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Microwave Assisted Synthesis of Triazolobenzoxazepine and Triazolobenzoxazocine Heterocycles

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Abstract - Intramolecular click chemistry was utilized to effect synthesis of the benzofused, triazole ring systems. The trimethylsilyl group was found to impede the reaction progress, and therefore, conditions employing in situ removal of the TMS group coupled with microwave irradiation gives the penultimate targets with good conversion.

The synthesis of 1,2,3-triazole ring systems represents an interesting study in structural diversity.[1] The widespread application of a 1,3 dipolar cycloaddition with readily prepared substituted azides and alkynes offers a broad spectrum of triazole species containing unique structural elements.[2] The relatively straightforward chemistries applied to synthesize these analogs cement the triazole motif as a key heterocycle in the medicinal chemists' aresenal. Although general in nature, the subtleties of this complex annulation are significant and often require fine tuning synthetic conditions in order to achieve the desired regiochemical control. To this end, a number of authors have published papers describing the highly refined nature of a given set of conditions applied to ensure the most desirable outcome. The directed synthesis of 1,5-triazoles can be achieved through the use of silicon as a directing group,[5] or inclusion of ruthenium complexes.[11] The corresponding 1,4-isomer can usually be obtained with the addition of copper (I) iodide.[7] In many cases, nearly absolute regiochemical control can be obtained. The 1,2,3-triazole ring has established biologically relevant activity in a number of areas. Of recent interest include cardiovascular diseases,[1f] anti-HIV,[1e] and anti-bacterial agents,[1a,d] to name only a few. Given the ease of intermediate synthesis, the high degree of structural flexibility, and the biological importance of these molecules, investigative studies into the mechanistic understanding of different synthetic approaches offers a field worthy of exploration.

Over the course of the last decade, a number of benzofused heterocyclic systems have been targeted.[3,6] Interestingly, very few have broached the issue of a 1,3 dipolar cycloaddition to afford seven and eight membered fused triazole systems. Of note is the work by Alajarin et al in the synthesis of triazolobenzodiazepines,[6] where utilization of a novel triphenylphosphorane affords a number of N-phenyl triazole systems. Of particular interest to our group was the work of Chowdhury et al, in which a one pot synthesis of isoindolotriazoles is described,[3] and sufficient utility is demonstrated. However, the specific targeting of the triazolobenzoxazepine and triazolobenzoxazocine systems have yet to be described. Herein, we report the successful synthesis and characterization of both fused, tricyclic ring systems **1** and **2**, shown in Figure 1.

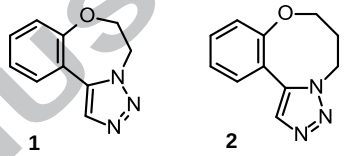
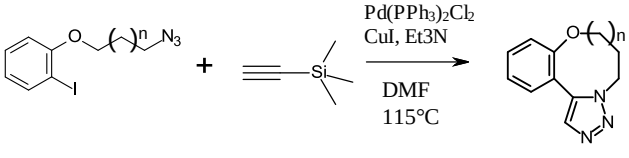


Figure 1. Triazolobenzoxazepine **1** and triazolobenzoxazocine **2**.

Initial scanning of the literature revealed the previously mentioned Chowdhury paper, and their convenient one pot synthesis of isoindolotriazoles. A number of structural analogs were prepared highlighting the utility of the reaction, noting minimal impact of substituting the alkyne on the overall yield. Further analysis of the proposed mechanism suggested that application to larger ring synthesis, while favourable according to Baldwin's rules, may not be quite as straightforward. In our hands, application of this route according to Scheme 1 provided **1** and **2,** in very low yield (12% and 10% yields, respectively). In this particular set of conditions, several aspects were hypothesized to conspire against a successful reaction. First, inherent entropic cost in preparing seven and eight membered rings cannot be discounted. Second, silicon containing alkynes, although directing to the 1,5 regioisomer, may decrease reaction rates not observed in the isoindolotriazole system. It is quite plausible that the activation energies required for the 1,3-dipolarcycloaddition with the silyl group intact, were sufficiently high as to impede the reaction. And third, the presence of even residual amounts of copper (I) iodide should actually retard the overall rate, as the reaction strives to deliver the preferred 1,4 regioisomer under those conditions.



n = 0, 12% yield
n = 1, 10% yield

Scheme 1. Penultimate step of the literature inspired synthesis of **1** and **2.**

Keywords: click chemistry, 1,3-dipolar cycloaddition, microwave, triazole.

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