phenyl protons), 8.00 (ψd, 2H, phenyl protons), 8.70 (s, 1H); ms: m/z (%) 559 (M^+), 531, 480, 466, 455 (100), 388, 343, 313, 286, 243, 195, 181, 170, 115, 93, 77, 56.

2-Cyano-3-(*p*-tolyl)-*N*-[4-(4-antipyrinyl)-5-(*p*-tolylazo)-thiazol-2-yl)-2-propeneamide (**21b**).

This compound was obtained as orange crystals, mp 237-238°, yield: 2.35 g (82%); uv/visible (CH_3OH): λ max 460 nm; ir (KBr): 3046, 2922, 2214 (CN), 1650, 1602, 1589, 1494, 1421, 1374, 1299, 1205, 1181 cm^{-1}; ^{1}H nmr (CF_3COOD): δ 2.45 (s, 3H), 2.50 (s, 3H), 3.00 (s, 3H), 3.70 (s, 3H), 7.30-7.75 (m, 11H, phenyl protons), 8.00 (ψd, 2H, phenyl protons), 8.65 (s, 1H); ^{13}C nmr (CF_3COOD): δ 13.1, 21.5, 21.8, 33.7, 97.9, 98.9, 115.5, 123.6 (2C), 128.5 (2C), 129.4, 130.8 (2C), 130.9 (2C), 131.2 (2C), 132.4 (2C), 133.2, 139.0, 144.0, 145.9, 148.4, 148.7, 149.2, 157.0, 159.7, 160.1, 160.5, 165.9; ms: m/z (%) 573 (M^+), 545, 480, 466, 455 (100), 404, 388, 343, 313, 286, 243, 195, 170, 115, 91.

REFERENCES AND NOTES

[1] J. V. Metzger, in Comprehensive Heterocyclic Chemistry, Vol **6**, K. T. Potts, ed, Pergamon Press, Oxford, 1984, pp 235-331; R. Barone, M. Chanon and R. Gallo, in Thiazole and its Derivatives, Vol. **34/2**, J. V. Metzger, ed, Wiley, New York, 1979, p. 9ff.; L. Forlani, *Targets in Heterocyclic Systems*, **1**, 75 (1997).

[2] N. Amishiro, S. Nagamuro, E. Kobayashi, K. Gomi and H. Saito, *J. Med. Chem.*, **42**, 669 (1999).

[3] K. Hattori, N. Fujii, A. Tanaka and F. Takamura, WO Patent 99/21843 to Fujisawa Pharmaceutical Co., LTD; *Chem. Abstr.*, **130**, 325140s (1999).

[4] M. Cheung, K. C. Glennon, K. E. Lackey and M. R. Pell, WO Patent 99/21859 to Glaxo Group LTD ; *Chem. Abstr.*, **130**, 325139y (1999).

[5] K. Yamaguchi, M. Yada, T. Tsuji, Y. Hatanaka, K. Goda and T. Kobori, *Bioorg. & Med. Chem. Lett.*, **9**, 957 (1999).

