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SYNTHESIS OF FUSED 1,2,4-THIADIAZOLINES BY INTRAMOLECULAR CYCLOADDITION-ELIMINATION REACTIONS OF 4-METHYL-5-(CYANO TETHERED)IMINO-Δ^2-1,2,3,4-THIATRIAZOLINES

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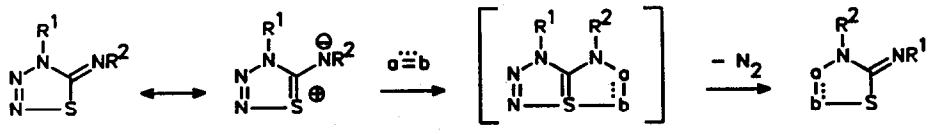
Dedicated to Prof. C.W. Rees for his Fundamental Contribution to Heterocyclic Chemistry

Abstract. A series of 5-imino-1,2,3,4-thiatriazolines, bearing a cyano tether at the imine function, were prepared and converted into fused 1,2,4-thiadiazole derivatives by thermolysis; these are **12a** → **13**, **20a** → **21**, **20b** → **22** and **29** → **30** (Schemes 2-5). In one case, the precursor thiatriazole also underwent an intramolecular cycloaddition-elimination reaction to give a fused 1,2,4-thiadiazole; namely **17a** → **18**. Thiatriazoline **33**, with an aryl group attached directly to the imine function, thermolyzed to the benzothiazole **34**.

4-Alkyl-5-(alkyl or aryl)imino-Δ^2-1,2,3,4-thiatriazolines **1** are known to react as masked 1,3-dipoles (see resonance structure) with electrophilic unsaturated systems (a⩲b) to give, after loss of nitrogen, a new series of heterocycles **3**.[1-5] The reactions are assumed to proceed via thiapentalenoid intermediates **2** having a tetravalent sulfur atom. Since the products **3** also possess a thioimidate function capable of reacting as a masked 1,3-dipole, further reactions with the unsaturated a⩲b reagent are possible leading to isomeric products (**3**, R^1 and R^2 interchanged). For instance, the reactions of **4** with ethyl cyanoformate and with p-toluenesulfonyl cyanide in refluxing chloroform yield 1,2,4-thiadiazolines **5** by two consecutive cycloaddition-elimination reactions.[5]



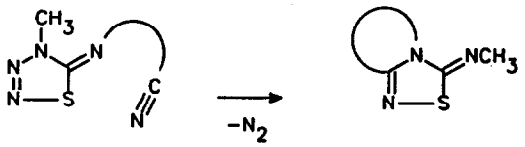
1 **2** **3**

4 5

R = EtOCO, Ts

In a further phase of our research we have investigated the intramolecular version of these cycloaddi on-elimination reactions (Scheme 1) by tethering a nitrile group to the imine function of **1**.[6] Both thre carbon and four-carbon tethers have been used, sometimes with a benzene ring as part of the tetheri sidechain. The results are discussed below.

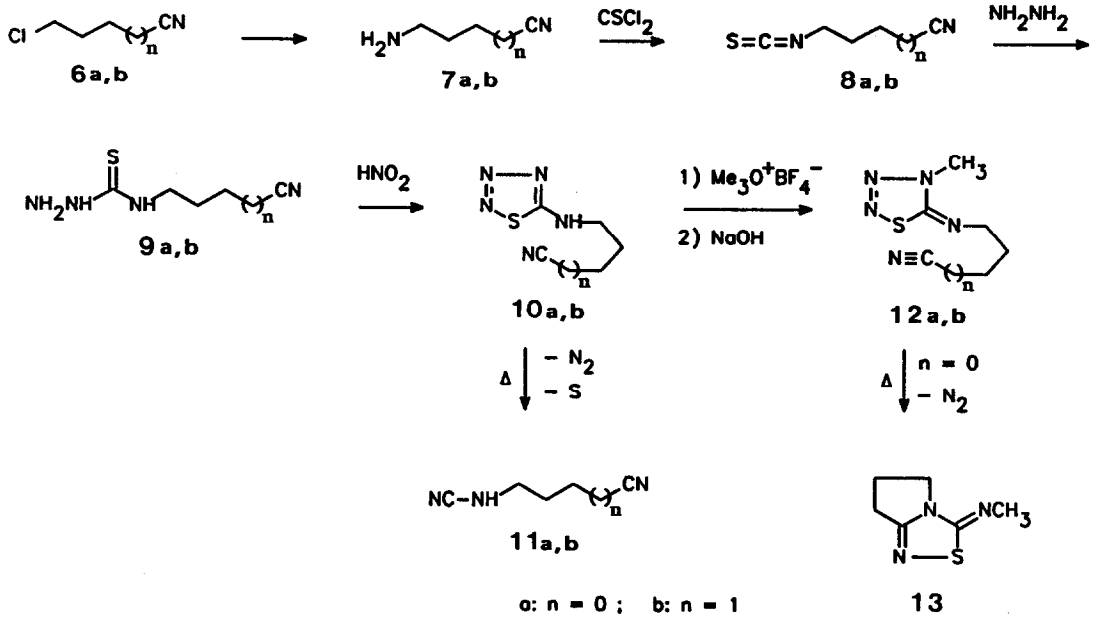
Scheme 1



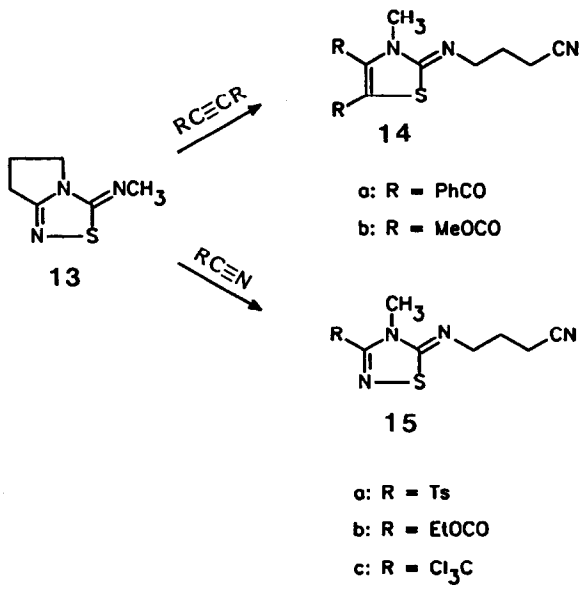
The functionalized thiatriazoles **10a,b** were prepared from 3-chloropropionitrile **6a** and 4-chlorobutyr nitrile **6b** respectively by the sequence shown in Scheme 2. These thermolabile compounds degraded benzene at 75 °C to give the expected [7] cyanamides **11a,b**. In order to methylate **10a,b** under mi conditions and exclusively at the N-4 position,[4a] Meerwein's reagent was utilized and furnished **12a,b** the sole reaction products. Thermolysis of **12a** in ethanol at 75 °C resulted in extrusion of nitrogen a formation of an oil which was characterized as the pyrrolo[2,1-c][1,2,4]thiadiazole **13** on the basis spectral analyses. In particular, the IR spectrum was devoid of a nitrile absorption at about 2250 cm^{-1}, a the ^{13}C NMR spectrum showed resonances consistent with a 1,2,4-thiadiazoline ring structure having exocyclic methylimino substituent (see Experimental).[5] For microanalysis, the oil **13** was converted into t crystalline picrate.

