

## Intramolecular Cycloaddition–Elimination Reactions of 4-Methyl-5-(substituted)-imino- $\Delta^2$ -1,2,3,4-thiatriazolines

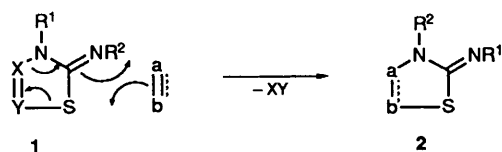
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4-Methyl-1,2,3,4-thiatriazolin-5-imines, bearing a cyanopropyl, *o*-cyanobenzyl or *o*-(cyanomethyl)-benzyl group at the exocyclic imine function, thermolyse smoothly to give, after loss of nitrogen, fused 1,2,4-thiadiazole derivatives **7**, **11** and **12**.

Much effort is presently devoted to the intramolecular version of cycloaddition reactions, such as Diels–Alder reactions<sup>1</sup> and 1,3-dipolar cycloaddition reactions.<sup>2</sup> This communication reports a novel extension of this chemistry.

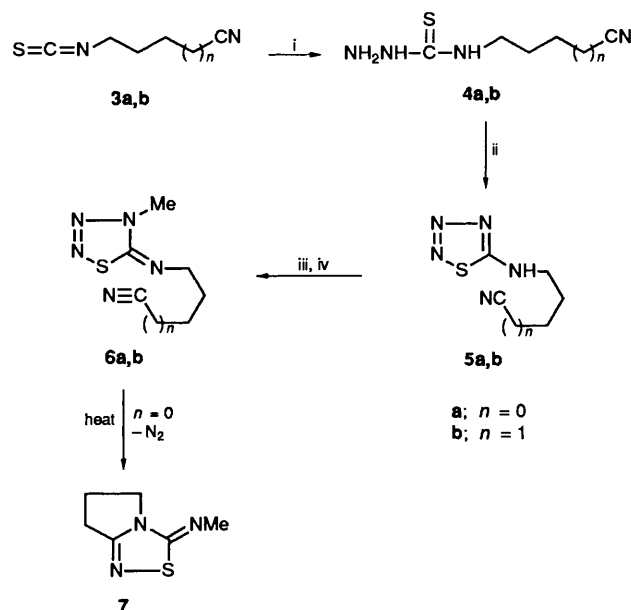
Heterocycles **1**, possessing an exocyclic imine function in the  $\alpha$ -position to a ring-sulfur atom, can react as masked 1,3-dipoles with selected unsaturated reactants to furnish new heterocyclic rings **2** by a cycloaddition–elimination process.<sup>3</sup>



Thiatriazolin-5-imines **1** ( $X = Y = N$ ) may be considered as prototype molecules of this process since nitrogen is eliminated during the reactions with electrophilic unsaturated systems. Their intermolecular cycloaddition–elimination reactions were studied in detail with isothiocyanates,<sup>4</sup> isocyanates,<sup>5</sup> ketenes<sup>6</sup> and electrophilic nitriles,<sup>7</sup> and were shown to proceed *via* hypervalent sulfur intermediates<sup>5b</sup> and by a different mechanism<sup>4d</sup> from that of the 1,3-dipolar cycloadditions studies by Huisgen.<sup>8</sup> We now report the first intramolecular reactions of these heterocycles **1** ( $X = Y = N$ ) by connecting a nitrile function through a three- or four-atom tether to the exocyclic imine function.

5-(3-Cyanopropyl)aminothiatriazole **5a** (m.p. 65 °C, 72%) was prepared from the known<sup>9</sup> isothiocyanate **3a** by the classical method<sup>10</sup> of hydrazination and nitrosation (Scheme 1). Methylation of thiatriazole **5a** with Meerwein's reagent occurred exclusively at the 4-position<sup>6a</sup> and furnished thiatriazoline **6a** as a yellow–brown oil in 91% yield. This compound thermolysed at 70 °C with extrusion of nitrogen to give an oil which was characterized as the pyrrolo[2,1-*c*][1,2,4]thiadiazole **7** (66%) on the basis of spectral analyses and by its conversion into the corresponding picrate (m.p. 195 °C).\*

The intramolecular reaction described above could not be extended to the higher homologue by elongation of the tethering sidechain with one methylene unit. Thus, thiatriazoline **6b** (yellow–orange oil) was synthesized in 29% yield from 4-cyanobutyl isothiocyanate<sup>9</sup> **3b** *via* the thiosemicarbazide **4b** and the thiatriazole **5b** (m.p. 53 °C) (Scheme 1), and proved to be thermally stable in benzene at 75 °C for 1 day (<sup>1</sup>H NMR control); in refluxing toluene it decomposed to unidentified products. This result demonstrates that the formation of a 5/6-fused heterocycle is disfavoured over a 5/5-fused system.



