An unexpected formation of pyrazolopyrimidines during the attempted to obtain 5-substituted tetrazoles from carbonitriles

Jéssica Venância Faria, Maurício Silva dos Santos, Percilene Fazolin Vegi, Julio Cesar Borges, Alice M. R. Bernardino

Departamento de Química Orgânica, Instituto de Química, Universidade Federal Fluminense, 24020-150 Niterói, RJ, Brazil
Instituto de Física e Química, Universidade Federal de Itajubá, 37500-903 Itajubá, MG, Brazil

ABSTRACT

In this Letter, we described the synthesis of new 5-(5-amino-1-aryl-1H-pyrazole-4-yl)-1H-tetrazoles 2a–c from 5-amino-1-aryl-1H-pyrazole-4-carbonitriles 1a–c as well as the unexpected 1H-pyrazolo[3,4-d]pyrimidine derivatives 6a–c from 5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a–c, instead of 5-(5-amino-1-aryl-3-methyl-1H-pyrazole-4-yl)-1H-tetrazoles 5a–c as desired. In an attempt to obtain these tetrazole derivatives containing the methyl group at C3-position in the pyrazole ring, the amino group in 5-amino-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile 4c was protected by the reaction with sodium hydride and di-tert-butyl-dicarbonate (Boc). The tetrazole derivative 5c was synthesized from the protected compound 7c using analogue methodology to obtain 2a–c and 6a–c.

In recent years, tetrazoles have received considerable attention because they represent an important class of heterocycles, which exhibit a wide range of biological activity, including antiprotozoal, antihypertensive and antibiotic effects. Tetrazoles show greater lipophilicity and hence may serve as non-classical isosteres for the carboxylic acid group. The classical method for the preparation of 5-substituted tetrazoles occurs through the reaction of nitriles with sodium azide and ammonium chloride in DMF, at 120–130 °C, by an [3+2] cycloaddition.

Recently, our research group reported the synthesis of new 5-(1-aryl-1H-pyrazole-4-yl)-1H-tetrazoles from 1-aryl-1H-pyrazole-4-carbonitriles, sodium azide and ammonium chloride in DMF as solvent, for 14 h at 120–130 °C. In the course of our search for new tetrazole derivatives, we prepared three new 5-(5-amino-1-aryl-1H-pyrazole-4-yl)-1H-tetrazoles 2a–c using analogue methodology (Scheme 1). 5-Amino-1-aryl-1H-pyrazole-4-carbonitriles 1a–c were reacted with sodium azide (2 equiv) and ammonium chloride (2 equiv) in DMF at 130–140 °C. After 16–18 h tetrazoles 2a–c were isolated in good yields: 62–74%. Lower temperatures resulted in long time reaction.

We have also investigated the influence of the methyl group at C3-position in the pyrazole ring. In an attempt to synthesize new tetrazoles from 5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a–c, employing the same methodology, the desired compounds 5-(5-amino-1-aryl-3-methyl-1H-pyrazole-4-yl)-1H-

tetrazoles 5a−c were not obtained. Thus, we have investigated alternative methodologies. When we worked with sodium azide and ammonium chloride in DMF at 120−130 °C for 48 h, unexpected products were isolated (Scheme 2). After purification by recrystallization, FT-IR spectra data showed C=N band as well as NH₂ bands. However, in 1H NMR spectroscopy it was found in each compound two singlet signals related to the methyl group: 2.66−2.67 ppm and 2.71−2.72 ppm. Besides, two aryl groups were identified in aromatic region. The 13C NMR analysis showed signals corresponding to 1H-pyrazolo[3,4-d]pyrimidine system. In mass spectra (ESI−MS) the mass/charge ratio values of molecular ion peaks obtained were higher than expected for the derivatives 5a−c. According to all analytical results, 6-(5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a−c were isolated. Since the analogues 5-(5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 6a−c were obtained, as mentioned above, the presence of the methyl group at C3-position in the pyrazole ring affects the reaction. We have also examined the influence of ammonium chloride and sodium azide in this reaction. When we worked with 5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a−c, ammonium chloride (2 equiv) in DMF the reaction did not proceed. We tried using different temperatures, from 120 °C to under reflux, as well as different reaction times, from 24 h to 48 h. Treatment of 5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a−c with sodium azide (2 equiv) in DMF did not generate the desired products using the same conditions.

With regard to mechanism, the reaction starts by a nucleophilic attack of the amine group of one molecule to nitrile of another one. Afterwards, an intramolecular cyclization produces the pyrazolo[3,4-d]pyrimidine system. Compounds 6a−c are new, but 1H-pyrazolo[3,4-d]pyrimidine obtained from 5-amino-1-aryl-1H-pyrazole-4-carbonitriles has been published in the literature. Salaheldin et al. synthesized 6-(5-amino-1-aryl-1H-pyrazole-4-yl)-1-aryl-1H-pyrazolo[3,4-d]pyrimidin-4-amine by reacting 5-amino-1-aryl-1H-pyrazole-4-carbonitriles with triethanolamine and ethanol under reflux for 6 h. Taylor & Borror described the synthesis of similar products after several hours, using sodium ethoxide and ethanol in reflux. Smith et al. employed potassium t-butoxide, in toluene, microwave at 160 °C.

Since 1H-pyrazolo[3,4-d]pyrimidines present wide applicability in medicinal chemistry such as being anticancer, antibacterial, antileishmanial, antitrypanosomal, and antiviral, the biological activity of compounds 6a−c will be evaluated.

In another experiment the raw material 5-amino-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile 4c was reacted with sodium hydride and di-tert-butyl-dicarbonate (Boc) to protect the amino group. The protected product obtained 7c was treated with sodium azide and ammonium chloride in DMF, at 130−140 °C, for 48 h. Analytical results showed that the tetrazole ring was obtained, the Boc protecting group was removed and compound 5c was completely characterized (Scheme 3).

In conclusion, the synthesis of new 5-(5-amino-1-aryl-1H-pyrazole-4-yl)-1H-tetrazoles 2a−c from 5-amino-1-aryl-1H-pyrazole-4-carbonitriles 1a−c occurred as expected in good yields. The presence of the methyl group at C3-position in 5-amino-1-aryl-3-methyl-1H-pyrazole-4-carbonitriles 4a−c impeded the formation of analogue tetrazoles 5a−c and the unexpected 1H-pyrazolo[3,4-d]pyrimidine derivatives 6a−c were isolated. Tetrazole 5c was synthesized employing an alternative synthetic route. In the first step, compound 4c was protected by the reaction with sodium hydride and di-tert-butyl-dicarbonate (Boc). After that, tetrazole was obtained using analogue methodology to obtain 2a−c and 6a−c. Therefore, this synthetic route can be employed to access 5-(5-amino-1-aryl-3-methyl-1H-pyrazole-4-yl)-1H-tetrazoles 5a−c planned initially (Scheme 1) and other derivatives from this system.
Acknowledgments

We thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Rede Mineira de Química (RMQ), Universidade Federal Fluminense (PROPP/UFF) and Centro de Estudos e Inovação em Materiais Biofuncionais Avançados/UNIFEI for fellowships and financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.033.

References and notes