Short Communication

A Simple Synthesis of Condensed *N*-Methyl-Substituted 1,3-Oxazines*

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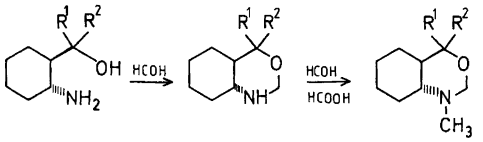
Although the synthesis and the chemical transformation of 1,3-oxazines have been thoroughly investigated,[2,3] only few reports deal with the synthesis of corresponding condensed tetrahydro-1,3-oxazines.[4–12] All of the latter reported syntheses were achieved by starting from 1,3-aminoalcohols and aldehydes or ketones, with the exception of the formation of 1,3-perhydrobenzoxazines from isoxazolidines by photochemical and base-catalyzed rearrangements, as reported by Le Bel *et al.*[4]

The 2-(*p*-nitrophenyl)-*cis*- and -*trans*-4,5- and -5,6-tetramethylenetetrahydro-1,3-oxazines have been thoroughly investigated stereochemically by X-ray diffraction,[13] ^{1}H and ^{13}C NMR spectroscopy[11,14–16] and by dynamic NMR methods.[16] The *trans* isomers attain diequatorial chair-chair conformations; the *cis* forms are also conformationally homogeneous systems, with *O-in* or *N-in* conformations in the case of *N*-unsubstituted 5,6-tetramethyleneoxazines[14,16] and 4,5-tetramethyleneoxazines,[16] whereas the *cis* forms of *N*-methyl- and *N*-benzyl-substituted 4,5-tetramethylene derivatives favour the *N-out* conformation.[11,14]

Boiko *et al.*[8] reported that *trans*-4,5-tetramethylenetetrahydrooxazines (**2**), prepared from the correspondingly substituted aminoalcohols (**1**), can easily be *N*-methylated with formaldehyde-formic acid mixture (Scheme 1). In a recent paper[11] we described the use of this method to methylate (*r*-4, *c*-2, *c*-5)- and (*r*-4, *c*-2, *t*-5)-2-(*p*-nitrophenyl)-4,5-tetramethylenetetrahydro-1,3-oxazines (**4a, b**) but instead of obtaining the corresponding **5a, b** only *p*-nitrobenzaldehyde could be isolated. From the unisolated second product we concluded that the liberated aminoalcohol reacted with formaldehyde to yield bis(1,3-oxazine).[17]



1 **2** **3**

Scheme 1.

We have now repeated these experiments and found that besides *p*-nitrobenzaldehyde, the *N*-methyl-substituted 1,3-oxazines **6a** and **6b** are formed. These compounds were prepared previously by reaction of *N*-methyl-*cis*- and -*trans*-2-hydroxymethylcyclohexylamine, respectively, with formaldehyde.[12] The **4**→**6** reaction can be explained *via* ring-chain tautomerism of **4**, followed by "*transimination*",[18,19] ring closure, and a Leuckart[20] methylation (Scheme 2).

Results and discussion

Direct syntheses of derivatives **6** and **9** (Scheme 3), using the above ring closure method applied previously to the synthesis of a *N*-methyl-1,3-

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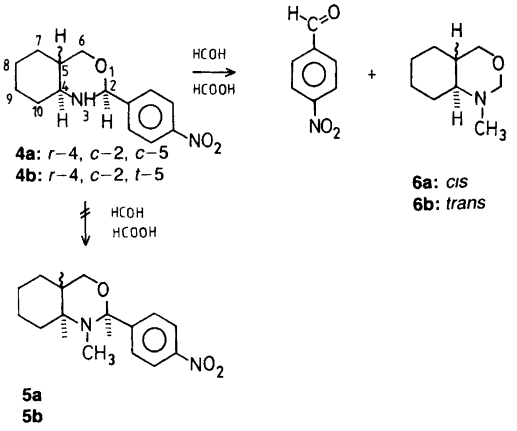
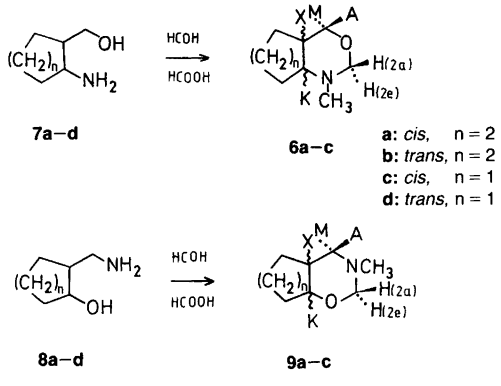


Scheme 2.

