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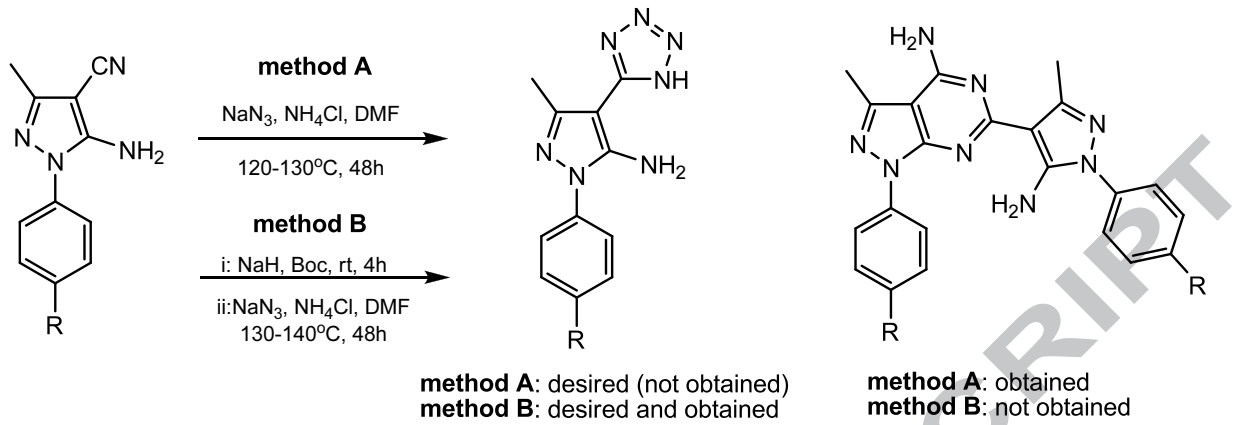
Graphical Abstract



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

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Abstract

In this letter, we described the synthesis of new 5-(5-amino-1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **2a-c** from 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **1a-c** as well as the unexpected 1*H*-pyrazolo[3,4-*d*]pyrimidines derivatives **6a-c** from 5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-carbonitriles **4a-c**, instead of 5-(5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **5a-c** as desired. In attempt to obtain these tetrazole derivatives containing the methyl group at C3-position in pyrazole ring, the amino group in the 5-amino-1-(4-methoxyphenyl)-3-methyl-1*H*-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**.

Keywords: unexpected reaction, pyrazolo[3,4-*d*]pyrimidine, tetrazole, cycloaddition.

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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 antiprozoal, antihypertensive and antibiotic effects.[1] Tetrazoles show greater lipophilicity and hence may serve as non-classical isosteres for the carboxylic acid group.[2] 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.[3] Recently, our research group reported the synthesis of new 5-(1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles from 1-aryl-1*H*-pyrazole-4-carbonitriles, sodium azide, ammonium chloride in DMF as solvent, during 14 hours at 120-130°C.[4] In the course of our search for new tetrazole derivatives, we prepared three new 5-(5-amino-1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **2a-c** using analog methodology (Scheme 1). 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **1a-c** were reacted with sodium azide (2 equiv.), ammonium chloride (2 equiv.) in DMF at 130-140°C. After 16-18 hours the tetrazoles **2a-c** were isolated in good yields: 62-74%. Lower temperatures resulted in long time reaction.

Scheme 1

We have also investigated the influence of the methyl group at C3-position in pyrazole ring. In attempt to synthesize new tetrazoles from 5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-carbonitriles **4a-c**, employing the same methodology, the desired compounds 5-(5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **5a-c** weren´t obtained. Thus, we have investigated alternative methodologies. When we worked with sodium azide, ammonium chloride in DMF at 120-130°C for 48 hours, unexpected products were isolated (Scheme 2). After purification by recrystallization, FT-IR spectra data showed C=N band as well as NH_2 bands. However, in ^{1}H NMR spectroscopy it was found in each compound two singlet signals related to methyl group: 2.66-2.67 ppm and 2.71-2.72ppm. Besides, two aryl groups were identified in aromatic region. The ^{13}C NMR analysis showed signals which corresponding to 1*H*-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, the 6-(5-amino-1-aryl-3-methyl-1*H*-pyrazol-4-yl)-1-aryl-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine derivatives **6a-c** were isolated. Since the analogs 5-(5-amino-1-aryl-1*H*-pyrazole-4-yl)-1*H*-tetrazoles **2a-c** were obtained, as mentioned above, the presence of methyl group at C3-position in 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-1*H*-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 hours to 48 hours. Treatment of 5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-carbonitriles **4a-c** with sodium azide (2 equiv.) in DMF did not generated the products desired using the same conditions.

