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Unexpected highly regioselective macrocyclization of *o*-allylic *N*-carbonyl substituted anilines

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Abstract—An unexpected bromocyclocarbamoylation of *o*-allylic *N*-BOC-anilines has been observed producing 2-oxo-3,1-benzoxazocine derivatives through an 8-*endo*-*trig* process, which on heating ring-transformed into a [6.5.5] tricyclic fused oxazolidinone compounds. A mixture of both heterocycles was obtained when the starting *N*-BOC anilines were heated with NBS in THF. The process seems to be general for related *N*-carbonyl substituted anilines. © 2002 Published by Elsevier Science Ltd.

As part of an ongoing project related with the synthesis of benzo-fused nitrogen heterocycles, we planned to obtain them by cyclo-functionalization[1] of the double bond of *o*-allylic *N*-BOC anilines **2** promoted by an electrophilic source of bromine species. This kind of process would produce 3-bromo-1,2,3,4-tetrahydroquinolines or 2′-bromoalkyl-2,3-dihydro-1*H*-indoles through a 6-*endo* or 5-*exo*-trigonal ring closure[2] (Fig. 1). The presence of the bromo atom in these heterocycles could be of interest in order to further develop the molecule.

So when the starting *o*-functionalized *N*-BOC aniline **2a**[3] (Scheme 1) was treated with bromine in the presence of sodium bicarbonate it did not yield the initially expected indole or quinoline derivatives but surprisingly the isolated product (78%) was the 6-acetoxy-5-bromo-4-methyl-2-oxo-1,4,5,6-tetrahydro-2*H*-benzo[*d*][3,1]-oxazocine (**3a**) which stemmed from an unusual 8-*endo*-trigonal halocyclo-carbamoylation[4] with the oxygen atom of the carbamate acting as the nucleophilic centre instead of the nitrogen atom.[5]

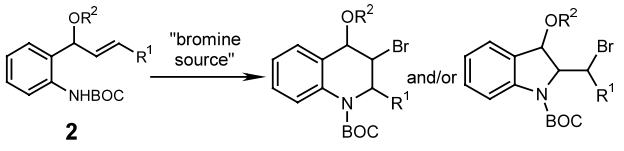
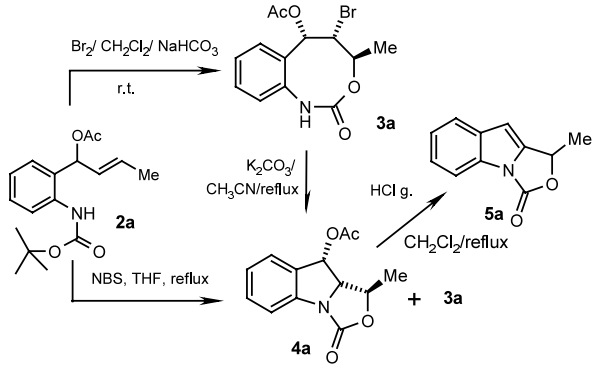


Figure 1.



Scheme 1.

The structure of this compound was confirmed by X-ray analysis[6] (Fig. 2). The *cis* relationship between the bromo and acetoxy groups can be justified by a kinetically controlled bromocyclization induced by the presence of the base acting as acid scavenger.[7]

This benzo-fused eight-membered heterocycle **3a** smoothly ring contracted to the rigid [6.5.5] tricyclic fused oxazolidinone derivative **4a** (62%) (X-ray analysis,[6] Fig. 3) after reflux in acetonitrile, by means of an intramolecular SN_2 process.[8] Both heterocycles were simultaneously obtained when **2a** was heated in refluxing THF in the presence of NBS.[9]

Finally, acid promoted elimination of the acetoxy group in **4a** (HCl g/Cl_2CH_2) yielded the corresponding indolo fused oxazolidone derivative **5a** (90%).

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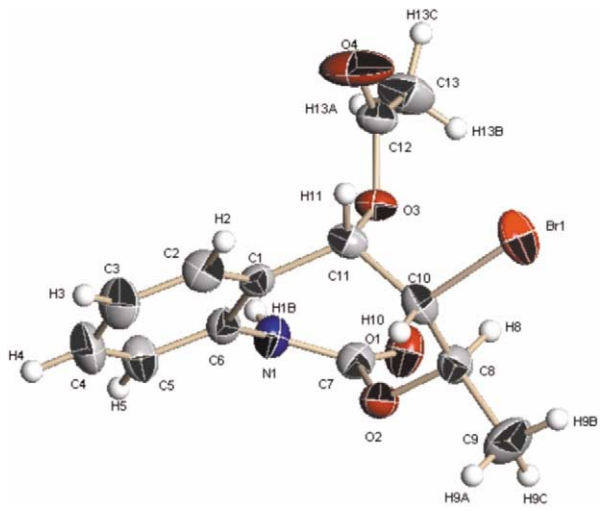