The presence of a thioimidate structural unit in compound **13** is further illustrated by its capacity undergo cycloaddition-ring opening reactions with electrophilic unsaturated systems (Scheme 3). T reactions with dibenzoylacetylene and diethyl acetylenedicarboxylate occurred at room temperature a yielded the thiazolines **14a,b**. Similary, electrophilic nitriles furnished the 1,2,4-thiadiazolines **15a-c**, a the following order of reactivity was observed: TsCN (20°C) > EtO_2C-CN (60°C) > CCl_3CN (90°C).

Scheme 2



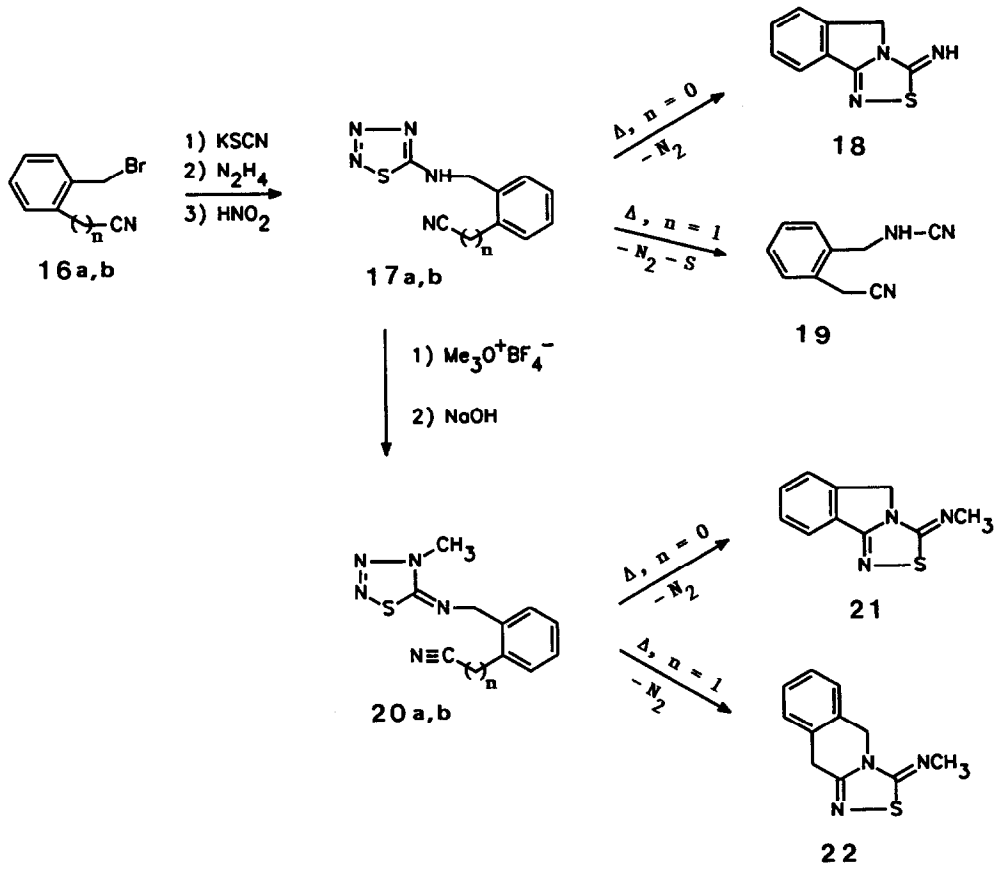
Scheme 3



In contrast to **12a**, compound **12b** proved to be stable on heating in benzene or ethanol; in refluxing toluene it decomposed to unidentified products. These experiments demonstrate that the formation of a 5/6-fused heterocycle is disfavored over a 5/5-fused system.

To investigate the influence of a benzene ring in the tethering sidechain on the intramolecular reactions, the thiatriazoles **17a** and **17b** were prepared from the substituted benzylbromides **16a,b** (Scheme 4). Surprisingly, **17a** thermolyzed in methanol to the [1,2,4]thiadiazolo[3,4-a]isoindole **18**, whereas **17b** furnished the normally expected cyanamide **19**. When **17a** was methylated with Meerwein's reagent, the tetrafluoroborate salt of **20a** could be isolated, but it decomposed with vigorous nitrogen evolution when treated with aqueous sodium hydroxide. The resulting product was identified as the [1,2,4]thiadiazolo[3,4-a]isoindole **21**.

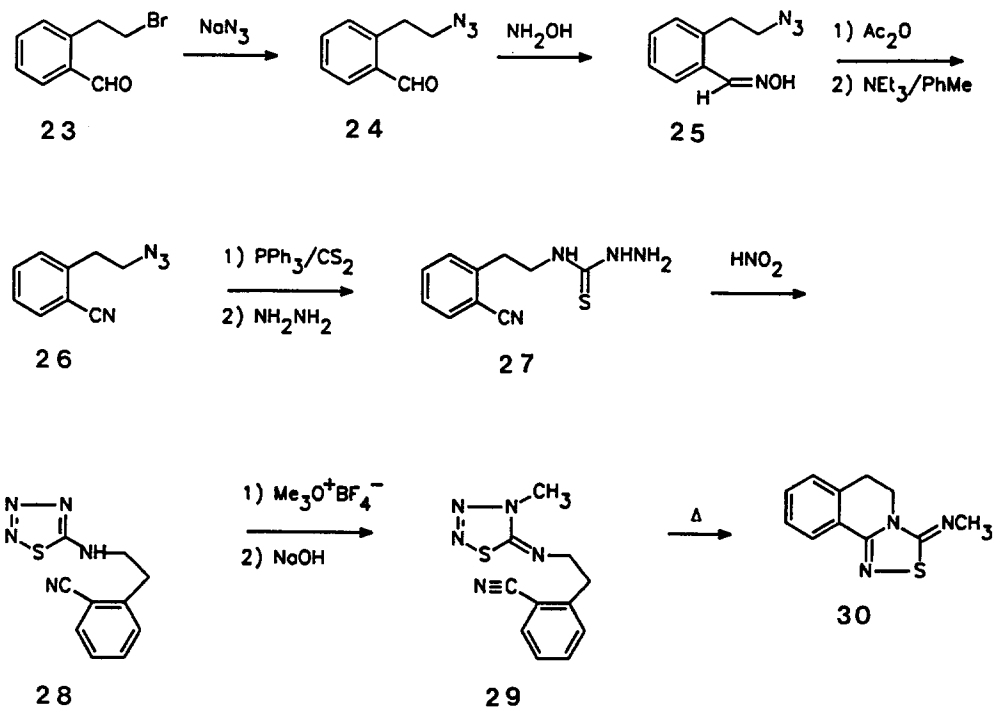
Scheme 4



Compound **20b** is more stable than **20a** and was readily obtained by methylation of **17b** and subsequent base treatment. It thermolyzed in ethanol at 70 °C to give the [1,2,4]thiadiazolo[4,3-b]isoquinoline **22**. Thus, in going from **12b** to **20b** the formation of a 6/6-fused system becomes feasible, probably due to the entropic assistance brought about by restricting the mobility of the sidechain.