Scheme 1 Reagents: i,  $N_2H_4$ ; ii,  $HNO_2$ ; iii,  $Me_3O^+ BF_4^-$ ; iv,  $NaOH$

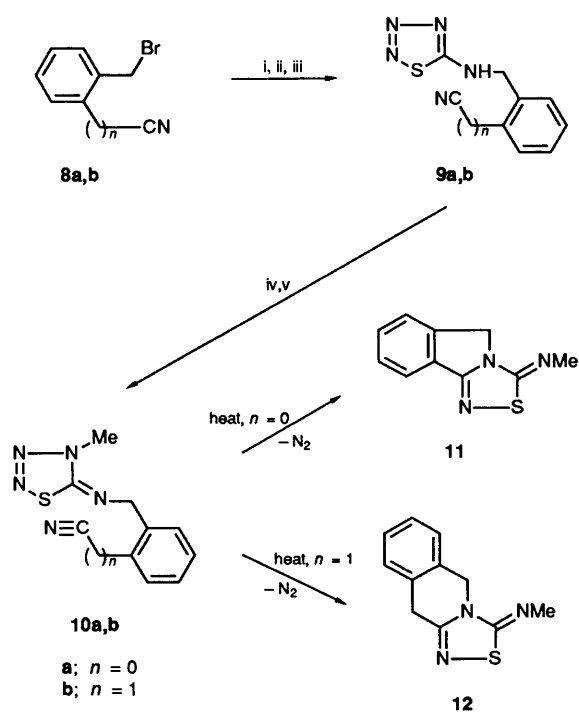
The introduction of a benzene ring into the tethering sidechain facilitates the intramolecular process (Scheme 2). Thus, the thiatriazoles **9a** (m.p. 80 °C decomp., 54%) and **9b** (m.p. 105 °C, 48%) were prepared from the substituted benzyl bromides **8a** and **8b** *via* the corresponding isothiocyanates and thiosemicarbazides, and then methylated with Meerwein's reagent. In the case of compound **9a**, treatment of the methylated salt with sodium hydroxide induced a spontaneous elimination of nitrogen from compound **10a** with formation of the [1,2,4]thiadiazolo[3,4-*a*]isoindole **11** (m.p. 174 °C, 54%). Compound **10b** (m.p. 72 °C) could be isolated (50%) and characterized,\* but decomposed smoothly in ethanol at 75 °C (24 h) to furnish the [1,2,4]thiadiazolo[4,3-*b*]isoquinoline **12** (m.p. 121 °C) in 65% yield. Hence, the formation of a 6/6-fused system is assisted by a favourable entropic effect brought about by restricting the sidechain mobility.

### Experimental

*Typical Procedure:* 6,7-Dihydro-3-methylimino-3H,5H-pyrrolo[2,1-*c*][1,2,4]thiadiazole **7**.—To an ethanolic solution (30 cm<sup>3</sup>) of isothiocyanate **3a** (2.65 g, 21 mmol) was added, at –20 °C, aq. hydrazine (*ca.* 50%, 3.15 g, 3 equiv.) dissolved in ethanol (10 cm<sup>3</sup>), and the whole was stirred with cooling for 10 min. The precipitated thiosemicarbazide **4a** was filtered off and washed with diethyl ether (3.3 g, 99%), m.p. 117–118 °C (from ethanol).

Aq. sodium nitrite (1.5 g, 22 mmol in 14 cm<sup>3</sup>) was added

\* All compounds were unambiguously characterized by <sup>1</sup>H and <sup>13</sup>C NMR, and IR spectroscopic data.



**Scheme 2** Reagents: i, KSCN; ii,  $\text{N}_2\text{H}_4$ ; iii,  $\text{HNO}_2$ ; iv,  $\text{Me}_3\text{O}^+\text{BF}_4^-$ ; v, NaOH

dropwise to an ice-cooled solution of compound **4a** (3.3 g, 21 mmol) in 10% hydrochloric acid (14  $\text{cm}^3$ ). The resulting precipitate **5a** was filtered off and dried [if compound **5a** separated as an oil, the mixture was extracted twice with chloroform (50  $\text{cm}^3$ ), dried ( $\text{MgSO}_4$ ) and evaporated] (2.58 g, 73%), m.p. 65 °C (needles from  $\text{CH}_2\text{Cl}_2$ -hexane).

