The Reaction of Ethyl 2-Chloroacetoacetate with 2-(Alkylamino) Alcohols: an Unexpected Formation of the 2-Methyloxazolidine Ring†

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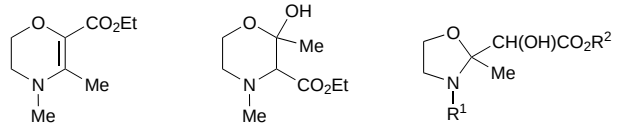
The reaction of 2-(alkylamino) alcohols and ethyl 2-chloroacetoacetate in the presence of sodium alkoxides proceeds with unexpected formation of 2-hydroxy-2-(2-methyloxazolidin-2-yl)acetic esters instead of the aza analogues of carboxin (5,6-dihydro-1,4-oxazines) as previously reported in the literature.

Carboxin (2-methyl-5,6-dihydro-1,4-oxathiine-3-carboxanilide) and its 4,4-dioxide analogue are well known as synthetic fungicides and are the active components of many commercially available pesticides with worldwide use.[1–3] As part of our efforts to synthesise oxazine analogues of these compounds we became interested in the possibility that they may be prepared by the reaction of 2-chloroacetoacetate derivatives with 2-(alkylamino) alcohols instead of the 2-mercapto alcohols as used in the synthesis of carboxin.[4]

To our knowledge the only example of such a reaction, which appeared in the literature as a collateral result in another type of investigation, is the interaction of ethyl 2-chloroacetoacetate with 2-(methylamino)ethanol.[5] In this case the 5,6-dihydro-1,4-oxazine structure **1** was attributed to the reaction product.



1 **2** **3**

Our attempt to repeat the cited reaction under the same conditions as used by Baues and co-workers[5] led us to a compound with the same melting point as that reported by the authors. However, its IR and ^{1}H NMR spectra revealed clearly the presence of a hydroxy group in the molecule and its mass spectrum supported a non-dehydrated structure. These observations prompted us to study this interaction in detail.

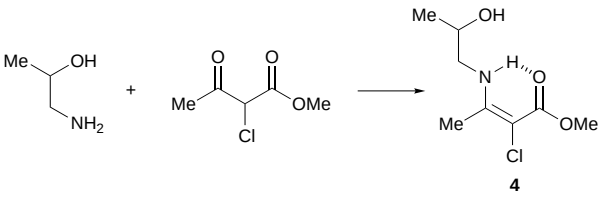
For this purpose we studied the behaviour of 2-(methylamino)- and 2-(ethylamino)-ethanol towards 2-chloroacetoacetic esters. The reaction was carried out under the same reaction conditions as used by Baues. The ^{1}H NMR spectra of the products indicated a signal for an OH group as well as a signal for CH, both appearing as doublets (J 5–6 Hz). After D_2O had been added, the signal for the OH disappeared and the doublet for CH turned to a singlet. This fact shows unambiguously that the hydroxy group and the methine proton are connected to the same carbon atom. This conclusion obliged us to reject the structure **2** on a possible reaction products, as may have been suggested from the analogous reaction of 2-chloro ketones with 2-amino alcohols.[6,7] This rejection of structure **2** was supported by our failure to transform the products into the corresponding 5,6-dihydro-1,4-oxazines by dehydration in the presence of hydrochloric[8] or toluene-*p*-sulfonic acid.[9]

On the other hand, reaction of methyl 2-chloroacetoacetate with 1-aminopropan-2-ol, in the absence of base, gave the crystalline product **4** (see Scheme 1). This reaction is well known for acetoacetic esters,[10–12] but in this case the isolation of **4** shows that the initial attack of the nucleophic nitrogen centre occurs on the carbon atom of the carbonyl group (nucleophilic addition reaction) and not on the one connected to the chlorine atom (nucleophilic substitution reaction).

Supported by data from elemental analysis and IR and mass spectroscopy, we concluded that the reaction of 2-(alkylamino) alcohols with 2-chloroacetoacetic esters results, most likely, in products with the corresponding 2-hydroxy-2-(2-methyloxazolidin-2-yl)acetic acid structure **3**.

On the basis of all these results we propose a probable mechanism (shown in Scheme 2) for the interaction between 2-chloroacetoacetic esters and 2-(alkylamino) alcohols. The key step is the formation of the epoxide ring. The attack of the OH group on the carbon atom at position 3 (attack 'a') leads to products **3**. None of the alternative product **5** (attack 'b') was observed under these reaction conditions.