The [1,2,4]thiadiazolo[3,4-a]isoquinoline **30**, an isomer of **22**, could similarly be obtained by thermolysis of the thiatriazoline **29** in benzene. A convenient method for the synthesis of **29** starts from o-(bromoethyl)benzaldehyde **23** and proceeds through a series of transformations shown in Scheme 5. All the reactions occurred smoothly and in good yields, except the conversion of the azide **26** into the thiosemicarbazide **27** which involves the intermediate formation of a phosphorane and an isothiocyanate (overall yield 26%).

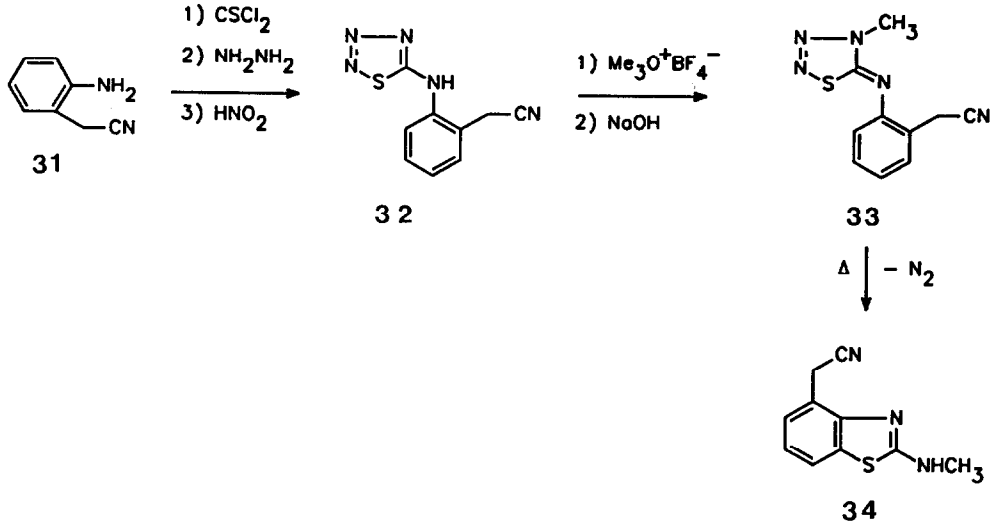
Scheme 5



Finally, when the benzene ring is attached directly to the imine function, such as in **33**, no intramolecular reaction with the nitrile function is observed. Compound **33**, prepared as shown in Scheme 6, thermolyzed in toluene at 90 °C to give the benzothiazole derivative **34**. This corresponds to the known

decomposition pathway of aryl substituted 5-iminothiatriazolines.[8] It is evident that the nucleophilicity of the imine nitrogen in **33** is decreased by the phenyl substituent, thus excluding reaction with the unactivated nitrile function.

Scheme 6



EXPERIMENTAL

5-(3-Cyanopropylamino)-1,2,3,4-thiatriazole (10a).

To an ethanolic solution (30 ml) of **8a** (2.65 g, 21 mmol) (prepared from 3-chloropropionitrile **6a** as reported)[9] was added at -20°C three equiv. of aq. hydrazine (ca 50%, 3.15 g) dissolved in 10 ml of ethanol, and the whole was stirred with cooling for 10 min. The precipitate **9a** was filtered off and washed with diethyl ether; yield 99% (3.3 g), mp 117-118°C (from EtOH).

Aq. sodium nitrite (1.5 g, 22 mmol in 14 ml) was added dropwise to an ice-cooled solution of **9a** (3.3 g, 21 mmol) in 10% hydrochloric acid (14 ml). The resulting precipitate **10a** was filtered off and dried (if **10a** separated as an oil, the mixture was extracted twice with 50 ml of chloroform, dried over $MgSO_4$ and evaporated); yield 73% (2.58 g), mp 65°C (needles from CH_2Cl_2/n-hexane); IR (KBr) 3350 (s, NH), 2250 cm^{-1} (w, CN); ^1H NMR (250 MHz, DMSO-d_6) δ 1.9 (quint., 2H, C-CH_2-C), 2.6 (t, 2H, CH_2CN), 3.5 (m, 2H, CH_2N), 8.9 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 13.8, 24.1 and 45.1 (C-C-C-N), 119.9 (CN), 177.2 (C-5). Anal. Calcd for $C_3H_7N_5S$ (mol wt 169): C, 35.49; H, 4.17. Found: C, 35.68; H, 4.00.

5-(4-Cyanobutylamino)-1,2,3,4-thiatriazole (10b).

This compound was similary prepared from 4-cyanobutyl isothiocyanate (**8b**)[9] in 52% overall yield, mp 53°C (from CH_2Cl_2/Et_2O); IR (KBr) 3220 (s, NH), 2250 (w, CN), 1600 cm^{-1} (s); ^1H NMR (250 MHz, DMSO-d_6) δ 1.5-1.8 (m, 4H, C-CH_2CH_2-C), 2.55 (t, 2H, CH_2CN), 3.45 (m, 2H, CH_2N), 8.95 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 15.9, 22.2 and 27.3 (aliphatic C-atoms), 45.8 (CH_2N), 120.5 (CN), 177.3 (C-5). Anal. Calcd for $C_6H_9N_5S$ (mol wt 183): C, 39.33; H, 4.95. Found: C, 39.53; H, 4.76.

3-Cyanopropylcyanamide (11a).

A solution of **10a** (0.84 g, 5 mmol) in benzene (40 ml) was heated at 75°C for 3h. After cooling, the reaction mixture was extracted with aq. sodium hydroxide (50 ml, 0.1 M), the aq. phase acidified with acetic acid and extracted with dichloromethane (100 ml). The organic layer was washed with aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated to give **11a** as an oil in 22% yield (0.12 g) (a control experiment in $CDCl_3$ at 60°C indicated that this is the only product formed); IR (neat) 3300 (s, NH), 2220 cm^{-1} (s, CN); ^1H NMR (250 MHz, $CDCl_3$) δ 1.95 (quint., 2H, C-CH_2-C), 2.55 (t, 2H, CH_2CN), 3.2 (t, 2H, CH_2N), 4.8 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.2, 25.1 and 44.0 (C-C-C-N), 115.8 (NHCN), 118.7 (CN).

