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A new method for the formation of 2,4-disubstituted oxazoles: internal transfer of oxidation state through a molecular framework

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Abstract

A new method for the synthesis of 2,4-disubstituted oxazoles is described from readily available starting materials. The synthesis avoids the necessity for the oxidation of an oxazoline to an oxazole by utilising an internal transfer of oxidation state across a molecular framework and has been performed on multigram scale.

Keywords: oxazoline; oxazole; oxidation.

Oxazoles are found in many naturally occurring and biologically active materials as sub-structures within more complicated molecular arrays.[1–9] In particular oxazoles functionalised at both the 2- and 4-position with differing oxidation state of the appending carbon atom have found important application in the synthesis of the more complex natural products.[1,5,8,9] We have been interested in the pyrrolidine 5,5-*trans*-fused lactam[10] **1**, containing a 2,4-disubstituted oxazole, as a potential therapy for respiratory diseases such as acute respiratory distress syndrome, cystic fibrosis, emphysema and chronic bronchitis. In conjunction with our wider programme aimed at developing a manufacturing route for **1**, (Fig. 1) we sought an efficient, scalable, and inexpensive route into the potassium salt of carboxylic acid **2** (R=K, X=pyrrolidino). This route should also be suitable for scale up to pilot plant, be safe, environmentally acceptable and avoid the need of chromatography for purification.

In this paper we wish to present a new method for the preparation for 2,4-disubstituted oxazoles that fulfils the above requirements. In particular the facile preparation of 'chloro oxazole' **7** may find application in the synthesis of more elaborate oxazole containing molecules. Imidate **4** was prepared on multigram scale by a modification of the literature procedure[11] whereby dichloroacetonitrile **3** was added to a cold (−10°C) solution of a catalytic quantity of sodium methoxide in methanol. Serine methyl

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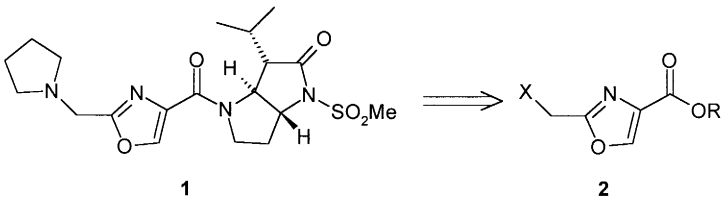
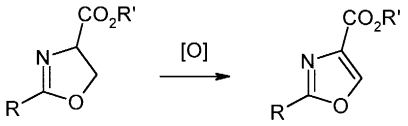


1 2

Fig. 1.

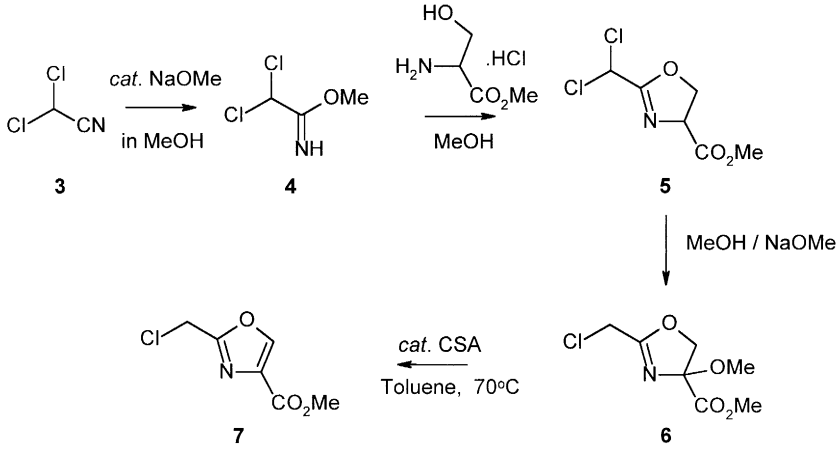
ester hydrochloride was added to the imidate **4** to give the dichlorooxazoline **5**[12] in a crude yield of 88% (Scheme 2).

Central to our strategy for the synthesis of oxazoles from oxazolines was the avoidance of oxidising agents. The oxidation of an oxazoline heterocycle to the corresponding oxazole analogue (Scheme 1) is a well known reaction in organic synthesis, and there are a number of synthetic methods to achieve this transformation. Generally these methods[13] require the use of environmentally unacceptable metals, solvents and reagents.