All compounds **3** were obtained as mixtures of diastereoisomers. The isomeric ratio, determined according to the signals for C—CH_3 for both isomers in the ^{1}H NMR spectra, is about 4:1 in all cases. The reaction products, initially obtained as oils, crystallized and after two recrystallizations



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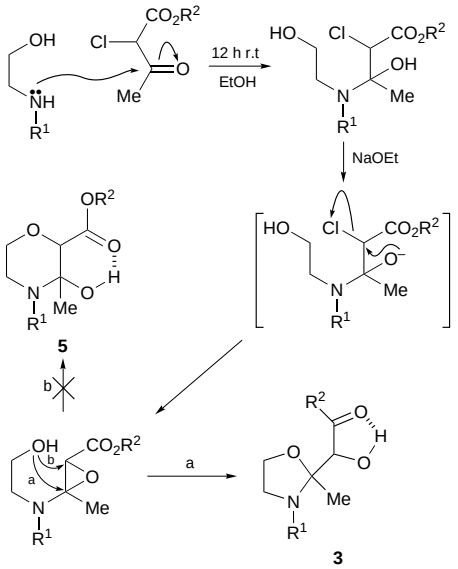
Scheme 1



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Scheme 2

*To receive any correspondence.

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from light petroleum the diastereoisomer **A** was obtained pure. In the case of **3b**, column chromatography of the residual oil allowed separation of the two isomers **A** and **B**.

Experimental

Melting points were determined on a Boetius hot-stage microscope and were uncorrected. ^{1}H NMR spectra were recorded on Brucker AVANCE DRX-250 (250 MHz) and Tesla BS 487 C (80 MHz) spectrometers and IR spectra on a Specord 75 IR spectrometer. Column chromatography was carried out using 0.032–0.063 mm silica gel (Merck) and with cyclohexane–acetone (3:1 v/v) as mobile phase. Light petroleum used for recrystallizations was the fraction of bp range 50–70 °C.

Methyl 2-Chloro-3(2-hydroxypropylamino)but-2-enoate (**4**).—Methyl 2-chloroacetoaceate (21.1 g, 180 mmol) was added dropwise with stirring (1.5 h) to 1-aminopropan-2-ol (28.1 g, 375 mmol). The reaction mixture was stirred for 12 h at room temperature and heated for an additional 1 h at 50 °C. The resulting red oil was extracted several times with diethyl ether (700 ml). The solvent was evaporated and the resulting yellow oil crystallised. Recrystallisation from water gave the *chloro ester* **4** as colourless crystals (24.3 g, 65%), mp 86–88 °C, ν_{max}/cm^{-1} ($CHCl_3$) 3645 (OH), 3320 (NH), 1660 (C=O), 1600 (C=C); δ_H ($CDCl_3$, 80 MHz) 1.25 (3 H, d, *J* 6.0 Hz, C*H*$_3$CH), 2.22 (3 H, s, CCH_3), 2.75 (1 H, br s, OH), 3.28 (2 H, m, NCH_2), 3.75 (3 H, s, OCH_3), 4.03 (1 H, m, C*H*CH$_3$); *m*/*z* (EI) 208 (MH^+) (Found: C, 47.07; H, 6.94; N, 6.68. $C_8H_4ClNO_3$ requires C, 46.27; H, 6.94; N, 6.68%).

General Procedure for the Synthesis of 2-Hydroxy-2-(2-methyloxazolidin-2-yl)acetic Esters (**3**).—To a stirred alcohol (methanol or ethanol) solution of the corresponding amino alcohol (125 mmol) was added dropwise a solution of 2-chloroacetoacetic ester (63 mmol) in anhydrous alcohol. The reaction mixture was stirred for 12 h at room temperature and sodium alkoxide (methoxide or ethoxide), obtained from 1.38 g sodium and 50 ml anhydrous alcohol, was then added. After refluxing for a further 1 h, the alcohol was evaporated *in vacuo* and water was added. The mixture was extracted with chloroform (3 × 100 ml), dried ($MgSO_4$) and the solvent was evaporated. The crude product was distilled *in vacuo* to give the analytically pure compounds.

