Fine tuning the outcome of 1,3-dipolar cycloaddition reactions of benzimidazolium ylides to activated alkynes

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1. Introduction

The interest in pyrrolo[1,2-α]benzimidazole and pyrrolo[1,2-α]quinoxaline derivatives has increased significantly over time, mainly due to their biological and pharmacological properties. Pyrrolo[1,2-α]quinoxalines substituted at C-4 with alkylpiperazines present both high affinity and selectivity for anti-serotonin 5-HT3 receptors.1 Pyrrolo[1,2-α]quinoxaline-carboxylic acid hydrazide derivatives showed antimycobacterial activity against Mycobacterium tuberculosis,2 while 4-substituted pyrrolo[1,2-α]quinoxalines exhibited antiparasitic activity upon Leishmania amazonensis and Leishmania infantum strains.3 2-(Aminomethyl)-4-phenyl-pyrrolo[1,2-α]quinoxaline derivatives revealed a central dopamine antagonist activity,4 (pyrrolo[1,2-α]quinoxaline-5-(4H)-yl)sulfonyls and carbonyls were tested as oestrogenic receptor modulators,5 whereas pyrrolo[1,2-α]quinoxalin-4-yl-hydrazides can be used for treating cancer and disorders associated with angiogenesis.6 Antitumour agents based on the pyrrolo[1,2-α]benzimidazole ring system were designed as new DNA cross-linkers mimicking the mitomycin antitumour agents against various human cancer cells,7 and different 2-oxo-pyrrolo[1,2-α]benzimidazole-3-carboxyl derivatives demonstrated therapeutic properties on central nervous system disorders.8

An interesting synthetic pathway to construct the pyrrolo[1,2-α]benzimidazole system is based on the classical 1,3-dipolar cycloaddition reaction of benzimidazolium ylides with electron-deficient alkynes or alkenes. This process usually starts with the preparation of benzimidazolium salts, in situ conversion into corresponding salts may also be isolated for further property studies.9i

Alternatively, the benzimidazolimum function,6 Antitumour agents based on the pyrrolo[1,2-α]benzimidazolium salts 6, pyrrolo[1,2-α]quinoxalinium quaternary salts 8, as well as 4-methoxy-4,5-dihydropyrrolo[1,2-α]quinoxalines 9, were separated, fully characterized and their interconversions are presented, together with a proposed reaction mechanism.

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1,3-Dipolar cycloaddition reactions of benzimidazolium ylides, generated from 3-phenacylbenzimidazolium bromides, to non-symmetrical activated dipolarophiles in various reaction conditions led to complex mixtures of pyrrolo[1,2-α]benzimidazole and pyrrolo[1,2-α]quinoxaline derivatives. In order to explain all experimental results, the influence of reaction conditions on the reaction products was investigated. For the first time, 4-hydroxy-4,5-dihydropyrrolo[1,2-α]quinoxaline derivatives 6, pyrrolo[1,2-α]quinoxalinium quaternary salts 8, were separated, fully characterized and their interconversions are presented, together with a proposed reaction mechanism.

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