Synthesis of Fused Dihydro-1,2,4-thiadiazolimines from Cyano-substituted Azides and Acyl Isothiocyanates

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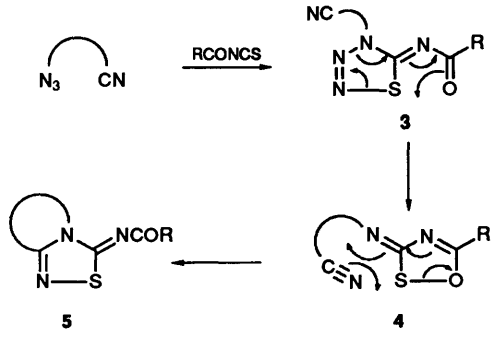
Organic azides, bearing a nitrile function at the γ- or δ-position, react with acyl isothiocyanates to give fused dihydro-1,2,4-thiadiazolimines. Representative examples are given. In the case of 2-cyanobenzyl azide and benzoyl isothiocyanate, the formation of **9b** is accompanied by two side products, **15** and **16**. Mechanisms are presented to explain the formation of the products.

4-Alkyl-5-(alkyl or aryl)imino-4,5-dihydro-1,2,3,4-thiatriazoles are known to react with unsaturated systems by a cycloaddition–elimination process and *via* thiapentalene intermediates.[1] Recently, we reported the first intramolecular version of this reaction, **1** → **2**, by connecting a nitrile group through a three- or four-atom tether to the exocyclic imine function, giving fused 1,2,4-thiadiazole derivatives.[2]

1 **2**

We now report an alternative method for preparing such heterocycles by tethering the nitrile group at the 4-position of the dihydrothiatriazole. The proposed tandem reaction is outlined in Scheme 1 where each step is supported by previous

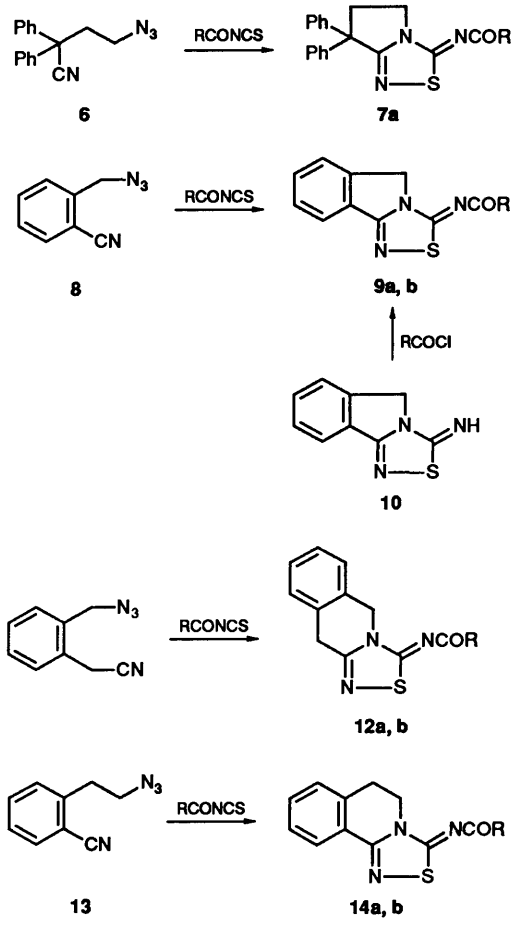


3 **4** **5**

Scheme 1

findings. Indeed, alkyl azides are known to cycloadd to the C=S function of electrophilic isothiocyanates,[3] and, in our cases, the resulting dihydrothiatriazoles **3** are expected to be unstable since they would decompose by anchimeric assistance of the carbonyl function.[4,5] The 1,2,4-oxathiazol-3-imines **4** formed possess a reactive thioimidate structural unit, similar to **1**, and should be capable of undergoing intramolecular cycloaddition–ring-opening reactions, leading to the fused thiadiazoles **5**. This reaction concept proved to be successful; the results are shown in Scheme 2.

