A Novel, One-pot Synthesis of 2*H*-Benz[*e*]-1,3-oxazine-2-thiones†

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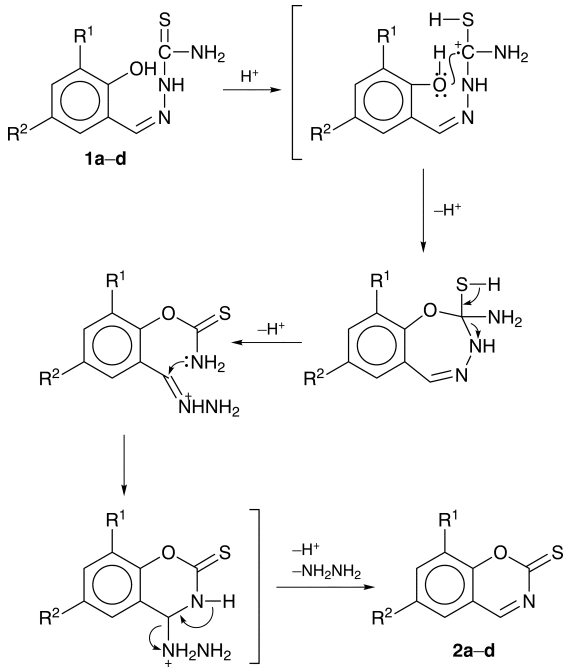
A novel, acid-catalysed cyclisation of salicylaldehyde thiosemicarbazones (**1a**–**d**) yields new 2*H*-benz[*e*]-1,3-oxazine-2-thiones (**2a**–**d**) in a one-pot procedure.

Salicylaldehyde has been used as a bifunctional building block for preparing various oxygen heterocycles of chemical and biological interest.[1–5] In pursuing our work on the utilization of thiosemicarbazones in heterocyclic syntheses[6–8] we have devised a facile, one-pot, general synthetic method for hitherto unreported benzoxazines **2** using salicylaldehyde as the basic starting material.

The present synthesis involves a novel, acid-catalysed cyclization of salicylaldehyde thiosemicarbazones **1** to benzoxazines **2** (Scheme 1). After some preliminary experimentation, it was found that the envisaged cyclization (**1** → **2**) was effective with concentrated H_2SO_4 at 5–25 °C to yield the benzoxazines **2** in high yields (78–86%). However, the use of AcOH, poly(phosphoric acid) (PPA) or dilute H_2SO_4 at various temperatures (5–100 °C) was far less effective resulting in either no cyclization or relatively very low yields (16–55%). The probable mechanism shown is supported by the confirmed formation of hydrazine during the reaction.



Scheme 1

Benzoxazines **2** are required as intermediates for developing potential anticandidal drugs designed to use the peptide transport system as a means for drug delivery.[9–11] The easy availability of salicylaldehyde thiosemicarbazones **1** and simple operations under mild conditions makes the present cyclization a general synthetic method for benzoxazines of the type **2**.

Experimental

Mps were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 993 spectrometer. ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer using [$^2H_6$]dimethyl sulfoxide as solvent and $SiMe_4$ as internal standard; *J* values are given in Hertz. Mass spectra were recorded on a JEOL D-300 mass spectrometer at 70 eV. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser.

Preparation of 2H-*Benz*[e]-1,3-*oxazine*-2-*thiones* **2**. *General Procedure*.—Salicylaldehyde thiosemicarbazone **1** (10 mmol) was dissolved in concentrated H_2SO_4 (10 ml) under ice-cooling (maintaining the temperature of the reaction mixture at < 5 °C) and stirred in an ice-bath for 30 min at < 5 °C. The mixture was further stirred at room temperature (≈5 °C) for 4 h. The product was isolated by pouring the mixture into water (50 ml) followed by basification with concentrated NH_4OH under ice-cooling at < 5 °C. It was recrystallized from ethanol to obtain an analytical sample of **2** as white needles. **2a** ($R^1 = R^2 = H$): mp 142–143 °C, yield 80%; $\tilde{\nu}_{max}/cm^{-1}$ 1615 (C=N) and absence of OH, NH and NH_2 bands; δ_H 7.21–7.96 (m, 4 H, ArH), 8.48 (s, 1H, 4-H); *m*/*z* 163 (M^+) (Found: C, 58.6; H, 3.0; N, 8.4. C_8H_5NOS requires C, 58.9; H, 3.1; N, 8.6%). **2b** ($R^1 = H$, $R^2 = NO_2$): mp 192–195 °C, yield 83%; $\tilde{\nu}_{max}/cm^{-1}$ 1625 (C=N) and absence of OH, NH and NH_2 bands; δ_H 7.33 (d, *J* 9.5, 1H, 8-H), 7.99 (dd, *J* 9.5, 2.6, 1H, 7-H), 8.28 (d, *J* 2.6, 1H, 5-H), 8.59 (s, 1H, 4-H); *m*/*z* 208 (M^+) (Found: C, 45.9; H, 1.9; N, 13.3. $C_8H_4N_2O_3S$ requires C, 46.2; H, 1.9; N, 13.5%). **2c** ($R^1 = NO_2$, $R^2 = H$): mp 180–182 °C, yield 78%; $\tilde{\nu}_{max}/cm^{-1}$ 1625 (C=N) and absence of OH, NH and NH_2 bands; δ_H 7.30–8.16 (m, 4H, ArH), 8.63 (s, 1H, 4-H), *m*/*z* 208 (M^+) (Found: C, 46.4; H, 2.1; N, 13.4. $C_8H_4N_2O_3S$ requires C, 46.2; H, 1.9; N, 13.5%). **2d** ($R^1 = R^2 = Br$): mp 186–189 °C, yield 86%; $\tilde{\nu}_{max}/cm^{-1}$ 1620 (C=N) and absence of OH, NH and NH_2 bands; δ_H 8.17 (d, *J* 2.4, 5-H), 7.85 (d, *J* 2.4, 1H, 7-H), 8.61 (s, 1H, 4-H); *m*/*z* 321 (M^+) (Found: C, 29.7; H, 1.0; N, 4.5. $C_8H_3Br_2NOS$ requires C, 29.9; H, 0.9; N, 4.4%).

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References

1 C. N. O'Callaghan and T. B. M. McMurry, *J. Chem. Res.*, 1997, (*S*) 78; (*M*) 0643.
2 C. N. O'Callaghan, T. B. M. McMurry and C. J. Cardin, *J. Chem. Res.*, 1990, (*S*) 132; (*M*) 0901.
3 J. Svetlik, V. Hanus and J. Bella, *Liebigs Ann. Chem.*, 1989, 91.
4 J. Svetlik, F. Turecek and V. Hanus, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2053.
5 G. Jones, *Org. React.* (*N.Y.*), 1967, **15**, 204.
6 L. D. S. Yadav and D. R. Pal, *J. Chem. Res.* (*S*), 1997, 90.
7 L. D. S. Yadav, A. Vaish and S. Sharma, *J. Agric. Food Chem.*, 1994, **42**, 811.
8 L. D. S. Yadav and S. Sharma, *Synthesis*, 1993, 864.
9 T. E. Fickel and C. Gilvarg, *Nature* (*London*), 1973, **241**, 161.
10 J. M. Becker and F. Naider, in *Microorganisms and Nitrogen Source*, ed. J. W. Payne, Wiley, Chichester, 1980, p. 258.
11 P. J. McCartly, P. F. Troke and K. Gull, *J. Gen. Microbiol.*, 1985, **131**, 775.

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