

Synthesis of fused 1,2,4-thiadiazoles from ω -amino nitriles and thiocarbonyl isothiocyanates

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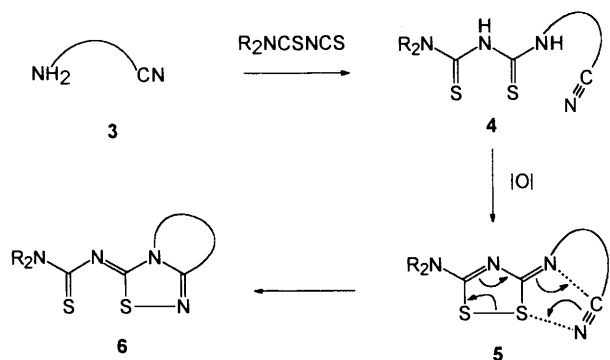
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Fused 1,2,4-thiadiazoles can be prepared in high yields from cyano substituted amines and thiocarbamoyl isothiocyanates by oxidation of the intermediate dithiobiurets.

3-(Substituted imino)-3*H*-1,2,4-dithiazoles **1** possess a thioimide function in which the electron flow from sulfur to the exocyclic nitrogen atom allows them to react as masked 1,3-dipoles.¹ Thus, they undergo cycloaddition–ring opening reactions with nitriles, heterocumulenes and activated olefins and acetylenes ($a \equiv b$) to give new five-membered heterocycles **2** via thiapentalenic intermediates.²



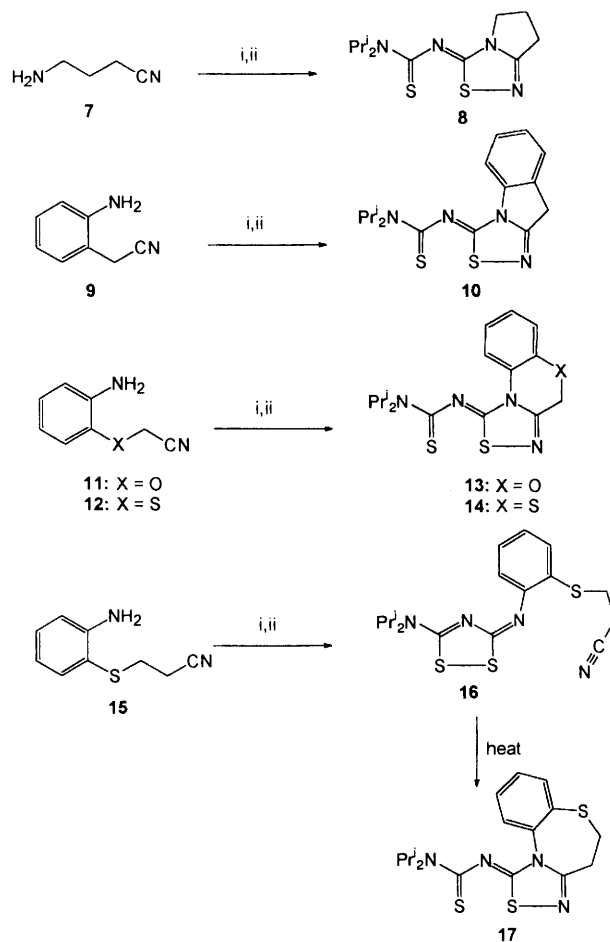
If the exocyclic imine of the dithiazole is connected through a three-, four- or five-atom tether with a nitrile function, *i.e.* structure **5**, the formation of 5/5, 5/6 and 5/7 fused 1,2,4-thiadiazoles is feasible. Compared with the sluggish intermolecular reactions of **1** with unactivated nitriles,³ the intramolecular reactions of **5** should be promoted by the entropy effect, and further enhanced by the presence of an *ortho*-benzene ring as part of the tethering side-chain. Based on these considerations we have devised a new and convenient synthetic method for fused 1,2,4-thiadiazoles starting from readily available reagents. As shown in Scheme 1, ω -amino nitriles are



Scheme 1

added to thiocarbamoyl isothiocyanates⁴ to give dithiobiurets **4** which are subsequently oxidized to the dithiazoles **5**. These compounds possess the necessary structural units to undergo a cyclo-substitution, giving access to the fused 1,2,4-thiadiazoles **6**. This synthetic methodology proved to be successful; the results are shown in Scheme 2.