This compound was independently prepared by adding dropwise 4-aminobutyronitrile (2.5 g, 30 mmol) to an equimolar mixture of cyanogen bromide (3.18 g, 30 mmol) and sodium carbonate (6.36 g) in ether (20 ml) at -20/-10°C. After stirring the suspension at -10°C for 2 h, the precipitate was filtered off at 0°C and the filtrate was evaporated to give **11a** in 28% yield (0.91 g).

4-Cyanobutylcyanamide (11b).

This compound was similarly obtained from **10b** as a colorless oil in 46% yield; IR (neat) 3250 (br, NH), 2230 cm^{-1} (s, CN); ^1H NMR (400 MHz, $CDCl_3$) δ 1.7-1.8 (m, 4H, C-CH_2CH_2-C), 2.45 (t, 2H, CH_2CN), 3.15 (m, 2H, CH_2N), 4.4 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.8, 22.2, 28.6 and 45.1 (aliphatic C-atoms), 116.2 (NHCN), 119.3 (CN). Anal. Calcd for $M^{+\cdot}$: 123.0796. Found: 123.07942.

5-(3-Cyanopropylimino)-4-methyl-1,2,3,4-thiatriazoline (12a).

A suspension of **10a** (2.58 g, 15.3 mmol) and trimethyloxonium tetrafluoroborate (2.26 g, 15.3 mmol) in dry dichloromethane (80 ml) was stirred at 5°C for 24 h. The reaction mixture was treated with aq. sodium hydroxide (200 ml, 2.5 M) and then extracted with dichloromethane (200 ml). The extracts were washed with water (200 ml), dried ($MgSO_4$) and evaporated to give **12a** as a yellow-brown oil in 91% yield (2.55 g); IR (neat) 2250 (m, CN), 1640 cm^{-1} (br, C=N); 1H NMR (250 MHz, $CDCl_3$) δ 2.05 (quint., 2H, C-CH_2-C), 2.55 (t, 2H, CH_2CN), 3.1 (t, 2H, CH_2N), 3.8 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ 14.8, 26.5 and 56.9 (C-C-C-N), 33.9 (CH_3N), 119.6 (CN), 156.2 (C-5).

This compound was further characterized as the picrate by treatment with 1.1 equiv. of picric acid in dichloromethane. After addition of ether, the precipitate was filtered off and crystallized from ethanol/aceton (3:2), mp 125-135°C (decomp.). Anal. Calcd for $C_{12}H_{12}N_8O_7S$ (mol wt 412): C, 34.95; H, 2.92. Found: C, 35.18; H, 2.87.

5-(4-Cyanobutylimino)-4-methyl-1,2,3,4-thiatriazoline (12b).

This compound was similarly obtained from **10b** as a yellow-orange oil in 56% yield; IR (neat) 2240 (w, CN), 1640 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 1.7-1.9 (m, 4H, C-CH_2CH_2-C), 2.4 (t, 2H, CH_2CN), 3.05 (t, 2H, CH_2N), 3.80 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ 17.0, 23.4 and 29.6 (aliphatic C-atoms), 33.9 (CH_3N), 58.9 (CH_2N), 119.6 (CN), 155.7 (C-5).

6,7-Dihydro-3-methylimino-3H,5H-pyrrolo[2,1-c][1,2,4]thiadiazole (13).

Method A. A solution of **12a** (3.0 g, 16.4 mmol) in ethanol (25 ml) was heated at 70°C until gas evolution ceased. After removal of the solvent, the resulting oil was chromatographed on silica gel with tetrahydrofuran as the eluent to give **13** as an oil in 66% yield (1.68 g).

Method B. A solution of **12a** (3.5 g, 19 mmol) in ethanol (30 ml) was heated at 70°C until gas evolution ceased. The reaction mixture was poured into a chloroform solution (150 ml) of picric acid (4.35 g, 19 mmol). After addition of ether, the picrate of **13** was filtered off in 60% yield (4.4 g), mp 195-197°C (from EtOH/Et_2O). This compound (1 g, 2.6 mmol) was suspended in dichloromethane (50 ml) and washed four times with aq. $NaHCO_3$ (50 ml,0.1 M). The organic layer was dried ($MgSO_4$) and evaporated to give **13** in 77% yield (313 mg); IR (neat) 1655 and 1605 cm^{-1} (s); ^1H NMR (250 MHz, $CDCl_3$) δ 2.4-2.8 (m, 4H, CH_2CH_2), 2.98 (s, 3H, CH_3N), 3.75 (t, 2H, CH_2N); ^{13}C NMR ($CDCl_3$) δ 25.2 and 25.3 (CH_2CH_2), 40.8 (CH_3N, $^1J_{CH}$ = 134.5 Hz), 42.6 (CH_2N), 160.6 (S-C=N), 164.2 (C-C=N). Anal. Calcd for $M^{+\cdot}$ 155.0517 (100%). Found: 155.0517. Anal. Calcd for the picrate $C_{12}H_{12}N_6O_7S$ (mol wt 384): C, 37.50; H, 3.15. Found: C, 37.62; H, 3.16.

2-(3-Cyanopropylimino)-4,5-dibenzoyl-3-methyl-Δ^4-thiazoline (14a).

A solution of **13** (0.355 g, 2.3 mmol) in dichloromethane (20 ml) was added to a suspension of dibenzoylacetylene (0.643 g, 2.74 mmol) in dichloromethane (20 ml) and the whole was stirred overnight at room temperature. The solvent was removed and the residue was chromatographed on silica gel with ether/light petroleum (1:1) as the eluent to give **14a** as an orange oil in 68% yield (0.61 g); IR (neat) 2250 (w, CN), 1680 (s, CO), 1625 cm^{-1} (br, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 2.0 (quint., 2H, C-CH_2-C), 2.5 (t, 2H, CH_2CN), 3.15 (t, 2H, CH_2N), 3.2 (s, 3H, CH_3N), 7.2-7.8 (4m, 10H, 2 Ph); ^{13}C NMR ($CDCl_3$) δ 15.0, 26.5 and 52.3 (C-C-C-N), 31.9 (CH_3N), 112.3 (C-5), 119.7 (CN), 128.1, 128.2, 128.8, 128.9, 132.2, 134.6, 135.4 and 138.0 (2 Ph C-atoms), 146.2 (C-4), 156.6 (C-2), 185.0 and 188.5 (2 CO).

This compound was further characterized as the picrate by treatment with 1.2 equiv. of picric acid in chloroform. After stirring for 2 h at room temperature, diethyl ether was added and the precipitate was filtered off and crystallized from chloroform/ether, mp 178-182°C. Anal. Calcd for $C_{28}H_{22}N_6O_9S$ (mol wt 618.6): C, 54.37; H, 3.58. Found: C, 54.13; H, 3.65.

2-(3-Cyanopropylimino)-4,5-dimethoxycarbonyl-3-methyl-Δ^4-thiazoline (14b).

