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Diazo-sulfones and -Nitriles in Oxazole Synthesis; Three Step Preparation of a Bis-Oxazole

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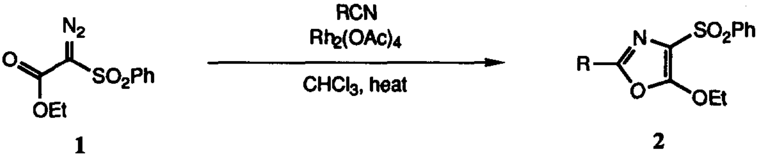
Abstract: Oxazole-4-sulfones and -nitriles are prepared by rhodium(II) catalysed addition of nitriles to the corresponding diazo compound: the 4-cyanooxazole **3** is readily converted into the bis-oxazoles **4** and **5**.

The recently described synthesis of bis- and tris- oxazoles using repetitive rhodium(II) acetate catalysed addition reactions of diazomalonates to nitriles,[1] prompts us to report our own related results. The synthesis of oxazoles has attracted much attention of late, presumably because of the presence of the ring system in a variety of complex natural products.[2] Although the route involving reaction of diazocarbonyl compounds with nitriles under a variety of conditions is well known,[3] the rhodium(II) catalysed variant is less well described, and is limited to simple diazoesters.[4,5] In continuation of our work on the use of other functionalised diazocarbonyl compounds such as diazo-sulfones, -phosphonates and -nitriles,[6-8] we were keen to investigate their reactions with nitriles as a route to 4-functionalised oxazoles.

The diazosulfone **1** reacted with a range of nitriles to give 4-benzenesulfonyloxazoles **2** in varying yields; some examples are shown in the Table. Although 4-benzenesulfonyloxazoles are known,[9] the present use of diazosulfones represents a useful extension of the rhodium carbenoid methodology.

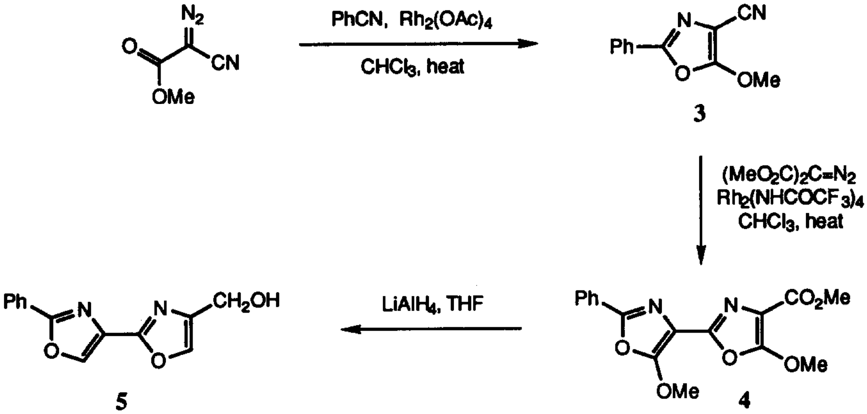


Table

R	*Yield (%)[a]*	*m.p. (°C)*	*R*	*Yield (%)[a]*	*m.p. (°C)*
Et	52	101-103	Ph	71	110-112
2-Cl-C_6H_4	56	145-147	4-Cl-C_6H_4	24	127-129
3-MeO-C_6H_4	24	121-123	4-MeO-C_6H_4	15	125-127

Note: [a] Yields refer to recrystallised material.

The need to prepare oxazoles with a functional group at the 4-position was stimulated by our interest in bis-oxazoles such as the hennoxazoles[10] and diazonamides,[11] in which the two heterocyclic rings are directly linked through their 4- and 2-positions. Although, in principle, the 4-sulfonyl group can be substituted, thereby allowing the preparation of more complex linked oxazoles, the corresponding 4-cyano derivatives could act as direct precursors to bis-oxazoles. Since it is also known that a 5-methoxy group can be cleaved reductively from an oxazole ring,[4] we investigated the use of methyl cyanodiazoacetate in the synthesis of bis-oxazoles with the intention of removing the unwanted alkoxy groups in the last step. Thus methyl diazocyanoacetate reacted with benzonitrile in refluxing chloroform in the presence of rhodium(II) acetate to give the 4-cyanooxazole **3**, m.p. 107-108°C, in 35% yield. Reaction of the 4–cyanooxazole **3** with dimethyl diazomalonate under similar conditions did indeed give the desired bis-oxazole **4**, m.p. 144-146°C, but in only 4% yield; presumably the presence of the 5-methoxy group adversely affects the reaction (*cf.* ref. 1). However, using rhodium(II) trifluoroacetamide, a catalyst that we have found useful for other carbenoid transformations,[12] the yield of bis-oxazole **4** was improved to 53%. Finally, as had been hoped, both methoxy groups were cleaved, with concomitant reduction of the ester, by reaction with lithium aluminium hydride. Thus, this first use of diazonitriles in oxazole synthesis represents a useful advance, bis-oxazole **5** being available *in just 3 steps* from the original nitrile precursor.



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