A suspension of this compound (2.58 g, 15.3 mmol) and trimethyloxonium tetrafluoroborate (2.26 g, 15.3 mmol) in dry dichloromethane (80  $\text{cm}^3$ ) was stirred at 5 °C for 24 h. The reaction mixture was treated with aq. NaOH (200  $\text{cm}^3$ ; 2.5 mol  $\text{dm}^{-3}$ ) and then extracted with dichloromethane (200  $\text{cm}^3$ ). The extracts were washed with water (200  $\text{cm}^3$ ), dried ( $\text{MgSO}_4$ ) and evaporated to give compound **6a** as a yellow-brown oil (2.55 g, 91%).

A solution of this compound (2.55 g, 14 mmol) in ethanol (25  $\text{cm}^3$ ) 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 compound **7** as an oil (1.43 g, 66%);  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  1655s and 1605s;  $\delta_{\text{H}}(\text{CDCl}_3)$  2.4–2.8 (4 H, m,  $\text{CH}_2\text{CH}_2$ ), 3.0 (3 H, s,  $\text{CH}_3\text{N}$ ) and 3.75 (2 H, t,  $\text{CH}_2\text{N}$ );  $\delta_{\text{C}}(\text{CDCl}_3)$  25.2 and 25.3 ( $\text{CH}_2\text{CH}_2$ ), 40.8 ( $\text{CH}_3\text{N}$ ,  $^1J_{\text{CH}}$  134.5), \*42.6 ( $\text{CH}_2\text{N}$ ), 160.6 ( $\text{SC}=\text{N}$ ) and 164.2 ( $\text{C}=\text{N}$ ) (Found for the picrate of **7**: C, 37.6; H, 3.2.  $\text{C}_{12}\text{H}_{12}\text{N}_6\text{O}_7\text{S}$  requires C, 37.50; H, 3.15).

### Acknowledgements

Financial support from the University, the N.F.W.O. and the 'Ministerie voor Wetenschapsbeleid' is gratefully acknowledged. S. Leurs is indebted to the I.W.O.N.L. for a fellowship.

\* *J* values are given in Hz.

### References

- W. Carruthers, in *Cycloaddition Reactions in Organic Synthesis*, eds. J. E. Baldwin and P. D. Magnus, Pergamon, Oxford, 1990, p. 140; E. C. Taylor, *Bull. Soc. Chim. Belg.*, 1988, **97**, 599.
- A. Padwa, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley-Interscience, New York, 1984, vol. 2, p. 277.
- V. N. Drozd and N. S. Zefirov, *Sulfur Reports*, 1981, **1**, 271.
- (a) G. L'abbé, A. Timmerman, C. Martens and S. Toppet, *J. Org. Chem.*, 1978, **43**, 4951; (b) G. L'abbé, K. Allewaert and S. Toppet, *J. Heterocycl. Chem.*, 1988, **25**, 1459; (c) G. L'abbé, K. Buelens, W. Franek and P. Delbeke, *Bull. Soc. Chim. Belg.*, 1989, **98**, 879; (d) G. L'abbé and K. Buelens, *J. Heterocycl. Chem.*, 1990, **27**, 199; (e) G. L'abbé and K. Buelens, *Tetrahedron*, 1990, **46**, 1281; (f) G. L'abbé, N. Weyns and K. Buelens, *Bull. Soc. Chim. Belg.*, 1990, **99**, 391.
- (a) G. L'abbé and E. Albrecht, *Bull. Soc. Chim. Belg.*, 1991, **100**, 27; (b) G. L'abbé, N. Weyns, I. Sannen, P. Delbeke and S. Toppet, *J. Heterocycl. Chem.*, 1991, **28**, 405.
- (a) N. H. Toubro and A. Holm, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1440; (b) G. L'abbé and I. Sannen, *Bull. Soc. Chim. Belg.*, 1991, **100**, 29.
- G. L'abbé and I. Sannen, *J. Heterocycl. Chem.*, 1991, **28**, 333.
- R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley-Interscience, New York, 1984, vol. 1, p. 1.
- A. F. McKay, D. L. Garmaise, R. Gaudry, H. A. Baker, G. Y. Paris, R. W. Kay, G. E. Just and R. Schwartz, *J. Am. Chem. Soc.*, 1959, **81**, 4328.
- E. Lieber, C. N. Pillai and R. D. Hites, *Can. J. Chem.*, 1957, **35**, 832.

Paper 1/05619K

Received 5th November 1991

Accepted 5th November 1991