Figure 2. X-Ray structure of benzoxazocine **3a**

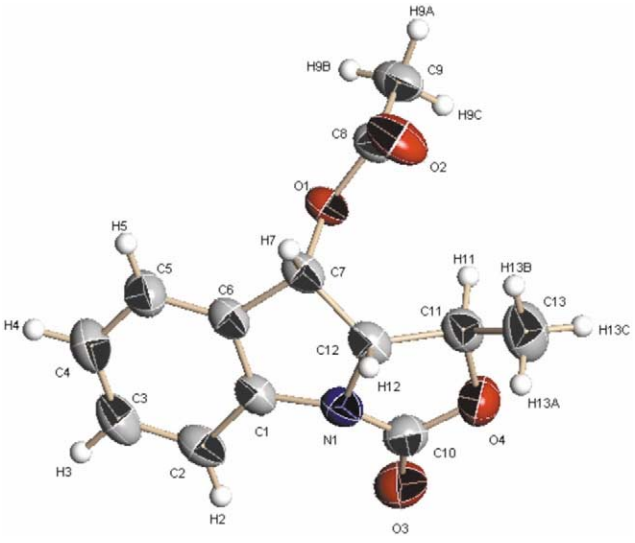


Figure 3. X-Ray structure of oxazolidinone **4a**

In order to study the scope of this process, we have modified some of the substituents in the starting *o*-functionalized aniline precursor. In the first instance, we have changed the methyl group in the olefinic position to *i*-Pr, compound **2b** (Fig. 1, $R^1 = i$-Pr, $R^2 = Ac$), with no changes in the regiochemistry of the process (**3b**, 71%, Fig. 4). However, when a phenyl group was placed there, compound **2c** (Fig. 1, $R^1 = Ph$, $R^2 = Ac$), the reaction clearly slowed down and a mixture of several products was obtained.

As regards the modification of the nature of the leaving group, the acetoxy group was replaced by a methoxy one, compound **2d** (Fig. 1, $R^1 = i$-Pr, $R^2 = Me$),[10] with no changes associated with the regiochemistry been observed, yielding the benzoxazocinone **3d** (Fig. 4) with a bromine atom replacing the methoxy group.

Finally, the nature of the nitrogen protecting group was also evaluated without significant changes. So from the

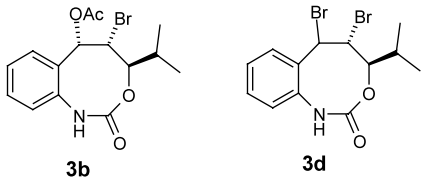
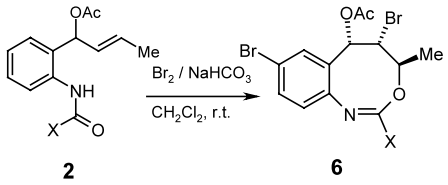


Figure 4.



Scheme 2.

ethyl carbamate **2e** (Scheme 2, X = OEt) the 6-acetoxy-5,8-dibromo-2-ethoxy-4-methyl-5,6-dihydro-4*H*-benzo[*d*]-[3,1]oxazocine (**6e**) was obtained with a bromine atom been introduced, *para* with respect to the nitrogen atom and, starting with the amides **2f** and **2g** (Scheme 2, X = Me and Ph, respectively) the 5,6-dihydro-4*H*-benzo[*d*][3,1]-oxazocines **6f** and **6g** were obtained[11] with similar yields.

New experiments are in progress in order to analyze more details of both the regio and stereoselectivity of this process.

Supplementary material

Spectroscopic data and experimental details for the preparation of all new compounds are available from the author upon request.

Acknowledgements

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5. A similar type of process has been recently observed: Brugier, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 37–43.
6. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 189683 (**3a**). CCDC 189684 (**4a**). Copies of the data can be obtained, free of charge, on application to CCDC. 12 Union Road. Cambridge CB2 1EZ. UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac. uk].
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8. A quite close rigid tricyclic fused oxazolidinone derivatives have been prepared showing interesting antibacterial activity. (a) Gleaver, D. M., et al. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1231–1236; (b) Gleaver, D. M.; Brickner, S. J. *J. Org. Chem*. **1996**, *61*, 6470–6474.
9. To a stirred solution of **2a** (100 mg, 0.33 mmol) in dry THF (2 ml) was added NBS (recently recrystallized and dried, 65 mg, 0.36 mmol) and the mixture was refluxed for 6 h. The solvent was eliminated on vacuo and the residue was purified as before to obtain 40 mg of the benzoxazocine **3a** (37%) and 28 mg of the tricyclic oxazolidinone **4a** (35%).
10. The methylation of the benzylic alcohol precursor of **2a**, failed to produce the expected methoxy derivative, meanwhile **2d** could be obtained.
11. These 5,6-dihydro benzoxazocines **6** were unstable compounds and we could only run their ^{1}H NMR spectra. Just in the case of the benzamido derivative **6g**, the phenyl group seemed to induce some additional stability which allowed us to perform a detailed NMR study within the next 24 h period.