

1,4-Oxazine†

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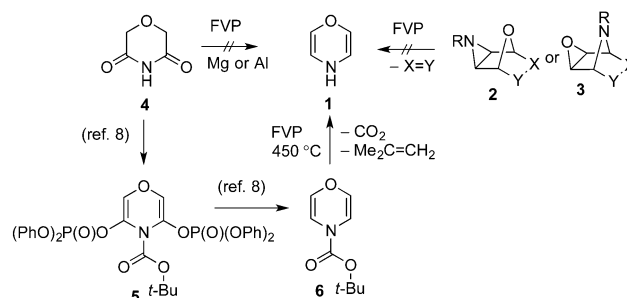
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The fundamental heterocyclic compound 1,4-oxazine has been generated using FVP. It is the first parent heterocycle among all the possible isomeric oxazines, thiazines and their heavier atom analogues to be characterised spectroscopically, and is shown to exist in solution entirely as the *4H*-isomer. X-ray structure determination of the *N*-Boc precursor shows significant deviations from theoretically predicted geometric parameters.

While six-membered ring heterocycles containing two group 15 atoms, exemplified by the three isomeric diazines, are well known, stable aromatic compounds, neutral analogues containing one or more group 16 atoms cannot be aromatic and are much less stable. For example, although both 1,4-dioxin¹ and 1,4-dithiin² were prepared at an early date, these compounds are rather unstable and highly reactive towards addition and polymerisation.^{1,3} Among the many possible parent six-membered ring heterocycles containing one group 15 atom and one group 16 atom, none appear to have been so far isolated or spectroscopically characterised, with the sole exception of 1,4-thiazine which was the subject of a single report in 1948,⁴ not subsequently reproduced.

1,4-Oxazine **1** is among the simplest heterocyclic compounds to be so far unknown. Although a fair number of substituted and ring-fused 1,4-oxazines are known, the parent compound has never been prepared and work on it has so far been restricted to theoretical predictions of bond lengths and electron distribution.⁵ Our long-standing interest in the area started with the unexpected formation of 1,4-dioxin in a retro-Diels–Alder reaction under conditions of flash vacuum pyrolysis (FVP), which allowed its NMR spectra to be recorded for the first time.⁶ However numerous attempts to extend the retro-Diels–Alder approach to formation of 1,4-oxazine by pyrolysis of derivatives **2** or **3** failed. Synthesis analogous to that of 1,4-thiazine by pyrolysis of cyclic imide **4**, either with or without



Scheme 1 Routes to 1,4-oxazine.

a reducing metal, was also unsuccessful as other processes intervened (Scheme 1).⁷

A breakthrough in the area occurred in 2007 when Coudert, Gillaizeau and co-workers described the three-step conversion of **4** *via* **5** into **6**, thus making a simple monosubstituted 1,4-oxazine readily available for the first time.⁸ We now report the removal of the *tert*-butoxycarbonyl group from **6** to generate the parent 1,4-oxazine **1** together with its spectroscopic characterisation. Wasserman achieved thermal deprotection of an aliphatic *N-tert*-butoxycarbonyl amine in the course of a synthesis of the alkaloid homaline by boiling either in quinoline or diphenyl ether,⁹ and a short time later Cava extended this method to heterocyclic derivatives when he described removal of *N-tert*-butoxycarbonyl groups from pyrroles and indoles in almost quantitative yield simply by heating the solids at 180–185 °C.¹⁰

This suggested to us that FVP might be the ideal technique for conversion of **6** into **1**: the purely thermal reaction involving no acids or bases would be further encouraged by high vacuum since two molecules of inert gaseous by-products are formed – isobutene and CO₂. The experimental set-up would also produce the oxazine directly in the liquid nitrogen-cooled cold trap giving the best chance for its isolation. In a brief model study, both *N*-*tert*-butoxycarbonylpiperidine and -pyrrole behaved well giving excellent yields of deprotected products together with isobutene and CO₂ at 450–500 °C and 10^{–2} Torr. When a sample of compound **6** was subjected to FVP at 450 °C and 10^{–2} Torr it gave some unreacted starting material at the

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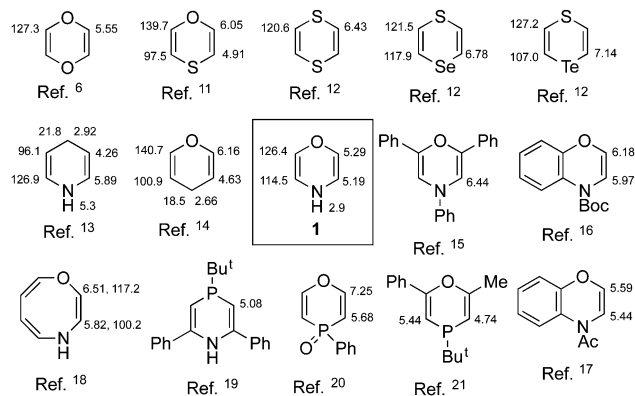