Thus, when a series of cyano-substituted azides was treated with an equimolar amount of trichloroacetyl isothiocyanate or benzoyl isothiocyanate, the fused 1,2,4-thiadiazoles of Scheme 2 were isolated and characterized by comparison of their spectral data with those of **2** (see Experimental section). In addition, compounds **9a** and **9b** were independently synthesized by acylation of the thiazolo[3,4-*a*]isoindole **10**, prepared previously by another method.[2]



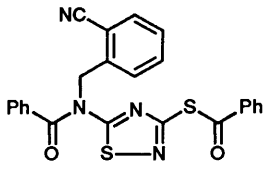
6 **7a** **8** **9a, b** **10** **12a, b** **13** **14a, b**

a: R = CCl_3
b: R = Ph

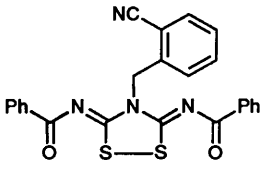
Scheme 2

The reactions furnished single products in all cases, except for azide **8** and the less reactive benzoyl isothiocyanate, where a substantial amount of thiadiazole **15** (12%) and traces of dithiazolidine **16** (0.4%) were isolated in addition to the fused heterocycle **9b** (22%). These side products are normally obtained from the reaction of benzyl azide with benzoyl isothiocyanate.[6]

In compound **15** the benzyl group has migrated to the exocyclic nitrogen atom during the reaction. A plausible explanation for this behaviour is presented in Scheme 3. Thus, the initially formed dihydrothiatriazole **17** would decompose *in situ* by anchimeric assistance of the carbonyl group to give the 1,2,4-oxathiazol-3-imine **18**. This compound can give rise to the



15



16

fused heterocycle **9b** by intramolecular cycloaddition–ring-opening, or to dithiazolidine **16** by intermolecular cycloaddition–ring-opening with a second molecule of isothiocyanate. We have shown[5] that a molecule of type **18** is also capable of reacting with the C=O function of the acyl isothiocyanate to give adduct **19**. The further sequence, from **19** to **15**, is speculative and comprises the elimination of benzoyl isothiocyanate to furnish the reactive intermediate **21**, followed by a re-addition of benzoyl isothiocyanate and benzoyl migration from nitrogen to sulfur in compound **23**, giving the rearranged product **15**. When the reaction was studied in more detail by ^{1}H NMR spectroscopic analysis of the crude reaction mixture under a variety of conditions, the results showed that the fused heterocycle **9b** is favoured over thiadiazole **15** by dilution as expected for an intramolecular *versus* intermolecular reaction of intermediate **18**. The best results were obtained when equimolar amounts of the reagents were refluxed in 1,2-dichloroethane for 2 weeks, giving 65% of **9b** and only 9% of **15**, in addition to 26% of unchanged azide **8**.

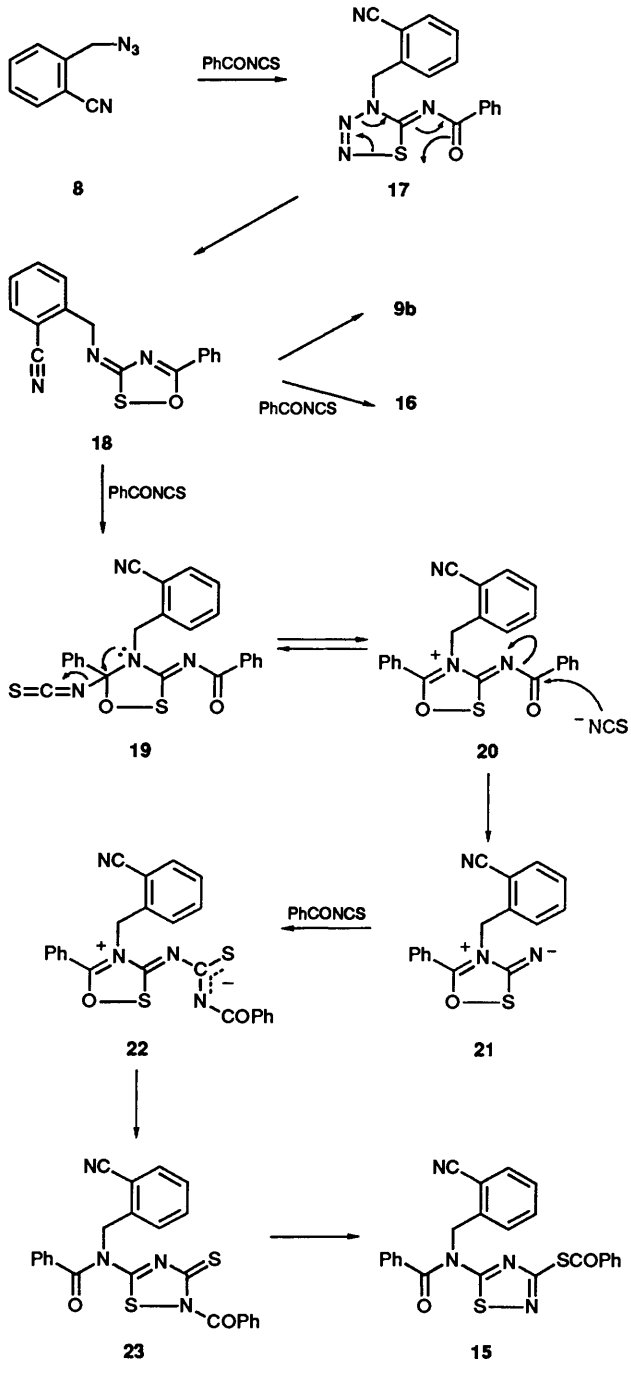
Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker WM-250 or AMX-400 spectrometer. The chemical shifts are reported in ppm relative to Me_4Si as an internal reference. The mass spectra were taken on a Kratos MS50 TC instrument operating at 70 eV.