Scheme 2

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. The compounds **6a-c** are new, but 1*H*-pyrazolo[3,4-*d*]pyrimidine obtained from 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles have been published in the literature. Salaheldin *et. al.*[5] synthesized 6-(5-amino-1-aryl-1*H*-pyrazol-4-yl)-1-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine reacting 5-amino-1-aryl-1*H*-pyrazole-4-

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carbonitriles with triethanolamine, ethanol under reflux by 6 hours. Taylor & Borror[6] described the synthesis of similar products after several hours, using sodium ethoxide and ethanol in reflux. Smith & co-workers[7] employed potassium *t*-butoxide, in toluene, microwave at 160°C.

Since 1*H*-pyrazolo[3,4-*d*]pyrimidines present wide applicability in medicinal chemistry such as anticancer,[8] antibacterial,[9] antileishmanial,[10] antitrypanosomal,[10] and antiviral,[11] the biological activity of compounds **6a-c** will be evaluated.

In another experiment the raw material 5-amino-1-(4-methoxyphenyl)-3-methyl-1*H*-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, during 48 hours. Analytical results showed that the tetrazole ring was obtained and the Boc protecting group was removed and the compound **5c** was completely characterized (Scheme 3).

Scheme 3

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

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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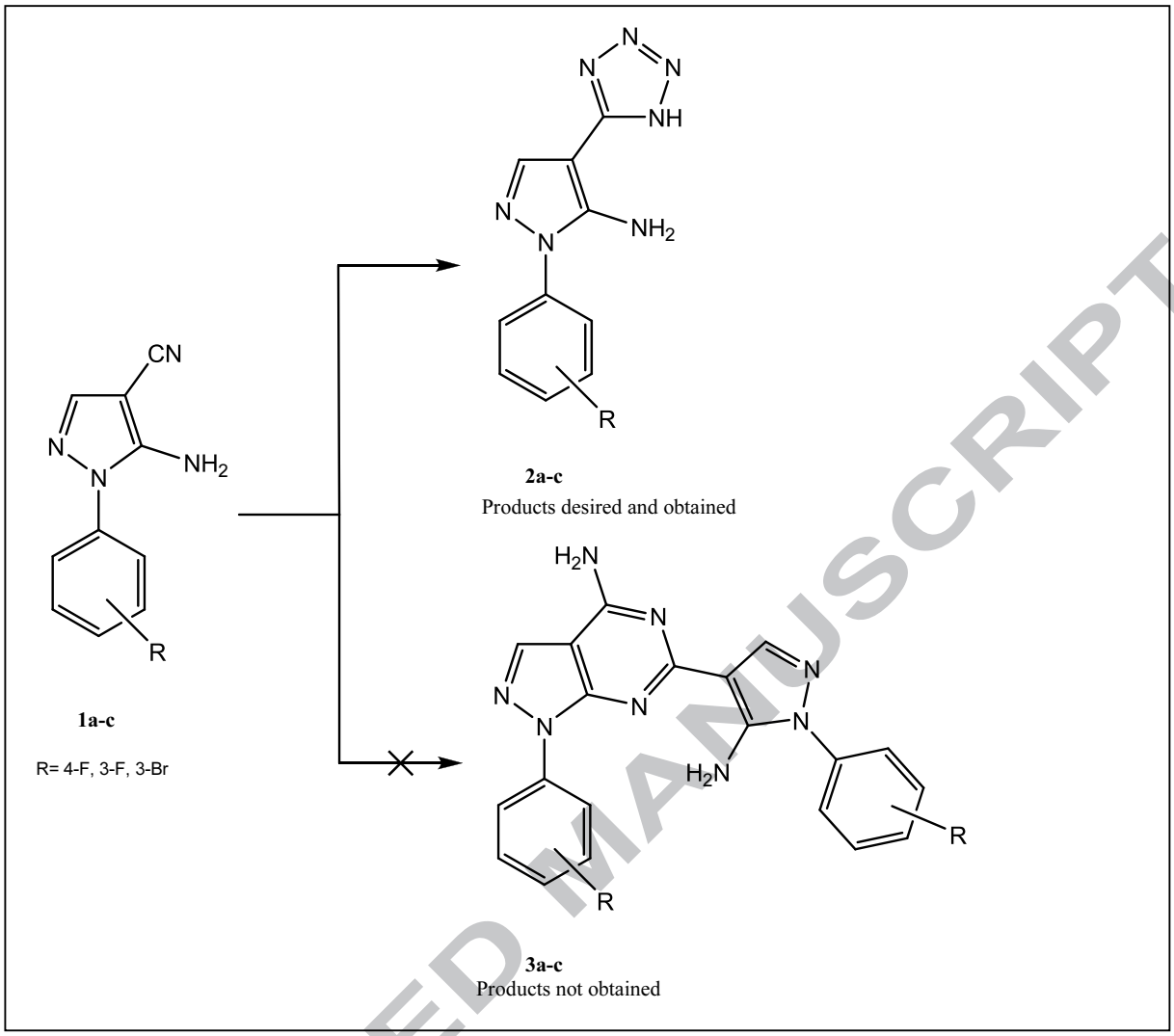