Table 1

Elemental Analyses of the New Compounds

Compound	Formula	C: Calc. (Found)	H: Calc. (Found)	N: Calc. (Found)
5	$C_{16}H_{16}N_4O_2S$	58.53 (58.67)	4.88 (4.95)	17.07 (16.88)
6	$C_{16}H_{15}ClN_4O_2S$	52.96 (52.89)	4.14 (4.10)	15.45 (15.40)
7a	$C_{23}H_{19}N_5O_2S_3$	55.98 (55.87)	3.85 (3.88)	14.20 (14.25)
7b	$C_{23}H_{19}N_5O_3S_2$	57.86 (57.91)	3.98 (3.82)	14.67 (14.75)
7c	$C_{23}H_{20}N_6O_2S_2$	57.98 (57.86)	4.20 (4.27)	17.65 (17.56)
9a	$C_{20}H_{15}N_3OS$	69.56 (69.43)	4.35 (4.22)	12.17 (12.04)
9b	$C_{25}H_{21}N_5O_2S$	65.93 (65.82)	4.61 (4.53)	15.38 (15.21)
11b	$C_{16}H_{16}N_4OS_3$	51.06 (51.11)	4.25 (4.22)	14.89 (14.83)
12b	$C_{17}H_{18}N_4OS_3$	52.31 (52.39)	4.61 (4.47)	14.36 (14.22)
13a	$C_{12}H_8N_2OS_3$	49.31 (49.43)	2.74 (2.87)	9.59 (9.73)
13b	$C_{17}H_{14}N_4O_2S_3$	50.74 (50.56)	3.48 (3.32)	13.93 (14.05)
14b	$C_{21}H_{17}N_5OS_2$	60.14 (60.03)	4.06 (4.17)	16.70 (16.54)
15a	$C_{18}H_{13}N_5OS$	62.24 (62.22)	3.74 (3.68)	20.17 (20.21)
15b	$C_{19}H_{15}N_5OS$	63.16 (63.24)	4.15 (4.19)	19.39 (19.43)
15c	$C_{19}H_{15}N_5O_2S$	60.48 (60.44)	3.98 (4.05)	18.57 (18.63)
16a	$C_{24}H_{17}N_7OS$	63.86 (64.11)	3.77 (3.91)	21.73 (21.55)
16b	$C_{26}H_{21}N_7OS$	65.13 (65.28)	4.38 (4.21)	20.46 (20.58)
16c	$C_{26}H_{21}N_7O_3S$	61.05 (60.92)	4.11 (4.23)	19.18 (19.33)
17a	$C_{29}H_{23}N_9O_2S$	62.03 (62.25)	4.10 (4.24)	22.46 (22.63)
17b	$C_{31}H_{27}N_9O_2S$	63.16 (63.41)	4.58 (4.80)	21.39 (21.23)
17c	$C_{31}H_{27}N_9O_4S$	59.90 (60.13)	4.35 (4.49)	20.29 (20.42)
18a	$C_{18}H_{12}N_4OS_3$	54.54 (54.38)	3.03 (3.12)	14.14 (14.03)
18b	$C_{19}H_{14}N_4OS_3$	55.61 (55.66)	3.41 (3.52)	13.66 (13.43)
19a	$C_{23}H_{18}N_6O_2S_3$	54.54 (54.45)	3.56 (3.43)	16.60 (16.51)
19b	$C_{24}H_{20}N_6O_2S_3$	55.38 (55.49)	3.84 (3.93)	16.15 (15.88)
20a	$C_{26}H_{19}N_5OS$	69.49 (69.44)	4.23 (4.29)	15.59 (15.64)
20b	$C_{27}H_{21}N_5OS$	69.98 (69.93)	4.53 (4.43)	15.12 (15.01)
21a	$C_{31}H_{25}N_7O_2S$	66.55 (66.59)	4.47 (4.53)	17.53 (17.42)
21b	$C_{32}H_{27}N_7O_2S$	67.01 (66.88)	4.71 (4.82)	17.10 (17.21)

[6] I. Hayakawa, Y. Tanaka and Y. Nagata, Japan Kokai, 77, 83, 588 (1976); *Chem. Abstr.*, **88**, 37785c (1978).

[7] T. Y. Shen, R. L. Olark, A. A. Pessolano, B. E. Witzel, E. Bruce and T. J. Lonza, U. S. Patent 4038396 (1975); *Chem. Abstr.*, ***78***, 152185y (1977).

[8] H. Beyer and D. Stehwien, *Arch. Pharm*., **286**, 13 (1953).

[9] G. Kaupp, J. Schmeyers and J. Boy, *J. Prakt. Chem*., **342**, 269 (2000).

[10] G. Kaupp, in Comprehensive Supramolcular Chemistry, Vol. **8**, J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Voegtle, J.-M. Lehn and J. A. Ripmeester, ed, Elsevier, Oxford, 1996, pp. 381-423 and 21 color plates.

[11] B. Dash, P. K. Mahapatra, D. Panda and J. M. Pattnaik, *J. Ind. Chem. Soc*., **61**, 1061 (1984).

[12] P. N. Bhargava and S. C. Sharma, *Bull. Chem. Soc. Japan*, **38**, 909 (1965).

[13] A. M. Mahmoud, H. A. El-Sherief and A. E. Abdel-Raman, *Eur. J. Med. Chem. Chim. Ther*., **16**, 383 (1981).

[14] V. Ariesan, Z. Cojocaru, M. Moga-Iuga, D. Ghiran, E. Chindris and L. Satfa, *Farmacia (Bucharest)*, **19**, 65 (1971).

[15] K. M. Dawood, A. M. Farag, E. A. Ragab and Z. E. Kandeel, *J. Chem. Res. Miniprint*, 622 (2000).

[16] R. H. Khan and R. C. Rastogi, *Ind. J. Chem. Soc., Sect. B*, **32**, 595 (1993).

[17] R. H. Khan, R. C. Rastogi and C. Ramesh, *J. Chem. Res. Synopses*, 160 (1991).

[18] J. Garin, E. Melendez, F. L. Merchan, D. Ortiz and T. Tejero, *Synthesis*, 368 (1987).

[19] D. Krishnaswamy, V. V. Govande, V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh, *Tetrahedron*, **58**, 2215 (2002).

[20] J. Garin, E. Melendez, F. L. Merchan and T. Tejero, *Synthesis*, 520 (1984).

[21] J. Garin, E. Melendez, F. L. Merchan and T. Tejero, *Synthesis*, 867 (1985).

[22] K. Bogdanowicz-Szwed and M. Krasodomska, *Monatsh. Chem*., **127**, 1273 (1996).

[23] H. Zollinger, Diazo Chemistry, VCH, Weinheim, 1994.