Trichloroacetyl isothiocyanate,[7] *o*-(azidomethyl)benzonitrile **8**[8] and *o*-(azidoethyl)benzonitrile **13**[2] were prepared following the literature procedures. 4-Azido-2,2-diphenylbutyronitrile **6** (m.p. 46 °C) and *o*-(azidomethyl)phenylacetonitrile **11** (oil) were obtained by treatment of the corresponding bromides with sodium azide.

6,7-*Dihydro*-7,7-*diphenyl*-3-*trichloroacetylimino*-3H,5H-*pyrrolo*[2,1-c][1,2,4]*thiadiazole* **7a**.—A solution of azide **6** (1 g, 3.8 mmol) and trichloroacetyl isothiocyanate (0.77 g, 3.8 mmol) in dry dichloromethane (10 cm^3) was heated at reflux for 22 h. After evaporation of the solvent, the residual oil was chromatographed on silica gel with diethyl ether–light petroleum (3:7) as the eluent to give compound **7a** (0.46 g, 28%), m.p. 195–197 °C (from $CHCl_3$–hexane); δ_H 3.39 and 4.25 (4 H, 2 t, CH_2CH_2N) and 7.28–7.40 (10 H, m, 2 Ph); δ_C 41.2 (C-6, $^1J_{CH}$ 136), 43.7 (C-5, $^1J_{CH}$ 149), 55.4 (C-7), 94.3 (CCl_3), 127.2, 127.9, 128.9 and 140.8 (Ph C-atoms), 164.8 (C-7a) 172.7 (CO) and 178.2 (C-3); *m/z* 437/439 ($M^{\cdot+}$, 1%), 320 ($M^{\cdot+}$ − CCl_3, 100), 234 ($M^{\cdot+}$ − CCl_3CONCS, 2) and 86 (11) (Found: C, 51.8; H, 3.3. $C_{19}H_{14}Cl_3N_3OS$ requires C, 52.01; H, 3.22%).

3-*Trichloroacetylimino*-3H,5H-[1,2,4]*thiadiazolo*[3,4-a]*isoindole* **9a**.—A solution of azide **8** (1.6 g, 10.3 mmol) and trichloroacetyl isothiocyanate (2.1 g, 10.3 mmol) in dry dichloromethane (12 cm^3) was heated at 40 °C for 30 h. The precipitate **9a** was collected, and the filtrate was concentrated, diluted with diethyl ether and cooled to give another crop of product **9a** (total yield 1.26 g, 37%), m.p. 213–215 °C; δ_H 5.26 (2 H, s, CH_2), 7.6–7.7 (3 H, m, aromatic H) and 8.05 (1 H, d, 9-H); δ_C 49.4 (C-5, $^1J_{CH}$ 149), 94.4 (CCl_3), 123.1, 124.5, 126.8, 129.6, 132.4 and 142.9 (aromatic C-atoms), 158.8 (C-9b), 172.7 (CO) and 177.9 (C-3); *m/z* 333/335 ($M^{\cdot+}$, 2%), 216 ($M^{\cdot+}$ − CCl_3, 100), 148 (9) and 116 (14) (Found: C, 39.5; H, 1.85. $C_{11}H_6Cl_3N_3OS$ requires C, 39.45; H, 1.81).



Scheme 3

This compound was also obtained in 65% yield by heating compound **10** with one equivalent of trichloroacetyl chloride and triethylamine in acetonitrile.