Thus, diisopropylthiocarbamoyl isothiocyanate⁴ was treated with 4-aminobutyronitrile⁵ **7**, *o*-aminobenzyl cyanide⁶ **9**, *o*-aminophenoxyacetonitrile⁷ **11** and *o*-aminophenylsulfanylacetonitrile⁸ **12** to give the corresponding dithiobiurets (see structure **4**). These compounds were subjected to oxidative



Scheme 2 Reagents: i, $\text{Pr}^i_2\text{NCSNCS}$; ii, Br_2 -pyridine

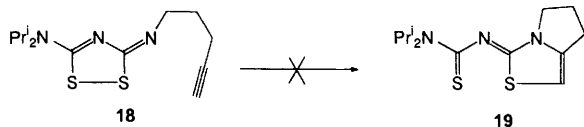
ring closure with bromine in the presence of pyridine at room temperature and furnished directly the rearrangement products **8**, **10**, **13** and **14** in high yields (95–98%). In the case of *o*-aminophenylsulfanylpropionitrile⁹ **15**, the corresponding dithiobiuret gave on oxidation the dithiazole **16** in 98% yield. This compound could be rearranged quantitatively into the thiadiazolo[3,4-*d*]benzothiazepine **17** upon refluxing in toluene.

The structures of the reaction products were unambiguously established by ¹H and ¹³C NMR, IR and mass spectral data.† In particular, the signals of the ring carbon atoms in the ¹³C NMR spectra agree with those of the same ring skeletons published recently.¹⁰ In addition, they all exhibit a thiourea C=S resonance at the expected position (δ 185–186).^{3b,11} These fused heterocycles belong to a general class of thiapentalene-like molecules having an S···S contact distance significantly shorter than the sum of the van der Waals radii (3.60 Å).^{3b,12}

† Spectral results are available as a supplementary publication SUP No. 57124 (3 pp.). For details of the Supplementary publications scheme, see Instructions for Authors (1996), *J. Chem. Soc., Perkin Trans. 1*, 1996, issue 1.

The dithiazole **16** shows typical IR $C\equiv N$ and $C=N$ stretching vibrations at 2247m and 1635s cm^{-1} respectively, and further spectral data in consonance with its structure.†

Finally, it is interesting to note that in contrast to the easy formation of compound **8**, the fused thiazole **19** could not be obtained from the acetylenic substituted 3-iminodithiazole **18**; instead decomposition occurred at room temperature to intractable tars. Compound **18** was prepared from 5-aminopent-1-yne by the sequence outlined above.



Experimental

General procedure

A solution of diisopropylthiocarbamoyl isothiocyanate⁴ (1 g, 4.95 mmol) and the cyano substituted amine (4.95 mmol) in dry diethyl ether (20 cm^3) was stirred at room temperature after which the precipitated dithiobiuret was filtered off after 15 min (yields 67–91%).

The dithiobiuret (1.50 mmol) was dissolved in dichloromethane (20 cm^3) containing pyridine (1.50 mmol) and a solution of bromine (1.50 mmol) in dichloromethane (20 cm^3) was added dropwise to it with vigorous stirring; the bromine colour disappeared immediately. The reaction mixture was washed with water (50 cm^3) and aqueous NaOH (0.05 mol dm^{-3} ; 50 cm^3), dried (MgSO_4) and evaporated to give the following products: **8** (95%), mp $223\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$), **10** (98%), mp $186\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$), **13** (98%), mp $156\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$), **14** (97%), mp $190.5\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$) and **16** (98%), mp $115\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-hexane}$).

Compound **16** (0.1 g) was refluxed overnight in toluene (300 cm^3) and yielded quantitatively **17**, mp $198\text{ }^\circ\text{C}$ (from $\text{CH}_2\text{Cl}_2\text{-hexane}$).

Acknowledgements

Financial support from the NFWO and the Ministerie voor Wetenschappenbeleid is gratefully acknowledged. This work has been accomplished with fellowships from the IWT (for B. D.) and the NFWO (for W. D.).

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Paper 5/07215H
Received 1st November 1995
Accepted 24th November 1995