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A synthesis of alkyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates

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Abstract—Reaction of ethyl 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates with sodium hydride in dioxane affords ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates. The structure of the products was unambiguously established by X-ray analysis as well as by ^{1}H–^{13}C and ^{1}H–^{15}N NMR correlation spectroscopy. © 2001 Published by Elsevier Science Ltd.

In the course of our recent work on the design and synthesis of serine protease inhibitors and fibrinogen receptor antagonists, derivatives of 2*H*-1,4-benzoxazine-3(4*H*)-one have served as useful peptidomimetic building blocks.[1,2] This heterocycle furnishes a skeleton suitable for introducing various functionalities in order to achieve a specific spatial orientation of pharmacophoric groups that interact with receptors or enzyme active sites. Among derivatives of 2*H*-1,4-benzoxazine-3(4*H*)-one, alkyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates[3,4] are especially suitable synthons which can be easily functionalized at positions 2 and 4, as well as at the ester group and aromatic ring substituents.

In this paper we report an unexpected synthesis of the hitherto unknown ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **3**, which constitute a set of new versatile peptidomimetic scaffolds. The structure of compounds possessing the general structure **3** was proved by ^{1}H–^{13}C and ^{1}H–^{15}N NMR correlation spectroscopy, as well as by X-ray crystallography.

4-Alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **2** were prepared as previously reported by phase-transfer alkylation of ethyl 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate (**1**).[3,4] Although it had generally been assumed that alkylation of 2*H*-1,4-benzoxazine-3(4*H*)-one derivatives occurs at the ring nitrogen,[5,6] we strove for a clear proof of the structure of compounds **2a**–**f**. The site of alkylation (*O*- versus *N*-alkylation) of **1** could not be established unambiguously using the usual methods of structure determination and NOESY experiments. We therefore performed an X-ray crystallographic analysis of **2d**[7] which unequivocally proved that alkylation of **1** occurred at the ring nitrogen atom.

On alkylation of **2a**–**f** at position 2 with alkyl halides in dioxane, using sodium hydride as a base,[4] the formation of a by-product, whose ^{1}H NMR spectrum lacked the signals of an additional alkyl group and of a proton at position 2, was consistently observed. The by-products additionally showed an exchangeable broad singlet at approximately 8 ppm in DMSO-d_6.[8] In order to clarify the formation and structure of the side products, the same reaction was performed with **2a**–**f** in the absence of alkyl halide, resulting in the formation of compounds **3a**–**f**, which were in all respects identical with the aforementioned by-products.[9,14]

Comparison of NOESY spectra[10] of **2a**,**d** and **3a**,**d** at 302 K revealed no significant differences, thus the initially assumed structure **4** was discarded. NOE cross

Keywords: peptidomimetic building blocks; alkyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates; X-ray structure; NMR correlation spectroscopy.

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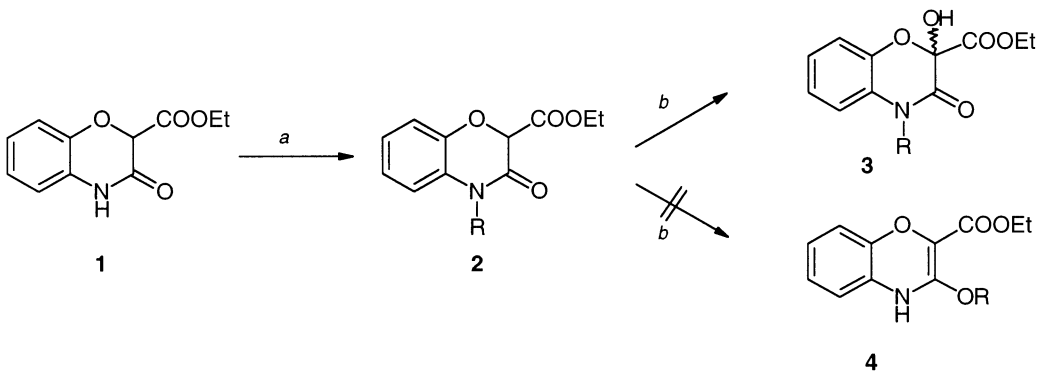
peaks were observed between aromatic H-5 and the methyl group in **2a** and **3a**, which, after integration, gave similar proton–proton distances (approx. 0.3 nm) in each structure. Similarly, **2d** and **3d** exhibited NOE cross peaks between the aromatic proton H-5 and the CH_2 of the benzyl group, indicating that these protons must be close to each other. No other relevant NOEs were observed in NOESY spectra so that, due to lack of restraints, the structure of **3a–f** could not be unambiguously determined (Scheme 1).

Detailed structure determination of **3a** in deuterochloroform, using both ^1H–^{13}C and ^1H–^{15}N NMR correlation spectroscopy and HSQC[11] and HMBC[12] pulse sequences with gradients for coherence selection, confirmed its structure unequivocally by a consistent set of through bond proton–carbon and proton–nitrogen correlations over two and three bonds. In particular, the correlation of N-4 at −255 ppm[13] with 5-H and protons of the 4-methyl group was observed in a ^1H–^{15}N correlation experiment. A similar ^1H–^{13}C correlation experiment revealed connectivities between the exchangeable broad singlet at 5.12 ppm and carbonyl carbon atoms at 161 and 167 ppm, as well as quaternary carbon at 93 ppm, thus indicating that in **3a** the hydroxyl group must be bound at position 2. The structure of **3a** suggested on the basis of these NMR experiments was unambiguously confirmed by X-ray analysis of the crystals obtained from **3a** (Fig. 1).[7]

Although a detailed mechanistic study has not been undertaken, the conversion of **2a–f** into **3a–f** can be regarded as an oxidation of the C-2 enolate anion by traces of air which might be present in the reaction mixture giving **3a–f** in equilibrium with the ring-opened phenolate-ketone. An S_N2-type displacement of a phenoxide by OH^- followed by ring-closure is, although theoretically possible, very unlikely.[15] We have found that the reaction proceeds similarly using either solid sodium hydroxide in dioxane or aqueous sodium hydroxide; in both cases an intense transient violet coloration indicating the intermediate formation of a phenolate anion was observed. Elaboration of this reaction under various conditions and the use of compounds **3a–f** as novel peptidomimetic scaffolds are currently in progress in our laboratory and will be reported in due course.