Reaction of o-(*Azidomethyl*)*benzonitrile with Benzoyl Isothiocyanate*.—A mixture of azide **8** (1 g, 6.3 mmol) and benzoyl isothiocyanate (1.03 g, 6.3 mmol) was heated without solvent at 80 °C for 24 h. A ^{1}H NMR spectroscopic analysis indicated the presence of 46% **9b** (δ 5.17) and 26% **15** (δ 5.67) in addition to 28% unchanged azide **8** (δ 4.60). The reaction mixture was subjected to column chromatography on silica gel with chloroform–hexane (4:1) as the eluent, giving three main fractions. The first fraction (100 mg) was crystallized from

chloroform–diethyl ether and yielded a 1:1 mixture of products **15** and **16** (20 mg). The second fraction (338 mg) was crystallized from chloroform–diethyl ether and yielded pure product **15** (154 mg). The third fraction furnished product **9b** (290 mg) and was purified by treatment with charcoal in refluxing dichloromethane. When the other fractions and filtrates were evaporated, a 1:1 mixture of products **9b** and **15** (295 mg) was obtained.

3-Benzoylimino-3*H*,5*H*-[1,2,4]thiadiazolo[3,4-*a*]isoindole **9b** (22%), m.p. 246–247 °C; δ_H 5.17 (2 H, s, CH_2), 7.4–7.6 (6 H, m, aromatic H), 8.05 (1 H, d, 9-H) and 8.35 (2 H, d, aromatic H); δ_C 48.9 (C-5), 122.9, 124.5, 127.4, 128.3, 129.3, 129.7, 131.8, 132.4, 135.0 and 142.9 (aromatic C-atoms), 157.6 (C-9b), 174.2 (C-3) and 176.5 (CO); *m/z* 293 ($M^{\bullet+}$, 65%), 216 ($M^{\bullet+}$ − Ph, 23), 105 ($PhCO^+$, 100) and 77 (Ph^+, 50) (Found: C, 65.55; H 3.9. $C_{16}H_{11}N_3OS$ requires C, 65.55; H, 3.78%).

This compound was also obtained in 69% yield by heating compound **10** with benzoyl chloride (1 equiv.) and triethylamine (2 equiv.) in acetonitrile for 2 h.

3-Benzoylthio-5-[*N*-benzoyl-*N*-(*o*-cyanobenzyl)amino]-1,2,4-thiadiazole **15** (12%), m.p. 167–169 °C; ν_{max}(KBr)/cm^{-1} 2223m (CN), 1688s and 1654s (CO); δ_H 5.68 (2 H, s, CH_2), 7.25–7.65 (12 H, m, aromatic H) and 7.93 (2 H, d, aromatic H); δ_C 52.0 (CH_2, $^1J_{CH}$ 142), 111.0 (*C*–CN), 116.4 (CN), 127.1–139.5 (aromatic C-atoms), 157.8 (C-3), 171.8 (CON), 177.6 (C-5) and 187.6 (COS); *m/z* 456 ($M^{\bullet+}$, 2%), 293 ($M^{\bullet+}$ − PhCOSCN, 18), 105 ($PhCO^+$, 100), 77 (Ph^+, 60) and 51 (14) (Found: C, 63.0; H, 3.6. $C_{24}H_{16}N_4O_2S_2$ requires C, 63.08; H, 3.53%).

3,5-Bis(benzoylimino)-4-(*o*-cyanobenzyl)-1,2,4-dithiazolidine **16**. This compound was obtained as a 1:1 mixture with product **15** in 0.4% yield; δ_H 6.27 (s, CH_2); δ_C 51.9 (CH_2), 171.1 (C-3 and C-5) and 176.9 (CO).

5,10-*Dihydro*-3-*trichloroacetylimino*-3H-[1,2,4]*thiadiazolo*-[4,3-b]*isoquinoline* **12a**.—A solution of azide **11** (1.8 g, 10.5 mmol) and trichloroacetyl isothiocyanate (2.14 g, 10.5 mmol) in dichloromethane (10 cm^3) was refluxed for 16 h. The precipitate **12a** was collected, and the filtrate was concentrated and cooled to give another crop of product (total yield 1.9 g, 52%), m.p. 192–194 °C; δ_H 4.24 and 5.43 (2 H, 2 s, 2 CH_2) and 7.34–7.46 (4 H, m, aromatic H); δ_C 32.1 (C-10, $^1J_{CH}$ 133), 48.7 (C-5, $^1J_{CH}$ 146), 94.5 (CCl_3), 126.7–129.7 (aromatic C-atoms), 153.9 (C-10a), 172.3 (CO) and 180.6 (C-3, $^3J_{CH}$ 3); *m/z* 347/349 ($M^{\bullet+}$, 2%), 230 ($M^{\bullet+}$ − CCl_3, 100) and 128 (10) (Found: C, 41.25; H, 2.3. $C_{12}H_8Cl_3N_3OS$ requires C, 41.34; H, 2.31%).