A solution of **13** (0.6 g, 3.87 mmol) and 1.1 equiv. of dimethyl acetylenedicarboxylate (0.605 g, 4.26 mmol) in chloroform (8 ml) was stirred overnight at room temperature. After removal of the solvent, the residual oil was chromatographed on silica gel with ether/light petroleum (3:1) as the eluent to give **14b** in 30% yield (0.35 g), mp

86°C (pale yellow crystals from EtOH); IR (KBr) 2260 (vw, CN), 1730 (s, CO), 1640 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (quint., 2H, C-CH_2-C), 2.5 (t, 2H, CH_2CN), 3.15 (t, 2H, CH_2N), 3.30 (s, 3H, CH_3N), 3.8 and 4.0 (2 s, 6H, 2 CH_3O); ^{13}C NMR ($CDCl_3$) δ 15.0, 26.6 and 52.3 (C-C-C-N), 31.7 (CH_3N), 52.25 and 53.6 (2 CH_3O), 102.8 (C-5), 119.7 (CN), 139.8 (C-4), 156.0 (C-2). Anal. Calcd for $C_{12}H_{15}N_3O_4S$ (mol wt 297): C, 48.48; H, 5.08. Found: C, 48.52; H, 4.99.

5-(3-Cyanopropylimino)-4-methyl-3-tosyl-Δ^2-1,2,4-thiadiazoline (15a).

A suspension of p-toluenesulphonyl cyanide (577 mg, 3.2 mmol) and **13** (412 mg, 2.7 mmol) in dichloromethane (30 ml) was stirred overnight at room temperature. The reaction mixture was worked up by column chromatography on silica gel with ether/light petroleum (4:1) as the eluent to give **15a** in 59% yield (530 mg), mp 95°C; IR (KBr) 2240 (w, CN), 1640 (s, C=N), 1350 and 1165 cm^{-1} (s, SO_2); ^1H NMR (250 MHz, $CDCl_3$) δ 2.0 (quint., 2H, C-CH_2-C), 2.5 (s and t, 5H, CH_3Ar and CH_2CN), 3.1 (t, 2H, CH_2N), 3.65 (s, 3H, CH_3N, $^1J_{CH}$ = 143 Hz), 7.4 and 7.9 (2 d, 4H, tosyl), ^{13}C NMR ($CDCl_3$) δ 14.9, 26.7 and 52.3 (C-C-C-N), 21.9 (CH_3Ar), 31.7 (CH_3N), 119.6 (CN), 129.9, 130.1, 132.8 and 147.0 (tosyl C-atoms), 155.5 (C-3), 161.5 (C-5); mass spectrum, m/z (%) 336 (5, $M^{+\cdot}$), 282 (91, $M^{+\cdot}$ - CH_2CH_2CN), 181 (100, $M^{+\cdot}$ - Ts), 155 (21, Ts^+), 91 (77, $C_7H_7^+$). Anal. Calcd for $C_{14}H_{16}N_4O_2S_2$ (mol wt 336): C, 49.98; H, 4.79. Found: C, 50.14; H, 4.83.

5-(3-Cyanopropylimino)-3-ethoxycarbonyl-4-methyl-Δ^2-1,2,4-thiadiazoline (15b).

A solution of **13** (0.6 g, 3.87 mmol) and three equiv. of ethyl cyanoacetate (1.15 g, 11.6 mmol) in chloroform (8 ml) was stirred at 60°C for 48 h. After removal of the solvent, the residual oil was chromatographed on silica gel with ether/light petroleum (4:1) as the eluent to give **15b** in 79% yield (0.78 g), mp 53°C (from EtOH); IR (KBr) 2260 (w, CN), 1730 (s, CO), 1640 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (t, 3H, CH_3-C), 2.0 (quint., 2H, C-CH_2-C), 2.5 (t, 2H, CH_2CN), 3.15 (t, 2H, CH_2N), 3.6 (s, 3H, CH_3N) 4.4 (q, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 13.9 and 63.0 (Et), 14.9, 26.7 and 52.3 (C-C-C-N), 32.7 (CH_3N, $^1J_{CH}$ = 142 Hz), 119.6 (CN), 148.7 (C-3), 156.9 (CO), 162.5 (C-5); Anal. Calcd for $C_{10}H_{14}N_4O_2S$ (mol wt 254): C, 47.23; H, 5.55. Found: C, 47.17; H, 5.40.

5-(3-Cyanopropylimino)-4-methyl-3-trichloromethyl-Δ^2-1,2,4-thiadiazoline (15c).

A solution of **13** (0.6 g, 3.87 mmol) and three equiv. of trichloroacetonitrile (1.68 g, 11.6 mmol) in toluene (8 ml) was stirred at 90°C for 24 h. After removal of the solvent, the residual oil was chromatographed on silica gel with ether/light petroleum (4:1) as the eluent to give **15c** as an orange oil in 86% yield (1.0 g); IR (neat) 2260 (w, CN) 1650 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (quint., 2H, C-CH_2-C), 2.55 (t, 2H, CH_2CN), 3.15 (t, 2H, CH_2N), 3.65 (s, 3H, CH_3N); ^{13}C NMR ($CDCl_3$) δ 15.0, 26.7 and 51.9 (C-C-C-N), 34.0 (CH_3N, $^1J_{CH}$ = 142.5 Hz), 88.1 (CCl_3), 119.6 (CN), 152.3 (C-3), 163.4 (C-5).

This compound was further characterized as the picrate by treatment with 1.2 equiv. of picric acid in chloroform, mp 160-168°C (from EtOH). Anal. Calcd for $C_{14}H_{12}Cl_3N_7O_7S$ (mol wt 528.7): C, 31.80; H, 2.29. Found: C, 31.95; H, 2.15.

5-(o-Cyanobenzylamino)-1,2,3,4-thiatriazole (17a).

A suspension of **16a** (5 g, 25.5 mmol), potassium thiocyanate (5.0 g, 51 mmol) and sodium iodide (1.5 g, 10 mmol) in dimethylformamide (25 ml) was heated with stirring at 90°C for 9 h. The reaction mixture was poured into water (150 ml) and extracted twice with ether (150 ml). The combined ether extracts were washed three times with water (200 ml), dried ($MgSO_4$) and chromatographed on silica gel with ether/light petroleum (1:1) as the eluent to give o-cyanobenzyl isothiocyanate in 71% yield (3.14 g), mp 35-37°C (from EtOH at -16°C).

To a solution of this compound (3.14 g, 18 mmol) in ethanol (50 ml) was added dropwise and with stirring at room temperature three equiv. of aq. hydrazine (ca 50%, 2.7 g) dissolved in 20 ml of ethanol. After stirring for 15 min., the resulting precipitate of o-cyanobenzylthiosemicarbazide was filtered off and washed with ether; yield 90% (3.34 g), mp 154-156°C.

To a suspension of this compound (3.34 g, 16.2 mmol) in 10% hydrochloric acid (30 ml) was added aq. sodium nitrite (1.44 g, 20.8 mmol in 15 ml) at room temperature, and the whole was stirred for 15 min. The resulting precipitate **17a** was filtered off, washed with water and dried in vacuo; yield 85% (2.98 g), mp 80-85°C (decomp.); IR (KBr) 3330 (s, NH), 2220 cm^{-1} (m, CN). Note: This compound evolved nitrogen when dissolved in DMSO or when crystallized from hot dichloromethane to give **18**. Also, the results of microanalysis corresponded to **18**.

