Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 2039-2042, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0168-W

Preparation Of New 2,4-Disubstituted Oxazoles

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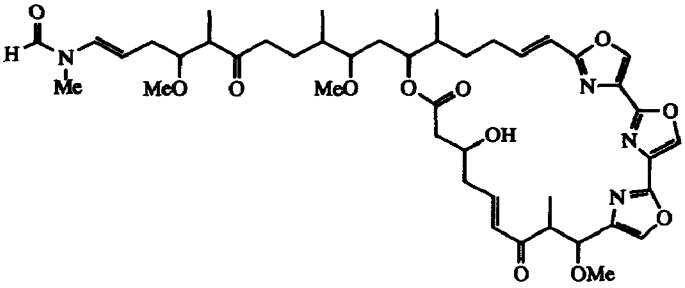
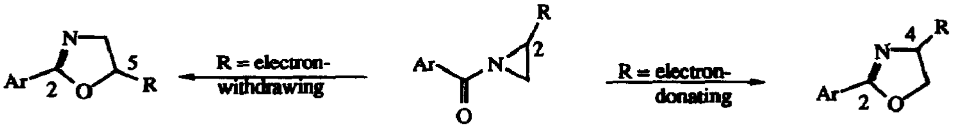
Abstract: Ring enlargement of *N*-acylaziridines followed by nickel peroxide oxidation provides a variety of 2,4-disubstituted-1,3-oxazoles suitable for bis- and tris-oxazole synthesis.

In recent years several molecules containing the tris-oxazole unit, such as halichondramide 1 have been isolated from the marine environment.[1] These molecules are potent anti-fungal agents. Consequently several groups have develope d syntheses of a variety of mono-, bis- and tris-(2,4-disubstituted)oxazoles.[2]



1 *Halichondramide*

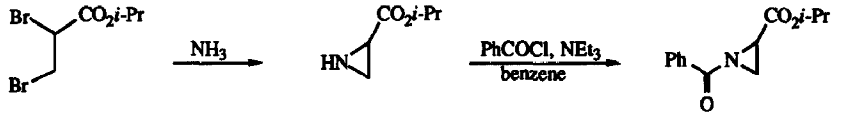
N-Acylaziridines can be ring-enlarged to give either 2,4- or 2,5-disubstituted oxazolines depending on the nature of the substituent on the aziridine ring and the reaction conditions. For example, in nucleophile-promoted ring enlargements, the inclusion of an electron-donating substituent (usually alkyl) at C2 provides 2,4-disubstituted oxazolines[3] whereas electron-withdrawing substituents (such as vinyl) lead to 2,5-disubstituted products (eqn. 1).[4]



2

(1)

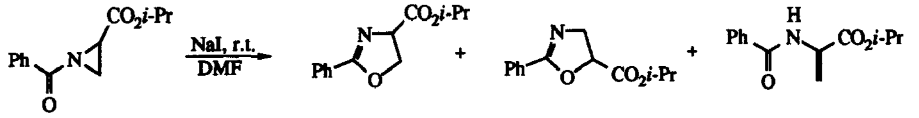
We were interested in applying ring enlargement reactions of *N*-acylaziridines to the preparation of 2,4-disubstituted oxazoles which could be used in the synthesis of bis- and tris-oxazole subunits such as those found in halichondramide **1**. In particular we were interested in examining this process with an electron-withdrawing group, namely an ester group, at C2 (e.g. **2a**, R = CO_2i-Pr). In principle, such a group could be used to couple with a second aziridine molecule either before or after the initial ring enlargement. The preparation of **2a** (R = CO_2i-Pr) is outlined below (eqn. 2).[5] Thus *iso*-propyl 2,3-dibromopropanoate was treated successively with ammonia and benzoyl chloride[6,7] giving **2a** in 54% yield.



(2)

2a

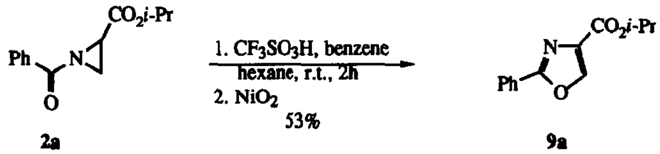
Following Dewar's method,[8] treatment of **2a** with sodium iodide in dimethylformamide gave, in addition to **3a**, the regioisomer **4a** and elimination product **5a** (eqn. 3). Several variations of the reaction conditions were tried (including replacing sodium iodide with sodium bromide, chlorotrimethylsilane/CH_3CN or iodotrimethylsilane/CH_3CN) but all proved unsatisfactory. To the best of our knowledge **2a** is the first example of an *N*-acylaziridine bearing a carboxylic ester group at C2 to be subjected to this ring-enlargement procedure. It seems likely that this group is the cause of the loss of regioselectivity.



