



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

Emilian Georgescu^a, Alina Nicolescu^{b,c}, Florentina Georgescu^d, Florina Teodorescu^b, Sergiu Shova^{c,e}, Adriana T. Marinoiu^f, Florea Dumitrascu^b, Calin Deleanu^{b,c,*}

^aResearch Center Oltchim, St. Uzinei 1, RO-240050 Ramnicu Valcea, Romania

^b"C. D. Nenitescu" Centre of Organic Chemistry, Romanian Academy, Spl. Independentei 202B, RO-060023 Bucharest, Romania

^c"Petru Poni" Institute of Macromolecular Chemistry, Romanian Academy, Aleea Grigore Ghica Voda 41-A, RO-700487 Iasi, Romania

^dTeso Spec S. R. L., Research Dept., Str. Muncii 53, RO-915200 Fundulea, Calarasi, Romania

^eInstitute of Chemistry, Academy of Sciences, Str. Academiei 3, MD-2028, Chisinau, Republic of Moldova

^fNational Research & Development Institute for Cryogenic and Isotopic Technologies, St. Uzinei 4, RO-240050 Ramnicu Valcea, Romania

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ABSTRACT

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-*a*]benzimidazole and pyrrolo[1,2-*a*]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-*a*]quinoxaline derivatives **6**, pyrrolo[1,2-*a*]quinoxalinium quaternary salts **8**, as well as 4-methoxy-4,5-dihydropyrrolo[1,2-*a*]quinoxalines **9**, were separated, fully characterized and their interconversions are presented, together with a proposed reaction mechanism.

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1. Introduction

The interest in pyrrolo[1,2-*a*]benzimidazole and pyrrolo[1,2-*a*]quinoxaline derivatives has increased significantly over time, mainly due to their biological and pharmacological properties. Pyrrolo[1,2-*a*]quinoxalines substituted at C-4 with alkylpiperazines present both high affinity and selectivity for *anti*-serotonin 5-HT₃ receptors.¹ Pyrrolo[1,2-*a*]quinoxaline-carboxylic acid hydrazide derivatives showed antimycobacterial activity against *Mycobacterium tuberculosis*,² while 4-substituted pyrrolo[1,2-*a*]quinoxalines exhibited antiparasitic activity upon *Leishmania amazonensis* and *Leishmania infantum* strains.³ 2-(Aminomethyl)-4-phenyl-pyrrolo[1,2-*a*]quinoxaline derivatives revealed a central dopamine antagonist activity,⁴ (pyrrolo[1,2-*a*]quinoxaline-5-(4*H*)-yl)sulfonyls and carbonyls were tested as oestrogenic receptor modulators,⁵ whereas pyrrolo[1,2-*a*]quinoxalin-4-yl-hydrazides can be used for treating cancer and disorders associated with angiogenesis

function.⁶ Antitumour agents based on the pyrrolo[1,2-*a*]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-*a*]benzimidazole-3-carboxyl derivatives demonstrated therapeutic properties on central nervous system disorders.⁸

An interesting synthetic pathway to construct the pyrrolo[1,2-*a*]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 benzimidazolium ylides in the presence of an inorganic or organic base and 1,3-dipolar cycloaddition reactions of benzimidazolium ylides with dipolarophiles affording pyrrolo[1,2-*a*]benzimidazoles in low to moderate yields.^{9a–h} Alternatively, the benzimidazolium salts may also be isolated for further property studies.⁹ⁱ

Our group has developed a simple one-pot, multi-component synthetic strategy towards *N*-bridgehead heterocyclic compounds. This strategy is based on the consecutive quaternization of the *N*-heterocycle compound, in situ generation of the heterocyclic *N*-

* Corresponding author. Tel.: +40 744 340456; fax: +40 21 3126101; e-mail addresses: calin.deleanu@yahoo.com, calind@icmpp.ro (C. Deleanu).