Scheme 1. Synthesis of tetrazoles. Reagents and conditions: NaN_3, NH_4Cl, DMF, 130-140^oC, 16-18h.

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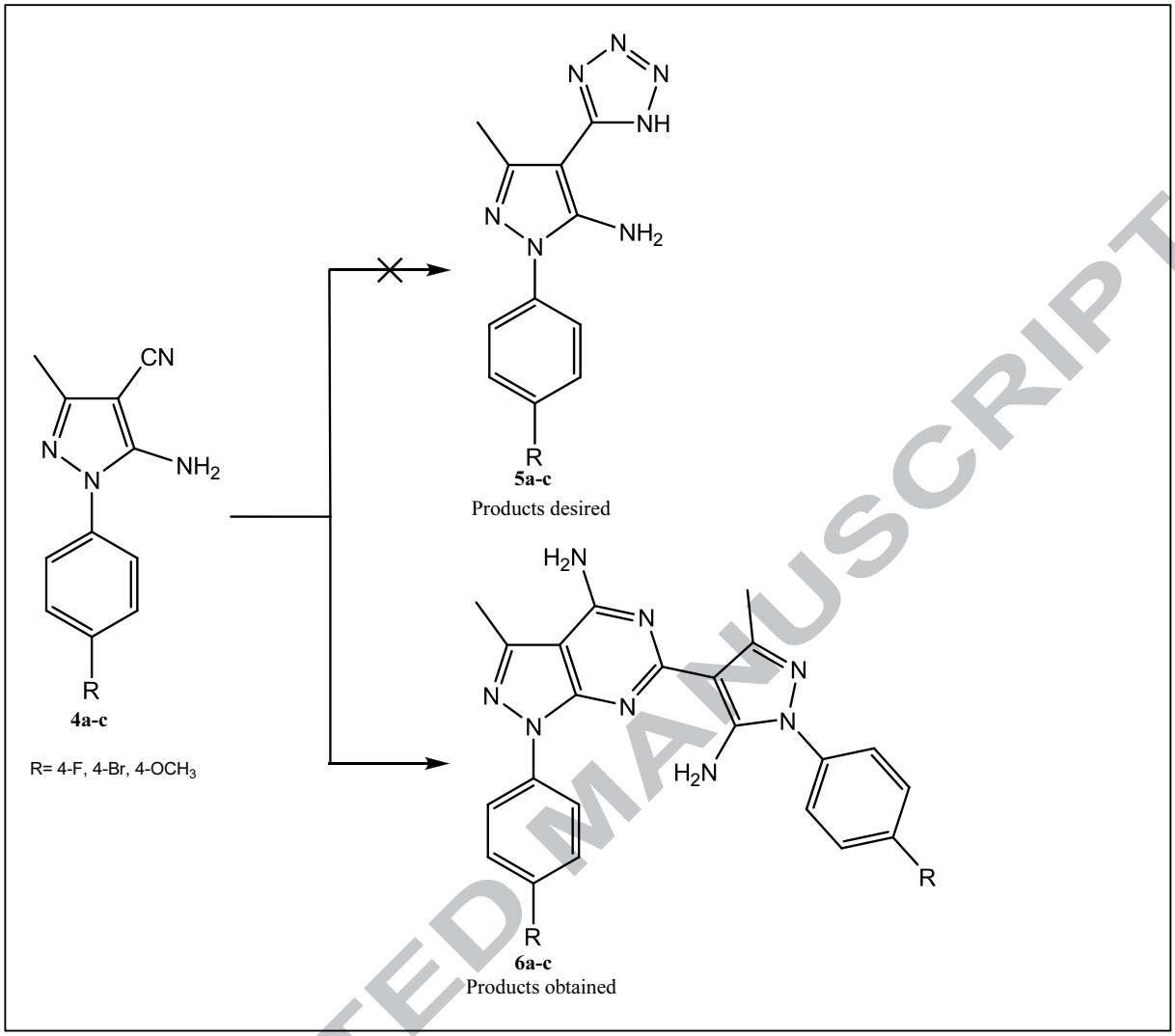