oxazolidine derivative,[21] were attempted starting from aminoalcohols **7a–d** and **8a–d.** In the case of *cis*- and *trans*-cyclohexane and *cis*-cyclopentane derivatives **7a–c** and **8a–c** the ring closure and *N*-methylation processes took place in good yield. The *trans*-cyclopentane derivatives **7d** and **8d** failed to react, even with a much longer reaction time. This result parallels our earlier findings with *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives.[22–24] In our opinion, *trans*-1,2-disubstituted 1,3-difunctional cyclopentanes undergo ring closure only when 1,3-heterocycles with delocalised bond systems are formed.[24] In the attempted reaction of **7d** and **8d**, the formation of a "normal" *N,N*-dimethyl-substituted Leuckart product[25,26] could not be observed either. Hence, the first step in reactions **7**→**6** and **8**→**9** is probably the formation of the oxazine ring, which is then followed by the methylation process (Scheme 3).



Scheme 3.

The ^{1}H NMR spectra of **6c** and **9c** are consistent with an envelope-chair conformation where N or O, respectively, is essentially axial in relation to the carbocyclic part.[16] It is, however, possible that **6c** also contains some of the *N*-equatorial form. This, and some other conformational questions, will be discussed in a forthcoming paper.

Experimental

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a JEOL GX-400 FT NMR spectrometer, using TMS as internal standard.

Attempted methylation. Compound **4a**[11] (0.26 g, 1 mmol) was heated under reflux with a formaldehyde (2 ml of 37 % aq. solution)/formic acid (2 ml, 100 %) mixture. After 1 h the mixture was poured onto 20 g of ice, left for 1 h and filtered to remove *p*-nitrobenzaldehyde (yield 72 %). The mother liquor was neutralized with Na_2CO_3 and extracted with chloroform (3×20 ml). The extract was dried (Na_2SO_4) and the solvent evaporated. The oily product was converted to its picrate salt (yield 51 %, m.p. 164–166 °C). After recrystallisation from ethanol/ether the base was liberated from the picrate and identified as **6a** on the basis of its ^{1}H NMR spectrum. Under the same conditions the corresponding *trans* form (**4b**)[11] gave *p*-nitrobenzaldehyde (66 %) and **6b**, which was isolated as its picrate (57 %, m.p. 166–168 °C).

Preparation of N-*methyl-tetrahydro-1,3-oxazines* (**6a–c, 9a–c**). Aminoalcohols **7a–c** or **8a–c**[27,28] (2 mmol) were heated under reflux with a mixture of 3 ml of formaldehyde solution (37 % in H_2O) and 3 ml of formic acid. After 1 h the mixture was poured onto 20 g of ice, neutralized with Na_2CO_3 and extracted with chloroform (3×20 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to afford an almost colourless oil which was then converted to its picrate or hydrochloride. **6a**: Yield 66 %, m.p. of picrate 164–166 °C from ethanol/ether. Lit.[12] m.p. 166–167 °C. **6b**: Yield 79 %, m.p. of picrate 167–

169 °C from ethanol/ether. Lit.[12] m.p. 166–170 °C. **6c**: Yield 74 %, m.p. of picrate 158–159 °C from ethanol/ether. Anal. $C_{14}H_{18}N_4O_8$: C, H, N. ^{1}H NMR (400 MHz, $CDCl_3$): δ_A 3.72 (J_{AM} −11.6, J_{AX} 4.6 Hz), δ_M 3.75 (J_{MX} 4.6 Hz), δ_K 2.64, $\delta_{H(2e)}$ 4.39 (J_{2e2a} −8.7 Hz), $\delta_{H(2a)}$ 3.73. **9a**: Yield 71 %, m.p. of HCl salt 217–219 °C from ethanol/ether. Lit.[12] m.p. 216–219 °C. **9b**: Yield 77 %, m.p. of HCl salt 212–214 °C from acetone/ether. Lit.[12] m.p. 213–216 °C. **9c**: Yield 74 %, m.p. of HCl salt 177–179 °C from acetone/ether. Anal. $C_8H_{16}ClNO$: C, H, N. ^{1}H NMR (400 MHz, $CDCl_3$): δ_A 2.43 (J_{AM} −11.8, J_{AX} 4.0 Hz), δ_M 2.94 (J_{MX} 1.8, $J_{H(2e)M}$ 1.8 Hz), δ_K 3.86, $\delta_{H(2e)}$ 4.33 (J_{2e2a} −8.1 Hz), $\delta_{H(2a)}$ 3.55.

When starting from **7d** or **8d**[28] the above procedure after 12 h reflux gave only the starting aminoalcohols (**7d**, 71 %; **8b**, 65 %) as hydrochlorides.

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