5-(o-Cyanomethyl)benzylamino-1,2,3,4-thiatriazole (17b).

This compound was similarly obtained from 1-(2-bromomethyl)phenylacetonitrile (**16b**)[10] in 53% overall yield, mp 105-107°C (needles from CH_2Cl_2 at -16°C); IR (KBr) 3210 (s, NH), 2260 cm^{-1} (m, CN); ^1H NMR (250 MHz, DMSO-d_6) δ 4.15 (s, 2H, CH_2CN), 4.70 (d, 2H, CH_2NH), 7.3-7.55 (m, 4H, Ar), 9.3 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.2 and 47.0 (2 CH_2), 118.6 (CN), 128.1, 128.4, 128.9, 129.0, 129.6 and 135.0 (Ar C-atoms), 177.0 (C-5). Anal. Calcd for $C_{10}H_9N_5S$ (mol wt 231): C, 51.93; H, 3.92. Found: C, 51.76; H, 3.97.

3-Imino-3H,5H-[1,2,4]thiadiazolo[3,4-a]isoindole (18).

A solution of **17a** (0.65 g, 3 mmol) in methanol (50 ml) was decomposed by heating at 65°C for 1 h. Then a stream of hydrogen chloride gas was bubbled through the solution, the solvent was evaporated an the residue was crystallized from ethanol to give **18** as the hydrochloride salt in 62% yield (0.42 g), mp 223-227°C; IR (KBr) 2950 (br, NH_2), 1640 cm^{-1} (s), ^1H NMR (400 MHz, DMSO-d_6) δ 5.17 (s, 2H, CH_2), 7.6-8.0 (t, t, d and d, 4 aromatic H), 10.9 (br, 2H NH_2); ^{13}C NMR (DMSO-d_6) δ 50.3 (CH_2), 122.4, 125.2, 125.4, 129.1, 132.5 and 145.2 (benzo C-atoms), 160.4 (C-9b), 173.3 (C-3); mass spectrum, m/z (%) 189 (100, $M^{+\cdot}$ of **18**), 161 (20), 129 (15), 116 (36, $CNC_6H_4CH_2^+$), 103 (15, $PhCN^{+\cdot}$). Anal. Calcd for $C_9H_8ClN_3S$ (mol wt 225.7): C, 47.90; H, 3.57. Found: C, 47.63; H, 3.67.

Characterization of **18**: mp 140°C; IR (KBr) 3310 and 3230 (w), 1630 and 1610 cm^{-1} (s); ^1H NMR (400 MHz, DMSO-d_6) δ 4.78 (s, 2H, CH_2), 7.5-7.8 (t, t, d and d, 4 aromatic H), 8.25 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 46.7 (CH_2), 121.4, 125.0, 127.3, 128.4, 131.1 and 145.5 (benzo C-atoms), 159.8 and 161.6 (C-3 and/or C-9b). Anal. Calcd for $C_9H_7N_3S$ (mol wt 189): C, 57.12; H, 3.73. Found: C, 57.00; H, 3.82.

o-(Cyanomethyl)benzylcyanamide (19).

A suspension of **17b** (0.75 g, 3.2 mmol) in benzene (40 ml) was heated at 70°C for 3 h. The sulfur precipitate

was filtered off and the filtrate was extracted with aq. sodium hydroxide (50 ml, 0.1 M). The aq. phase was acidified with acetic acid and extracted with dichloromethane (100 ml). The organic layer was washed with aq. $NaHCO_3$, water, and then dried ($MgSO_4$) and evaporated to give **19** as a yellow oil in 90% yield (0.5 g); IR (neat) 3300 (br, NH), 2230 cm^{-1} (s, CN); ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 2H, CH_2CN), 4.11 (s, 2H, CH_2N), 5.17 (br s, 1H, NH), 7.3-7.4 (m, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 21.1 and 47.1 (2 CH_2), 116.2 and 117.8 (2 CN), 128.8, 128.9, 129.5, 129.6, 130.3 and 133.8 (aromatic C-atoms). Anal. Calcd for $M^{+\cdot}$: 171.0796. Found: 171.0799.

5-(o-Cyanomethyl)benzylimino-4-methyl-1,2,3,4-thiatriazoline (20b).

A suspension of **17b** (1.64 g, 7.1 mmol) and trimethyloxonium tetrafluoroborate (1.05 g, 7.1 mmol) in dry dichloromethane (50 ml) was stirred at 5°C for 24 h. The precipitated thiatriazolium salt was filtered off and washed with ether; yield 76% (1.8 g).

This salt (1.7 g, 5.1 mmol) was suspended in dichloromethane (50 ml) and treated with aq. sodium hydroxide (5 g in 50 ml). The whole was extracted twice with dichloromethane (75 ml) and the extracts were dried ($MgSO_4$) and evaporated to give a crude product **20b** which was crystallized from diethyl ether in 66% yield (0.83 g), mp 72-74°C; IR (KBr) 2250 (w, CN), 1645 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 3.83 (s, 3H, CH_3N), 3.86 (s, 2H, CH_2CN), 4.25 (s, 2H, CH_2N), 7.3-7.5 (2m, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 21.3 and 60.8 (2 CH_2), 34.1 (CH_3N, $^1J_{CH}$ = 142.5 Hz), 117.7 (CN), 128.2, 128.4, 129.1, 129.3, 129.8 and 136.4 (aromatic C-atoms), 156.7 (C-5). Anal. Calcd for $C_{11}H_{11}N_5S$ (mol wt 245): C, 53.86; H, 4.52. Found: C, 54.03; H, 4.53.

3-Methylimino-3H,5H-[1,2,4]thiadiazolo[3,4-a]isoindole (21).

A suspension of **17a** (2.7 g, 12.4 mmol) and trimethyloxonium tetrafluoroborate (1.84 g, 12.4 mmol) in dry dichloromethane (80 ml) was stirred at 5°C for 24 h. The precipitated thiatriazolium salt was filtered off, dried and treated with aq. sodium hydroxide (20 g in 200 ml) which resulted in vigorous nitrogen evolution. The reaction mixture was extracted twice with dichloromethane (100 ml) and the combined extracts were washed with water (200 ml), dried ($MgSO_4$) and evaporated to give **21** in 60% yield (1.5 g), mp 174-175°C (from CH_2Cl_2/diethyl ether, 1:1); IR (KBr) 1660 (s), 1610 cm^{-1} (s); ^1H NMR (250 MHz, $CDCl_3$) δ 3.02 (s, 3H, CH_3N), 4.7 (s, 2H, CH_2), 7.4-7.8 (2m, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 41.3 (CH_3N, $^1J_{CH}$ = 135 Hz), 46.9 (CH_2), 122.2, 124.3, 127.7, 128.6, 131.1 and 144.2 (aromatic C-atoms), 159.7 (C-3), 160.8 (C-9b); mass spectrum, m/z (%) 203 (100, $M^{+\cdot}$), 161 (24), 116 (42, $CNC_6H_4CH_2^+$), 103 (9, $PhCN^{+\cdot}$).