(3)

2a **3a** (31%) **4a** (45%) **5a** (14%)

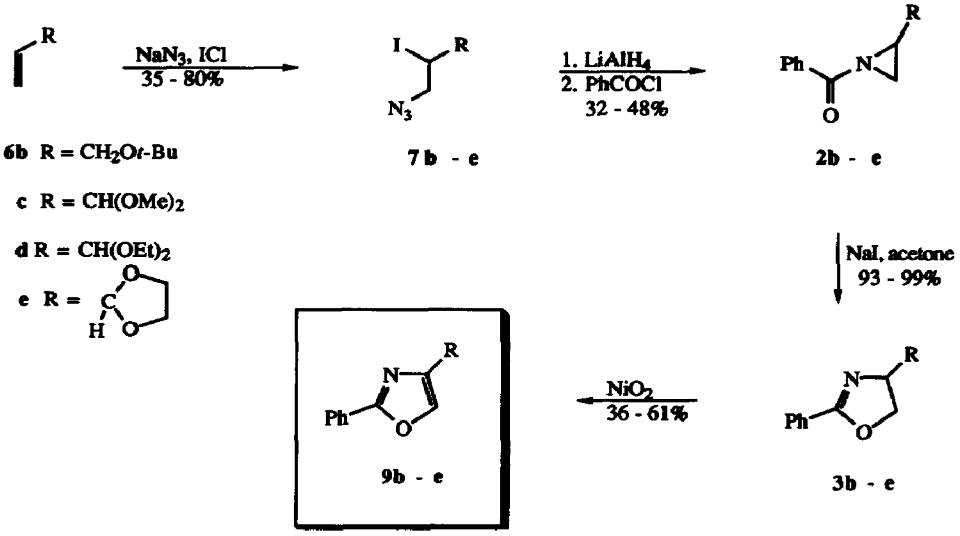
Acid-promoted ring enlargement[9] gave better results. Thus, treatment of **2a** with trifluoromethanesulfonic acid at room temperature gave a mixture of **3a** and **4a** in a 5.7 : 1 ratio. No evidence for the by-product **5a** was found. The major isomer **3a** was easily purified by chromatography on silica gel. Oxidation with nickel peroxide[10] then gave *iso*-propyl 2-phenyl-1,3-oxazole-4-carboxylate **9a** in 53% yield from **2a** (eqn. 4).



(4)

2a **9a**

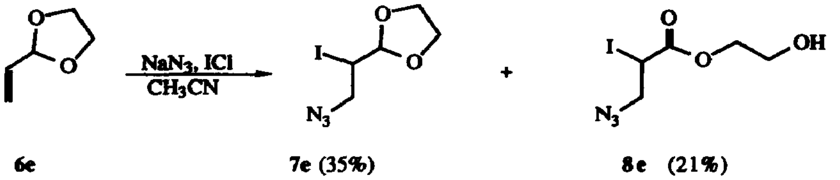
Returning to the iodide-promoted process it seemed logical to prepare *N*-acylaziridines with a latent carboxyl group (such as an acetal which could later be hydrolysed and oxidised) attached to C2 which would not interfere with the ring enlargement. Thus we prepared *N*-acylaziridines **2b** - **e** (Scheme 1).



Scheme 1

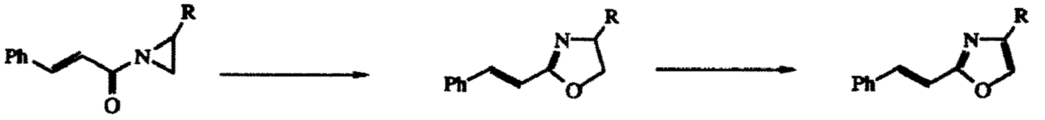
Azido-iodination[11] of alkenes **6b** - **e** proceeded in good yields although **7b** was contaminated by significant quantities of its regioisomer. **7c** and **7d** were produced as essentially single regioisomers. Reduction and benzoylation, followed by purification by chromatography on silica gel gave the *N*-benzoylaziridines **2b** - **e**. *Ring enlargement of **2b** - **e** followed by oxidation provided 2,4-disubstituted oxazoles **9b** - **e** smoothly and regiospecifically.*

Only **6e** suffered from a side-reaction producing the oxidatively ring-opened by-product **8e** as well as the desired iodo-azide **7e** (eqn. 5).



(5)

Encouraged by these results we prepared **9f** and **9g** which have a synthetically more versatile substituent at C2. Ring enlargement of **2f** and **2g** gave **3f** and **3g** in 83 and 78% yields respectively (eqn. 6). Oxidation with nickel peroxide gave oxazoles **9f** and **9g** in 85 and 72% yields respectively.[12]



(6)

2f	NaI, acetone 83%	**3f**	NiO_2 85%	**9f**
2g	CF_3SO_3H 78%	**3g**	NiO_2 72%	**9g**

2f, **3f** and **9f** R = $CH(OEt)_2$

2g, **3g** and **9g** R = CO_2*i*-Pr

The application of **9a** - **g** to the synthesis of bis- and tris-oxazoles will be reported shortly.

Acknowledgement:

We thank Professor T. F. Molinski (University of California, Davis) for helpful discussions.

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[12] The yield of this final oxidation was found to increase considerably when the nickel peroxide was added in portions over several hours. The addition of triethylamine to the hot reaction mixture immediately prior to workup also improved yields. A more detailed report of this oxidation procedure will be published shortly.

(*Received in UK* 30 *November* 1993; *accepted* 20 *January* 1994)