Scheme 2. The reaction leading to the synthesis of 1*H*-pyrazolo[3,4-*d*] pyrimidines. Reagents and conditions: NaN_3, NH_4Cl, DMF, 120-130°C, 48h.

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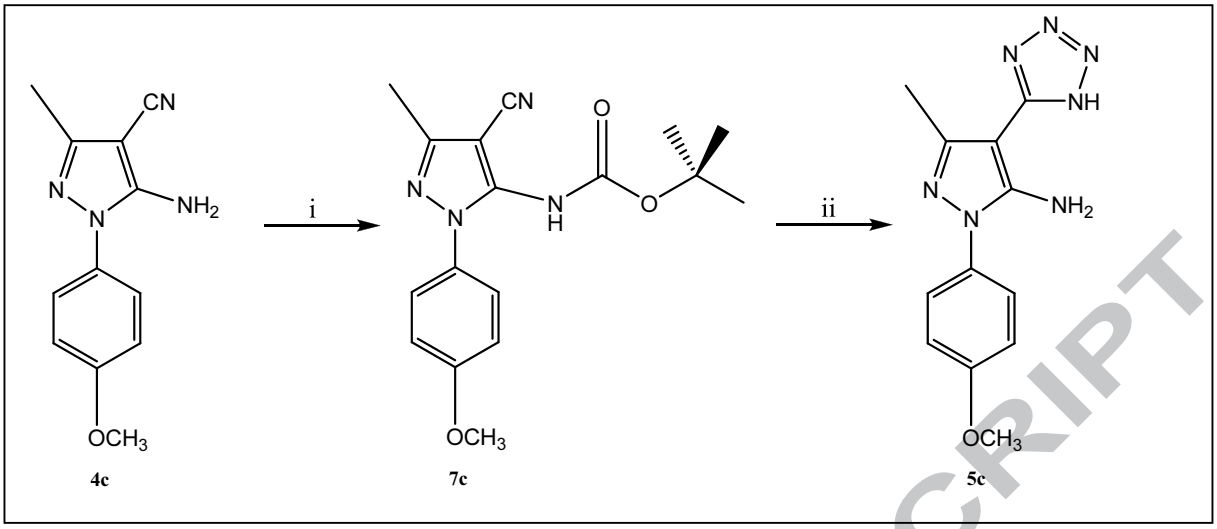

Scheme 3. Synthesis of tetrazoles. Reagents and conditions: i: NaH, Boc, room temperature, 4h; ii: NaN_3, NH_4Cl, DMF, 130-140^oC, 48h.

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