This compound was further characterized as the picrate by treatment with 1.2 equiv. of picric acid in dichloromethane, mp 243-248°C (from DMF/Et_2O). Anal. Calcd for $C_{16}H_{12}N_6O_7S$ (mol wt 432): C, 44.45; H, 2.80. Found: C, 44.42; H, 2.94.

5,10-Dihydro-3-methylimino-3H-[1,2,4]thiadiazolo[4,3-b]isoquinoline (22).

Compound **20b** (0.7 g, 2.85 mmol) was dissolved in warm ethanol (10 ml) and heated at 70°C for 24 h. After evaporation of the solvent, the residue was crystallized from diethyl ether to give colorless needles of **22** in 65% yield (0.40 g), mp 121-123°C; IR (KBr) 1635 cm^{-1} (s, C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 3.05 (s, 3H, CH_3N), 3.95 (s, 2H, CH_2C=N), 4.9 (s, 2H, CH_2N), 7.2-7.3 (m, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 32.3 (C-10), 40.6

(CH_3N, $^1J_{CH}$ = 135 Hz), 46.2 (C-5), 126.3, 127.2, 127.9 (x 2), 129.9 and 130.1 (aromatic C-atoms), 155.1 (C-10a), 163.5 (C-3); mass spectrum, m/z 217 (64, $M^{+\cdot}$), 130 (20, $CNCH_2C_6H_4CH_2^+$), 117 (33, $PhCH_2CN^{+\cdot}$), 103 (27), 91 (19, $C_7H_7^+$), 75 (39), 55 (48), 45 (100). Anal. Calcd for $C_{11}H_{11}N_3S$ (mol wt 217): C, 60.80; H, 5.10. Found C, 60.64; H, 5.08.

5-(o-Cyano)phenethylamino-1,2,3,4-thiatriazole (28).

A solution of o-(bromoethyl)benzaldehyde (**23**)[11] (15 g, 70 mmol), sodium azide (5.95 g, 91 mmol) and sodium iodide (0.5 g) in dimethyl sulfoxide (75 ml) was stirred overnight at 105°C. The reaction mixture was poured into ice-water (150 ml) and extracted twice with ether (150 ml). The ether extracts were washed with water (2 x 200 ml), dried ($MgSO_4$) and evaporated to give **24** as an oil in 94% yield (11.5 g).

To a solution of this compound (11 g, 63 mmol) in ethanol (150 ml) was added aq. hydroxylamine hydrochloride (5.3 g, 76.3 mmol) and sodium carbonate (5.3 g, 50 mmol in 75 ml), and the whole was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was extracted twice with ether (100 ml) and the extracts were washed with water (2 x 150 ml), dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on silica gel with ether/light petroleum (1:1) as the eluent to give **E-25** as an oil in 83% yield (9.9 g).

A suspension of **25** (8.5 g, 45 mmol) and sodium acetate (5 g, 61 mmol) in acetic anhydride (50 ml) was heated at 110°C for 2 h. Aq. sodium hydroxide (25 g in 150 ml) was added to the cooled solution, and the whole was extracted with ether (200 ml). The ether extract was washed with aq. sodium hydroxide (25 g in 150 ml) and with water (2 x 150 ml), dried ($MgSO_4$) and evaporated to give an oil containing mainly the acylated oxime together with a small amount of the nitrile **26**. This mixture was heated overnight in toluene (100 ml) with two equiv. of triethylamine (9 g). After removal of the solvent, the residu was chromatographed on silica gel with ether/light petroleum (1:1) as the eluent to give **26** as an impure oil in ca 79% yield (6.1 g).

To a solution of **26** (6.0 g, 35 mmol) in carbon disulfide (100 ml) was added on equiv. of triphenylphosphine (9.1 g). When nitrogen evolution ceased (after ca 30 min.) the solution was refluxed for 3 h. The excess of carbon disulfide was removed and the residue was extracted three times with light petroleum (100 ml). From the combined extracts a yellow orange oil (4.4 g) was obtained, which was dissolved in ethanol (50 ml) at -10°C and treated with aq. hydrazine (ca 50%, 1.5 g). After stirring for 1 h, the precipitated **27** was filtered off in 26% overall yield (1.97 g), mp 107-109°C.

Aq. sodium nitrite (0.61 g, 8.9 mmol in 10 ml) was added dropwise and with stirring to an ice-cooled suspension of **27** (1.95 g, 8.9 mmol) in a mixture of 10% hydrochloric acid (60 ml) and dichloromethane (60 ml). After 15 min., the organic phase was collected and the water solution was extracted with dichloromethane (60 ml). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) and with water (100 ml), dried ($MgSO_4$) and evaporated. The resulting orange oil (2.01 g) was chromatographed on silica gel with ether als the eluent to give **28** in 83% yield (1.70 g), mp 84-87°C, decomp.; IR (KBr) 3320 (s, NH), 2222 (s, CN), 1562 cm^{-1} (s); ^1H NMR (400 MHz, DMSO-d_6) δ 3.16 (t, 2H, CH_2Ar), 3.7-3.8 (m, 2H, CH_2N), 7.4-7.8 (2 d and 2 t, 4 aromatic H), 8.95 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 32.8 a,d 46.3 (CH_2CH_2N), 111.9, 127.4, 130.1, 132.8, 133.3 and 142.2 (Ar C-atoms), 117.7 (CN), 177.1 (C-5) (Note: This compound decomposes slowly in DMSO solution). Anal. Calcd for $C_{10}H_9N_5S$ (mol wt 231): C, 51.93; H, 3.92. Found: C, 51.75; H, 3.99.

5-(o-Cyano)phenethylimino-4-methyl-1,2,3,4-thiatriazoline (29).

A suspension of **28** (1.60 g, 6.9 mmol) and trimethyloxonium tetrafluoroborate (1.02 g, 6.9 mmol) in dry dichloromethane (40 ml) was stirred at 5°C for 2 days. Then, dichloromethane (100 ml) and aq. sodium hydroxide (10 g in 100 ml) were added, and the whole was stirred for 30 min. The organic phase was collected, washed with water (2 x 100 ml), dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on silica gel with ether/light petroleum (2:1) as the eluent to give **29** in 73% yield (1,24 g), mp 90-92°C, decomp. (from Et_2O at -16°C); IR (KBr) 2227 (s, CN), 1645 cm^{-1} (s, C=N); ^1H NMR (400 MHz, $CDCl_3$) δ 3.20 (t, 2H, CH_2Ar), 3.36 (t, 2H, CH_2N), 3.78 (s, 3H, CH_3N), 7.25-7.65 (td, d, td and dd, 4 aromatic H); ^{13}C NMR ($CDCl_3$) δ 34.0 (CH_3N, $^1J_{CH}$ = 142 Hz), 35.7 and 60.2 (CH_2CH_2N), 113.0, 126.9, 130.3, 132.7, 132.8 and 143.7 (aromatic C-atoms), 118.1 (CN), 156.1 (C-5). Anal. Calcd for $C_{11}H_{11}N_5S$ (mol wt 245): C, 53.86; H, 4.52. Found: C, 54.01; H, 4.46.