Ethyl 2-(2,3-dimethyloxazolidin-2-yl)-2-hydroxyacetate (**3a**). 2-(Methylamino)ethanol (9.4 g, 125 mmol) was treated with ethyl 2-chloroacetoacetate (10.4 g, 63 mmol) to give the *ethyl ester* **3a** (7.67 g, 60%), bp 116–120 °C at 0.05 Torr, mp 102–104 °C (from light petroleum), ν_{max}/cm^{-1} ($CHCl_3$) 3415 (OH), 1680 (C=O); δ_H ($CDCl_3$, 250 MHz) 1.16 (3 H, t, *J* 7.0 Hz, C*H*$_3$CH$_2$), 1.50 (3 H, s, CCH_3), 3.06–3.14 (1 H, m, 4-H), 3.11 (3 H, s, NCH_3), 3.48 (2 H, m, C*H*$_2$CH$_3$), 3.62 (1 H, m, 4-H), 3.75–3.92 (2 H, m, 2 × 5-H), 4.25 (1 H, d, *J* 5.4 Hz, H-α), 4.45 (1 H, d, *J* 5.4 Hz, OH); *m*/*z* (CI) 204 (MH^+) (Found: C, 53.74; H, 8.13; N, 6.90. $C_9H_{17}NO_4$ requires C, 53.19; H, 8.43; N, 6.89%).

Methyl 2-(2,3-dimethyloxazolidin-2-yl)-2-hydroxyacetate (**3b**). 2-(Methylamino)ethanol (9.4 g, 125 mmol) was treated with methyl 2-chloroacetoacetate (9.48 g, 63 mmol) to give the *methyl ester* **3b** (6.2 g, 52%), bp 118–122 °C at 0.05 Torr, mp 82–84 °C (from light petroleum); ν_{max}/cm^{-1} ($CHCl_3$) 3410 (OH), 1685 (C=O) (Found: C, 50.89; H, 7.86; N, 7.35. $C_8H_{15}NO_4$ requires C, 50.78; H, 7.99; N, 7.40%).

Two isomers were separated by column chromatography on silica gel (cyclohexane–acetone, 3:1 v/v). Isomer **A**, R_F 0.22, had mp 82–84 °C (from light petroleum) δ_H ($CDCl_3$, 250 MHz) 1.49 (3 H, s, CCH_3), 3.07–3.15 (1 H, m, 4-H), 3.11 (3 H, s, NCH_3), 3.22 (3 H, s, OCH_3), 3.61–3.93 (3 H, m, 4-H, 2 × 5-H), 4.26 (1 H, d, *J* 5.3 Hz, H-α), 4.45 (1 H, d, *J* 5.3 Hz, OH). Isomer **B**, R_F 0.15, was an oil, n_D 1.4837; δ_H ($CDCl_3$, 250 MHz) 1.29 (3 H, s, CCH_3), 3.09 (3 H, s, NCH_3), 3.23–3.36 (1 H, m, 4-H), 3.33 (3 H, s, OCH_3), 3.61–3.90 (3 H, m, 4-H, 2 × 5-H), 4.10 (1 H, d, *J* 6.0 Hz, OH), 4.44 (1 H, d, *J* 6.0 Hz, H-α).

Methyl 2-(3-ethyl-2-methyloxazolidin-2-yl)-2-hydroxyacetate (**3c**). 2-(Ethylamino)ethanol (11.1 g, 125 mmol) was treated with methyl 2-chloroacetoacetate (9.48 g, 63 mmol) to give the *methyl ester* **3c** (6.15 g, 48%), bp 108–115 °C at 0.05 Torr, mp 77–80 °C (from light petroleum), ν_{max}/cm^{-1} ($CHCl_3$) 3410 (OH), 1675 (C=O); δ_H ($CDCl_3$, 80 MHz) 1.20 (3 H, t, CH_3, *J* 6.8 Hz). 1.39 (3 H, s, CCH_3), 3.38 (3 H, s, OCH_3), 3.48–4.13 (6 H, m, 2 × 4-H, 2 × 5-H, C*H*$_2$CH$_3$), 4.11 (2 H, m, H-α, OH) (Found: C, 53.50; H, 8.39; N, 6.84. $C_9H_{17}NO_4$ requires C, 53.19; H, 8.43; N, 6.89%).

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