

Facile Synthesis of Novel 2-Hydroxytetrazole Derivatives *via* Selective *N*-2 Oxidation.

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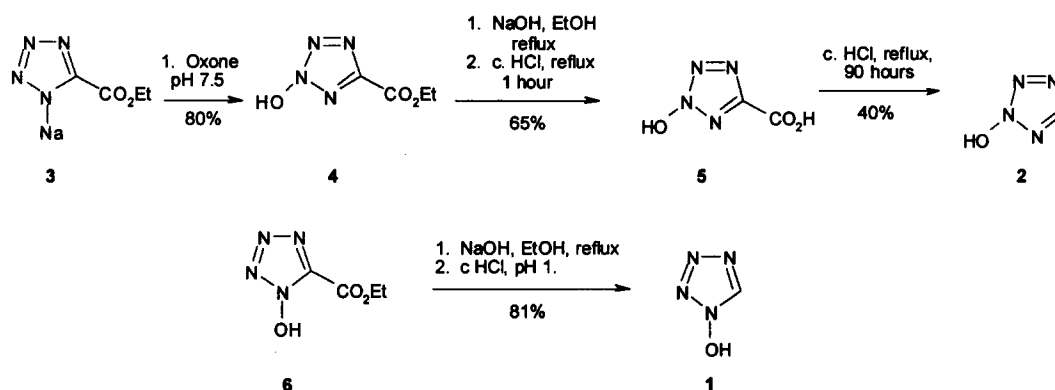
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Abstract: A highly selective oxidation of the sodium salt of ethyl tetrazole-5-carboxylate is reported which produces a novel class of hydroxytetrazole derivative which can then be converted to 2-hydroxytetrazole. A novel preparation of 1-hydroxytetrazole is also reported. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Several derivatives of 1-hydroxytetrazole have been prepared *via* the reaction of nitrile oxide derivatives and azide anion. For example, the preparation of 1-hydroxytetrazole **1** using sodium fulminate,¹ together with a series of 5-substituted 1-hydroxytetrazole derivatives (5-substituent = alkyl,² aryl,³ cyano,⁴ carboethoxy⁵) has been described. In comparison, only the unsubstituted 2-hydroxytetrazole derivative **2** has been reported by Begtrup, prepared *via* direct oxidation of 1*H*-tetrazole using sodium perborate.⁶ Recent interest in 2-hydroxytetrazole **2** has shown it to be a novel and efficient acylation catalyst in peptide synthesis⁷ and so a practical preparation of this compound is now required. Begtrup's synthesis of **2** is inefficient (17% yield), principally due to the poor *N*-1:*N*-2 chemoselectivity during the oxidation step (~ 1:2), culminating in protection (preparation of the *O*-benzyl ether), chromatography and deprotection steps being required to isolate the pure product. We wish to report an oxidation of the tetrazole ring which is highly *N*-2 selective, resulting in the facile preparation of novel substituted 2-hydroxytetrazole derivatives which are practical precursors to **2**.

Scheme 1.



Oxidation of the commercially available⁸ sodium salt of ethyl tetrazole-5-carboxylate **3** using oxone⁹ (potassium peroxymonosulphate, 2KHSO₅.KHSO₄.K₂SO₄) in aq. acetone at pH 7.5 results in almost exclusive formation of ethyl *N*-2-hydroxytetrazole-5-carboxylate **4** (*N*-2:*N*-1 selectivity ~ 70:1, as determined by hplc analysis) which can be isolated in pure form¹⁰ by direct crystallisation in 80% yield (Scheme 1). Treatment of **4** with sodium hydroxide in ethanol at reflux temperature for two hours, followed by acidification, results in the isolation of 2-hydroxytetrazole-5-carboxylic acid **5**¹⁰ in 81% yield. Decarboxylation of **5** requires forcing conditions (c. HCl/reflux/90 hours), and after work-up, affords 2-hydroxytetrazole **2** in 40% yield. The chemistry employed is advantageous over Begtrup's route in that the oxidation step is selective, isolation of products does not require derivatisation or chromatographic separation/purification, and reactions can be performed on a multi-gram scale.¹¹

Although ethyl 1-hydroxytetrazole-5-carboxylate **6** has been reported for some time, it was somewhat surprising to find that this compound had not been used as a precursor to 1-hydroxytetrazole **1**. Therefore, it interested to us to determine if a hydrolysis/decarboxylation sequence could be utilised to convert **6** into **1**. Preparation of **6**⁵ and subsequent treatment with sodium hydroxide in ethanol at reflux temperature, followed by acidification at room temperature results in spontaneous decarboxylation to give 1-hydroxytetrazole **1** in 81% isolated yield. The difference in reactivities between **5** and the carboxylic acid derived from **6** is currently under investigation.

In conclusion, a novel class of 2-hydroxytetrazole derivatives have been synthesised *via* selective ring oxidation and work is now ongoing to explore the preparation, reactivity and further application of these compounds. Results from these investigations will be reported in due course.

References and Notes.

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- 8 This compound was purchased from n. v. OMNICHEM, Coopallaan 91, B-9230 Wetteren, Belgium.
- 9 Reaction between compound **3** and dimethyl dioxirane proved problematic in our hands.
- 10 Yields quoted in this paper are unoptimised. All new compounds gave satisfactory analytical data.
- 11 **CAUTION:** We support the observations made by Begtrup's group regarding the explosive nature of *N*-hydroxytetrazoles. It is our experience that these compounds sometimes explode during melting point determinations which should therefore be performed with care.