5,6-Dihydro-3-methylimino-3H-[1,2,4]thiadiazolo[3,4-a]isoquinoline (30).

A solution of **29** (0.75 g, 3.06 mmol) in benzene (30 ml) was refluxed for 24 h. After removal of the solvent, the residue was crystallized from diethyl ether at -16°C to give **30** in 69% yield (0.46 g), mp 119-120°C; IR (KBr) 1650 cm^{-1} (s, C=N); ^1H NMR (400 MHz, $CDCl_3$) δ 3.06 (s, 3H, CH_3N), 3.11 (t, 2H, CH_2Ar), 3.98 (t, 2H, CH_2N), 7.2-7.45 (d, t and td, 3 aromatic H), 8.06 (d, 1 aromatic H), ^{13}C NMR ($CDCl_3$) δ 28.0 (C-6), 40.9 (CH_3N, $^1J_{CH}$ = 134 Hz, and C-5, $^1J_{CH}$ = 144 Hz), 125.9, 126.0, 127.5, 127.9, 131.4 and 135.5 (aromatic C-atoms), 153.4 (C-10b), 163.8 (C-3); mass spectrum, m/z (%) 217 (100, $M^{+\cdot}$), 216 (89), 187 (17), 130 (20, $CNC_6H_4CH_2CH_2^+$), 117 (12, $CNC_6H_4CH_3^{+\cdot}$), 77 (13, Ph^+), 69 (14), 42 (11, $MeN{=}CH^+$). Anal. Calcd for $C_{11}H_{11}N_5S$ (mol wt 217): C, 60.80; H, 5.10. Found: C, 60.86; H, 5.04.

5-(o-Cyanomethyl)anilino-1,2,3,4-thiatriazole (32).

To a solution of o-aminobenzyl cyanide (**31**)[12] (6.2 g, 46.9 mmol) and triethylamine (9.5 g, 93.8 mmol) in dichloromethane (75 ml) at -10°C was added dropwise and with stirring thiophosgene (5.4 g, 46.9 mmol) dissolved in 25 ml of dichloromethane. After stirring for 3 h. at room temperature, the solution was evaporated and the residue was extracted twice with ether (300 ml). The combined ether extracts were washed with water (300 ml), dried ($MgSO_4$), evaporated and chromatographed on silica gel with diethyl ether/light petroleum (1:1) as the eluent to give (o-cyanomethyl)phenyl isothiocyanate in 59% yield (4.8 g), mp 37-38°C (from EtOH at -16°C).

To a solution of this compound (2.1 g, 12 mmol) in ethanol (40 ml) was added at 0°C one equiv. of hydrazine (ca 50%, 0.76 g) dissolved in 10 ml of ethanol. (o-Cyanomethyl)phenylthiosemicarbazide crystallized out at 0°C and was collected in 72% yield (1.8 g), mp 124-127°C.

To a suspension of this compound (1.3 g, 6.3 mmol) in 10% hydrochloric acid (60 ml) was added dropwise aq. sodium nitrite (0.43 g, 6.3 mmol in 10 ml) at 0°C, and the whole was stirred for 15 min. The precipitated **32** was filtered off in 86% yield (1.18 g) and crystallized from dichloromethane/light petroleum at -16°C, decomp. at 80-83°C; IR (KBr) 3210 (br, NH), 2250 cm^{-1} (w, CN); ^1H NMR (400 MHz, DMSO-d_6) δ 4.08 (s, 2H, CH_2), 7.3-7.8 (t, m and d, 4H, Ar), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 19.6 (CH_2), 118.3 (CN), 123.3, 124.6, 126.7, 129.4, 129.9 and 138.3 (Ar C-atoms), 176.6 (C-5). Anal. Calcd for $C_9H_7N_5S$ (mol wt 217): C, 49.76; H, 3.22. Found: C, 49.95; H, 3.37.

5-(o-Cyanomethyl)phenylimino-4-methyl-1,2,3,4-thiatriazoline (33).

A suspension of **32** (1.0 g, 4.6 mmol) and trimethyloxonium tetrafluoroborate (0.68 g, 4.6 mmol) in dichloromethane (50 ml) was stirred at 5°C for 24 h. The reaction mixture was treated with aq. sodium hydroxide (10 g in 100 ml) and extracted twice with dichloromethane (200 ml). The combined extracts were washed with water (200 ml), dried ($MgSO_4$), evaporated and chromatographed on silica gel with diethyl ether/light petroleum (3:1) as the eluent to give **33** in 80% yield (0.85 g), mp 62-64°C (from Et_2O/light petroleum at -16°C); IR (KBr) 2250 (w, CN), 1620 cm^{-1} (s, C=N); ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 2H, CH_2), 4.0 (s, 3H, CH_3N), 6.95-7.45 (d, t and m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_2), 34.7 (CH_3N, $^1J_{CH}$ = 143 Hz), 118.1 (CN), 116.0, 124.4, 125.0, 129.5, 129.8 and 148.4 (Ar C-atoms), 156.0 (C-5). Anal. Calcd for $C_{10}H_9N_5S$ (mol wt 231): C, 51.93; H, 3.92. Found: C, 52.03; H, 3.94.

4-Cyanomethyl-2-methylaminobenzothiazole (34).

A solution of **33** (0.59 g, 2.6 mmol) in toluene (20 ml) was heated at 90°C for 3 days. After removal of the solvent, the residual oil was chromatographed on silica gel with diethyl ether/light petroleum (3:2) as the eluent to give **34** in 40.5% yield (0.21 g), mp 151-153°C (from toluene); IR (KBr) 3220 (br, NH), 2250 (w, CN), 1610 cm^{-1} (s); ^1H NMR (400 MHz, DMSO-d_6) δ 2.96 (d, 3H, CH_3N), 4.12 (s, 2H, CH_2), 7.04, 7.25 and 7.66 (t, d and d, 3H, Ar), 8.14 (q, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 19.8 (CH_2), 30.6 (CH_3N), 119.0 (CN), 119.9, 120.7, 120.8, 125.2, 130.3 and 150.8 (benzo C-atoms), 167.5 (C-2); mass spectrum, m/z (%) 203 (100, $M^{+\cdot}$), 188 (15), 175 (93), 162 (23), 148 (17), 134 (13), 118 (12), 103 (25), 91 (20, $C_7H_7^+$). Anal. Calcd for $C_{10}H_9N_3S$ (mol wt 203): C, 59.09; H, 4.43. Found: C, 59.03; H, 4.43.

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