Fig. 1 ^1H and ^{13}C NMR chemical shifts of **1** compared with related heterocycles.

furnace exit and in the cold trap an oil which was washed out with CDCl_3 for analysis.[‡] The spectrum proved to be extremely clean with peaks due to isobutene, the starting material **6** and a new A_2B_2 pattern at δ 5.19 and 5.29 (J 4.5 Hz) attributed to **1**. The NH appeared as a broad peak centred at δ 2.92. In the ^{13}C NMR spectrum all peaks were attributable to starting material **6**, isobutene, and 1,4-oxazine **1** with signals at δ 114.5 ($=\text{CH}-\text{N}$) and 126.4 ($=\text{CH}-\text{O}$). A comparison of these chemical shifts with those for comparable ring systems is shown in Fig. 1.

Both C and H values are almost halfway between those for the corresponding atoms in pyran and dihydropyridine – in some sense it may be considered a hybrid of these two structures. The ^1H chemical shift values are markedly lower than for the vinylogous 10π -1,4-oxazocine indicating the complete absence of aromaticity for this 8π -system. There was no evidence at all of the isomeric $2H$ structure which is perhaps surprising given the ready interconversion observed in such similar systems as $1H$ - and $3H$ -azepine.²² In an early report of ^1H NMR data supporting the transient existence of $2H$ -1,4-benzoxazine, the spectrum was obtained in TFA as solvent and so clearly refers to a protonated species.²³

A fully coupled ^{13}C NMR spectrum allowed determination of C–H coupling constants for **1** as shown in Table 1 and these make an interesting comparison with the values for **6**, 1,4-dioxin,⁶ 1,4-dithiin, 1,4-thiaselenin and 1,4-thiatellurin.¹²

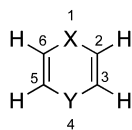
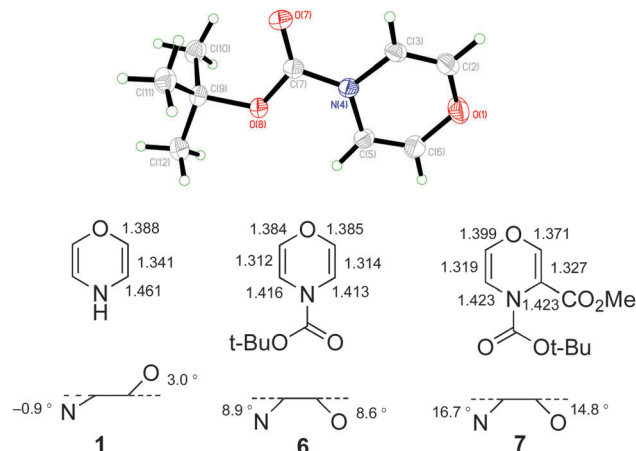


Table 1 CH coupling constants (Hz) for **1**, **6** and similar compounds

X	Y	$^1J_{\text{C2-H2}}$	$^2J_{\text{C2-H3}}$	$^3J_{\text{C2-H6}}$	$^1J_{\text{C3-H3}}$	$^2J_{\text{C3-H2}}$	$^3J_{\text{C3-H5}}$	Ref.
O	NH	196.9	10.8	5.2	178.4	14.0	5.2	^a
O	NBoc	197.6	11.1	6.2	187.8	14.9	3.2	^{a,b}
		198.4	11.1	6.3	187.8	14.9	3.3	
O	O	197.2	16.4	~0	197.2	16.4	~0	6
S	S	179.2	8.1	~0	179.2	8.1	~0	12
S	Se	178.8	7.7	2.0	181.2	7.7	~0	12
S	Te	177.8	6.2	1.9	177.5	5.8	~0	12

^a This work. ^b Two separate values for **6** due to restricted rotation of Boc.⁸



tube heated within a horizontal laboratory tube furnace at 450 °C and maintained at a pressure of 10^{-2} Torr by a rotary oil pump. The contact time in the hot zone under these conditions was estimated to be ca. 10 ms. The products were collected in a liquid nitrogen cooled U-shaped trap and, after the pyrolysis was complete, were dissolved out in CDCl_3 for analysis. The spectra showed the presence of unchanged **6**, isobutene, and **1**: δ_{H} (300 MHz, CDCl_3) 5.29 and 5.19 (4H, A_2B_2 pattern, $^3J(\text{H-H})$ 4.5 Hz) and 2.92 (1H, br s); δ_{C} (75 MHz, CDCl_3) 126.4 (CH-O) and 114.5 (CH-N); δ_{C} (uncoupled) 126.4 (ddd, J 196.9, 10.8 and 5.2 Hz) and 114.5 (ddd, J 178.4, 14.0 and 5.2 Hz); HRMS (ES^-): found 84.0462. $\text{C}_4\text{H}_6\text{NO}$ (MH^-) requires 84.0449.

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