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Novel One-Pot Multicomponent Strategy for the Synthesis of Pyrrolo[1,2-*a*]benzimidazole and Pyrrolo[1,2-*a*]quinoxaline Derivatives

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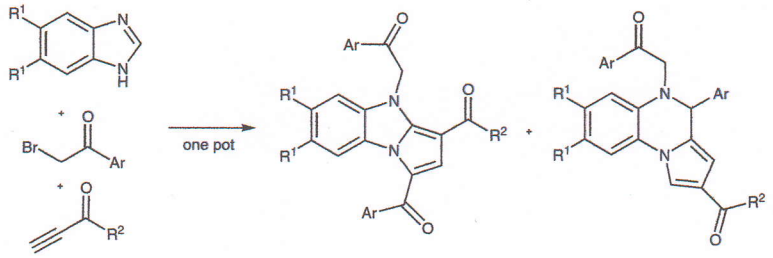

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Abstract A simple one-pot multicomponent procedure has been developed for the synthesis of pyrrolo[1,2-*a*]benzimidazole and pyrrolo[1,2-*a*]quinoxaline derivatives by heating a 1:2:1 molar mixture of a benzimidazole unsubstituted on the imidazole ring, a 2-bromoacetophenone derivative, and a nonsymmetrical activated alkyne in refluxing 2-ethyloxirane. The reaction can be performed under conventional reflux conditions or with microwave irradiation.

Key words heterocycles, ylides, cycloadditions, multicomponent reactions, fused-ring systems

Searches for new compounds that are based on the concept of privileged scaffolds (structures that can interact with a broad range of unrelated receptors) might be capable of identifying new biologically active compounds. Privileged structures typically consist of rigid polycyclic heteroatomic systems that are capable of orienting numerous substituents in the surrounding three-dimensional space. Such structures are considered to be excellent lead compounds, especially in cases when little is known regarding the structures of the corresponding receptors.[1]

In the course of our researches on innovative heterocyclic scaffolds, our interest was attracted to the synthesis of pyrrolo[1,2-*a*]benzimidazole and pyrrolo[1,2-*a*]quinoxaline compounds. These two heterocyclic scaffolds have been widely reported and investigated, mainly because of their biological properties. Pyrrolo[1,2-*a*]benzimidazole derivatives are known to act as antitumor agents,[2a–i] and some are useful for treating disorders of the central nervous system.[2j] The pyrrolo[1,2-*a*]quinoxaline system is found in various bioactive compounds that possess a broad spectrum of biological activities, including antituberculosis,[3a] antiparasitic,[3b] and central dopamine-antagonist activities.[3c] Compounds with this scaffold show a highly selective agonist affinity for serotonin receptors[3d] and they have shown activity in the treatment of cancer and of disorders associated with the angiogenesis function.[3e]

Several reviews on methods for the synthesis of pyrrolo[1,2-*a*]benzimidazole[4] and pyrrolo[1,2-*a*]quinoxaline derivatives[5] have recently been published. One interesting approach to the synthesis of pyrrolo[1,2-*a*]benzimidazoles is a classical multistep strategy involving a 1,3-dipolar cycloaddition reaction of a benzimidazolium ylide with an electron-deficient alkyne or alkene.[6] This method starts with the preparation of a benzimidazolium salt that is converted in situ into a benzimidazolium N-ylide in the presence of a base and a dipolarophile;[6a,b] this reaction usually gives small yields of the corresponding pyrrolo[1,2-*a*]benzimidazoles. Better yields are obtained when the 1,3-dipolar cycloaddition reactions take place in the presence of an organic base, such as triethylamine, and an oxidant, such as chromium trioxide.[6e]

Our group has developed a simple one-pot three-component strategy for the synthesis of a variety of pyrroloazines that is based on consecutive quaternization of an N-heterocycle, the generation in situ of a heterocyclic N-ylide, 1,3-dipolar cycloaddition, and aromatization.[7] This synthetic route starts with almost equimolar amounts of the N-heterocyclic compound, an α-bromocarbonyl derivative, and an activated alkyne in an epoxide that serves as both the reaction medium and an acid scavenger.