5,10-*Dihydro*-3-*benzoylimino*-3H-[1,2,4]*thiadiazolo*[4,3,b]-*isoquinoline* **12b**.—A mixture of azide **11** (172 mg, 1 mmol) and benzoyl isothiocyanate (163 mg, 1 mmol) was heated overnight at 80 °C, and then diluted with dichloromethane (5 cm^3) and diethyl ether (20 cm^3) to give product **12b** (255 mg, 83%), m.p. 200–201 °C (from $CHCl_3$–diethyl ether); δ_H 4.18 and 5.42 (4 H, 2 s, 2 CH_2), 7.3–7.6 (7 H, m, aromatic H) and 8.40 (2 H, d, aromatic H); δ_C 32.0 (C-10, $^1J_{CH}$ 132), 48.3 (C-5, $^1J_{CH}$ 144.5), 126.6–135.4 (aromatic C-atoms), 152.3 (C-10a), 176.1 (CO) and 177.1 (C-3); *m/z* 307 ($M^{\bullet+}$, 64%), 230 ($M^{\bullet+}$ − Ph, 27), 202 ($M^{\bullet+}$ − PhCO, 35). 175 (9), 130 (12), 105 (98), 103 (18) and 77 (Ph^+, 100) (Found: C, 66.4; H, 4.35. $C_{17}H_{13}N_3OS$ requires C, 66.43; H, 4.26%).

5,6-*Dihydro*-3-*trichloroacetylimino*-3H-[1,2,4]*thiadiazolo*-[3,4-a]*isoquinoline* **14a**.—A solution of azide **13** (0.5 g, 2.9 mmol) and trichloroacetyl isothiocyanate (0.5 g, 2.6 mmol) in dichloromethane (5 cm^3) was stirred at room temperature for 5 days. The precipitate **14a** was collected and the filtrate was chromatographed on silica gel with chloroform–hexane (4:1) as the eluent to give a second crop of product **14a** (total yield 430 mg, 46%), m.p. 235–236 °C; δ_H 3.29 and 4.57 (4 H, 2 t, 2 CH_2), 7.35–7.60 (3 H, m, aromatic H) and 8.2 (1 H, d, 10-H); δ_C 27.5 and 44.0 (CH_2CH_2N), 96.9 (CCl_3), 125.0, 126.7, 128.3 (× 2), 132.5 and 135.2 (aromatic C-atoms), 151.9 (C-10b), 172.4 (CO) and 180.9 (C-3); *m/z* 347/349 ($M^{\bullet+}$, 1%), 230 ($M^{\bullet+}$ − CCl_3, 100), 162 (7) and 128 (17) (Found: C, 41.45; H, 2.5. $C_{12}H_8Cl_3N_3OS$ requires C, 41.34; H, 2.31%).

5,6-*Dihydro*-3-*benzoylimino*-3H-[1,2,4]*thiadiazolo*[3,4-a]*isoquinoline* **14b**.—A mixture of azide **13** (0.5 g, 2.9 mmol) and benzoyl isothiocyanate (0.47 g, 2.9 mmol) was heated at 100 °C for 6 days, and then chromatographed on silica gel with diethyl ether–light petroleum (1:1) as the eluent to give product **14b** (0.15 g, 41%), m.p. 226–228 °C; δ_H 3.25 and 4.56 (4 H, 2 t, CH_2CH_2N), 7.3–7.55 (6 H, m, aromatic H), 8.19 (1 H, d, 10-H) and 8.36 (2 H, d, aromatic H); δ_C 27.7 and 43.5 (CH_2CH_2N), 125.5–135.6 (aromatic C-atoms), 150.7 (C-10b), 176.2 (CO) and 177.3 (C-3); *m/z* 307 ($M^{\bullet+}$, 100%), 306 (35), 230 ($M^{\bullet+}$ − Ph, 54), 191 (10), 105 ($PhCO^+$, 49) and 77 (Ph^+, 48) (Found: C, 66.2; H, 4.3. $C_{17}H_{13}N_3OS$ requires C, 66.43; H, 4.26%).

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