2,3	*a*	*b*	*c*	*d*	*e*	*f*
R	Me	Et	Pr	CH_2Ph	CH_2COOEt	$CH_2C_6H_4$-4-CN
yield (%)	23	24	38	26	22	20

Scheme 1. (a) RBr, BTEAC, K_2CO_3, CH_3CN, 60°C; (b) NaH, dioxane, rt.

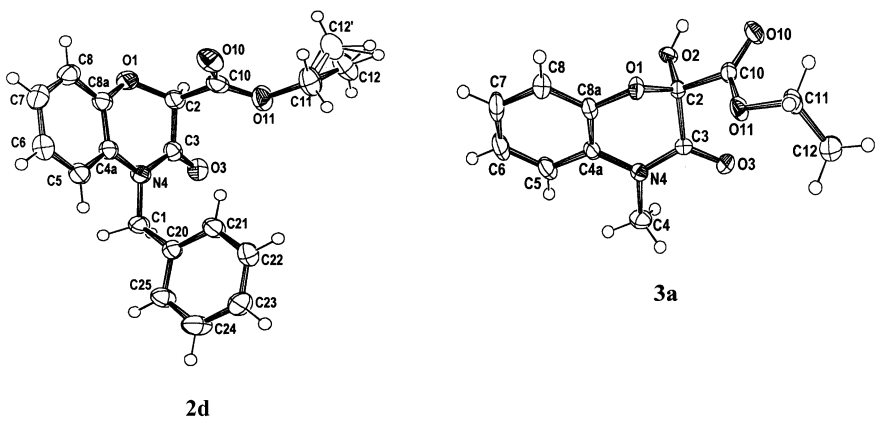


Figure 1. ORTEP diagrams of **2d** and **3a**.

In conclusion, an important feature of our finding is that ethyl 4-alkyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **3** can be obtained in one step from 4-alkyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates. The novel compounds **3a**–**f** are interesting peptidomimetic building blocks which offer numerous possibilities of functionalization.

Acknowledgements

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7. Compound **2d** crystallizes from ethanol/acetonitrile and forms colorless prismatic crystals in the monoclinic space group $P2_1/c$ with unit cell parameters $a=8.4058(1)$ Å, $b=16.7340(2)$ Å, $c=10.9222(3)$ Å, $\beta=99.2473(4)°$. Compound **3a** crystallizes from dichloromethane/petrolether and forms prismatic colorless crystals in the orthorhombic space group $Pn2_1c$ with unit cell parameters $a=10.2460(2)$ Å, $b=10.3464(2)$ Å, $c=10.9830(2)$ Å. Diffraction data were collected at 150(1) K with Mo Kα radiation and CCD detector. The bond lengths and angles are normal and in agreement with the values for related compounds. The details of both structures (CIF files) will be deposited in the Cambridge Structural Database.
8. The chemical shift of the exchangeable proton was approximately 5.2 ppm in $CDCl_3$. The by-product was generally obtained in 5–10% yield.
9. The crude yields of **3a**–**f** ranged from 25 to 55%.
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13. Relative to MeCN ($\delta=-135.83$ ppm) as external reference.
14. Preparation of compound **3a** (typical procedure):
To a stirred solution of ethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate **2a** (0.470 g, 2.0 mmol) in 1,4-dioxane (15 mL) cooled to 10°C, sodium hydride (0.057 g, 2.4 mmol) was added under an argon atmosphere. The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 5 h. The solvent was evaporated in vacuo and the residue dissolved in diethyl ether (15 mL). The solution was rinsed with 0.1 M HCl (2×10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using dichloromethane/methanol (100/1) as eluant to give analytically pure ethyl 4-methyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate **3a** as a white amorphous solid; yield: 0.115 g (23%); mp 98–101°C; IR (KBr): *v* 3376, 2991, 1750, 1675, 1609, 1502, 1394, 1294, 1229, 1140, 1048, 979, 860, 753, cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, $J=7.16$ Hz, $CH_2\underline{CH_3}$), 3.31 (s, 3H, N-$\underline{CH_3}$), 4.25 (q, 2H, $J=7.16$ Hz, $\underline{CH_2}CH_3$), 7.05–7.18 (m, 3H, Ar-$\underline{H}$), 7.23–7.26 (m, 1H, Ar-$\underline{H}$), 8.55 (s, 1H, -O$\underline{H}$) ppm; MS (70 eV, EI): *m*/*z* (%) 251 (M^+, 28), 235 (45), 189 (6), 178 (62), 150 (23), 94 (33), 77 (100), 65 (80). Anal. calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.48%. Found: C, 57.00; H, 5.14; N, 5.40%.
15. The authors wish to express their gratitude to the referee for his helpful suggestion concerning the reaction mechanism.