Novel Synthesis of New Polyfunctionalized Oxazoles *via* Ring Contraction of (3),5-(di)Chloro-1,4-oxazin-2-ones

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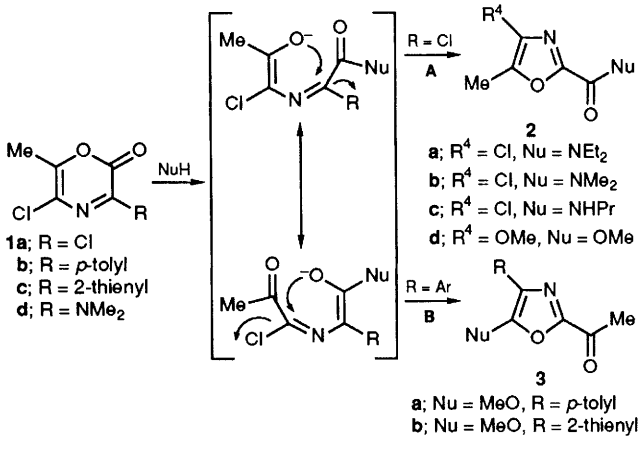
On treatment with nucleophiles, (3),5-(di)chloro-1,4-oxazin-2-ones undergo a ring contraction yielding new polyfunctionalized oxazoles which afford furan derivatives on reaction with acetylenes.

Oxazole derivatives possess a peculiar reactivity towards acids, bases, heat and dienophiles making them attractive in the synthesis of other heterocycles.[1] Although numerous synthetic routes to oxazoles have been reported, very few involve a ring transformation reaction and methods for oxazoles bearing a carbonyl group at C-2 are scarce. In this communication we report on a novel ring transformation of 1,4-oxazin-2-ones leading to new functionalized oxazoles.

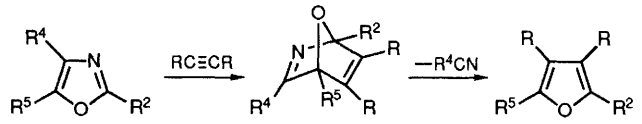
In a typical experiment, Et_2NH (2.1 equiv.) was added dropwise to a solution of 3,5-dichloro-6-methyl-1,4-oxazin-2-one **1a**[2] in $CHCl_3$ at −78 °C. Flash chromatography (SiO_2) of the reaction mixture yielded a product (71%) identified as the oxazole **2a**. Similarly, treatment of **1b**[3] with $KHCO_3$ (2 equiv.) in MeOH at room temperature for 3 h gave the oxazole **3a** in a high yield (91%).

The generation of both oxazoles is explained by a prior attack of the nucleophile on the lactone bridge (Scheme 1). After lactone cleavage the intermediate can be stabilized *via* two pathways depending on the substitution pattern. If R is a good leaving group (*e.g.* Cl), a ring closure occurs *via* pathway **A**. A similar mechanism has been proposed for the synthesis of benzoxazoles from 3-chlorobenzoxazin-2-ones[4] and of 1,2,3-triazoles from 1,2,4-triazin-3(2*H*)-ones.[5] Reaction of **1a** with dimethyl- and propyl-amine similarly gave oxazoles **2b** and **c** but treatment of **1a** in methanol (2 equiv. of K_2CO_3) at room temperature for 15 min afforded the oxazole **2d**. This 4-methoxy substituted compound probably arises from reaction of MeOH at the stage of the proposed intermediate. Prior formation of methyl 4-chloro-5-methyloxazole-2-carboxylate can be excluded as **2a** did not undergo substitution when treated with K_2CO_3 in methanol. A different pathway **B** is followed when R = (hetero)aryl: the intermediate resulting from compounds **1b** and **c** is now stabilized by an alternative ring closure yielding compounds **3a** and **b**.

The generation of oxazoles **2** and **3** instead of the 3-functionalized 1,4-oxazin-2-one is confirmed by their spectroscopic characteristics. Compounds **1d**,[3] **2b** and **3a** have slightly different ^1H NMR methyl resonance positions: δ 2.2, 2.4 and 2.5; significantly different values are observed in the ^{13}C NMR spectra (δ 15.6 for 6-Me in **1d**, δ 9.8 for 5-Me in **2b** and δ 25.4 for COMe in **3b**). Moreover, only one signal appears for NMe_2 in **1d** (δ 3.3) whereas the signal is split in **2b** (δ 3.1 and 3.5) owing to the hindered rotation around the amide group. Typically, a high δ value for the carbonyl group (δ 184.4) is found in ^{13}C NMR spectrum of **3a** whereas all signals of **1** and **2** appear below δ 155. Oxazoles of both type **2** and **3** lack the IR absorption around 1750 cm^{-1} and the 100% mass spectral peak at $M^+ - 28$ which is observed for **1d**.



Scheme 1



2a; R^2 = $CONEt_2$, R^4 = Cl, R^5 = Me
3a; R^2 = COMe, R^4 = *p*-tolyl, R^5 = OMe

4a
4b
R = CO_2Me

Scheme 2

The structure of above compounds was confirmed by carrying out some Diels–Alder reactions on their 2-azadiene system with dimethyl acetylenedicarboxylate (DMAD). As the Diels–Alder adduct spontaneously loses R^4CN *via* a retro-Diels–Alder reaction, furan derivatives would be expected.[6] Oxazoles **2a** and **3a** were found to undergo Diels–Alder reaction with DMAD generating the hitherto unknown furan derivatives **4a** and **b** (Scheme 2).

We conclude that (3),5-(di)chloro-1,4-oxazin-2-ones undergo ring transformation to yield oxazoles which offer access to tri- and tetra-substituted furans. Moreover, cycloadditions with alkenes or heterodienophiles provide a possible and promising route to pyridines[6] and heterocyclic five-membered rings,[7] respectively. The generation of these new polyfunctionalized oxazoles and their synthetic use in reactions with (hetero)dienophiles are under current investigation.

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