Scheme 1.

Treatment of the dichlorooxazoline **5** with one molar equivalent of sodium methoxide in methanol led to the elimination of chloride and formation of the methoxy-oxazoline **6**. The proton NMR of **6** contains a characteristic pair of doublets at δ_H 4.39 and 4.59 (J=10.5) for the ring CH_2 protons. This synthetic transformation has effectively transferred oxidation state of the *gem*-dichloro carbon to that adjacent to the methyl ester and offers an 'internal transfer of oxidation state through a molecular framework'. A similar elimination reaction has been observed in the synthesis of oxazolones in a tryptophan derivative.[14] Elimination of methanol from **6** by treatment with a catalytic amount of CSA in toluene at 70°C gave the chlorooxazole **7**[9] in 48% yield from dichloroacetonitrile **3**. (Scheme 2).



3 4 5 6 7

Scheme 2.

In summary, we have demonstrated a new method for the synthesis of 2,4-disubstituted oxazoles from readily available inexpensive starting materials on a multigram scale. This novel chemistry has safely been applied on scale in our pilot plant to provide multi-kilogram quantities of **7**. Our approach

to oxazoles has the potential to provide small heterocyclic building blocks that may be applied to the synthesis of more complex oxazole containing molecules.

1. Experimental

A solution of NaOMe in MeOH (25% w/w, 5.75 ml, 24.9 mmol) was diluted with MeOH (50 ml) and cooled to −10°C. Dichloroacetonitrile **3** (20 ml, 249 mmol) was added dropwise over 25 minutes whilst the temperature was maintained below 0°C. The mixture was stirred for a further 20 minutes at −5°C, then DL-serine methyl ester hydrochloride (38.7 g, 249 mmol) was added followed by methanol (40 ml). The mixture was stirred overnight, gradually warming to room temperature. CH_2Cl_2 (140 ml) and water (80ml) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (80 ml) and the combined organic extracts concentrated in vacuo to give dichlorooxazoline **5** (46.7 g, 88%, crude from dichloroacetonitrile) as an orange oil. To a solution of crude dichlorooxazoline **5** (46.2 g, 218 mmol) in methanol (40 ml) was added a solution of NaOMe in MeOH (25% w/w, 49.9 ml, 218 mmol) over 50 minutes, keeping the temperature below 10°C. The mixture was stirred overnight, gradually warming to room temperature. CH_2Cl_2 (140 ml) and water (80 ml) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (80 ml) and the combined organic extracts were concentrated in vacuo to give the methoxy oxazoline **6** (43.3 g, 84%, crude from dichloroacetonitrile **3** in the previous step) as an oil. To the methoxy oxazoline **6** (42.9 g, 207mmol) was added toluene (100 ml) and (±)-camphorsulphonic acid (7.21 g, 31.0 mmol) at room temperature. The solution was heated to 70°C for 50 minutes. The solution was cooled to room temperature and washed with aqueous K_2CO_3 solution (10% w/v, 60 ml) followed by water (80 ml). The combined aqueous extracts were back-extracted with toluene (120 ml) and the combined organic layers concentrated in vacuo to give the chlorooxazole **7** (30.1 g) as a brown solid.

An analytical sample of crude chlorooxazole (2.5 g) was purified by flash column chromatography for analytical purposes (25:75 EtOAc:iso-octane) to give the pure chlorooxazole product[9] (1.73 g, 48% isolated pure from dichloroacetonitrile **3** in this sequence) as a white solid. (Found: MH^+, 176.0127. $C_6H_6NO_3Cl$ requires MH^+, 176.0114); ν_{max} (Nujol mull)/cm^{-1} 1578 (C=C), 1715 (C=O); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, CO_2CH_3), 4.63 (2H, s, CH_2Cl), 8.27 (1H, s, O-CH=C); δ_C (100 MHz, $CDCl_3$) 35.31 (CO_2CH_3), 52.35 (CH_2Cl), 133.85 (C=C-CO_2CH_3), 145.07 (O-CH=C), 159.91 (C=N), 161.08 (CO_2CH_3).

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