On the reaction of indole-3-carbaldehyde with cyanothioacetamide: an unexpected approach to indolyl-substituted pyridines and thieno[2,3-b]pyridines

Victor V. Dotsenko[1,2]* and Sergey G. Krivokolysko[2,3]

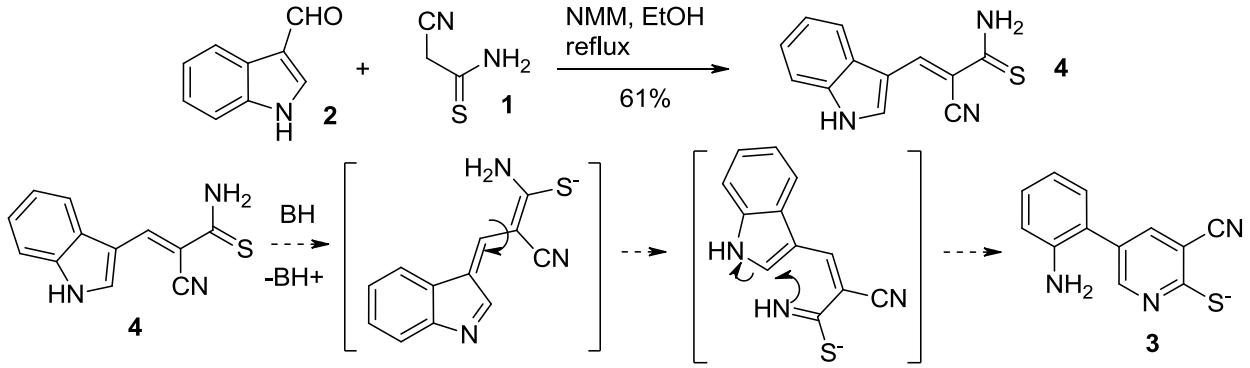
[1]Kuban State University, 149 Stavropolskaya str, Krasnodar, 350040 Russia
e-mail: victor_dotsenko@bigmir.net
[2]ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, Lugansk, 91034 Russia
[3]Lugansk State Medical University, 1-g 50 years of Lugansk Defence, Lugansk 91045, Russia

Abstract

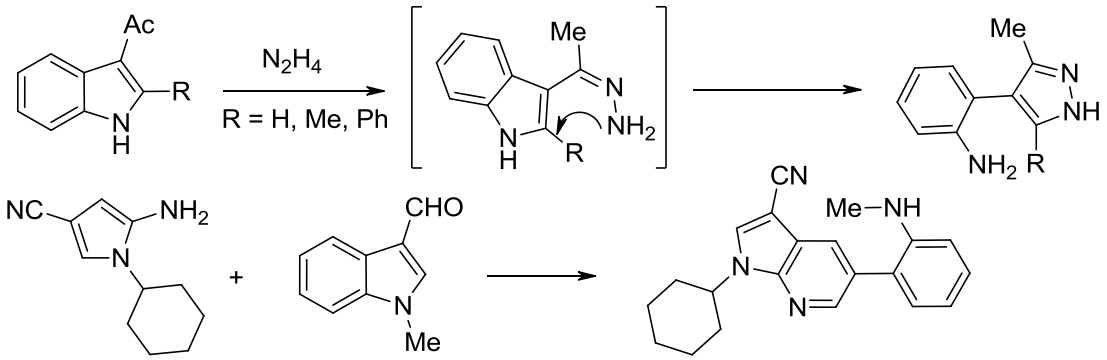
The reaction of cyanothioacetamide with indole-3-carbaldehyde in the presence of KOH surprisingly leads to potassium 6-amino-3,5-dicyano-4-(1H-indol-3-yl)pyridine-2-thiolate in good yield. The mechanism is discussed. Upon treatment with alkylating agents, the thiolate gave new 2-(alkylthio)pyridines and thienopyridines bearing 3-indolyl moiety.

Keywords
cyanothioacetamide, indole-3-carbaldehyde, Michael reaction, Thorpe-Ziegler cyclization, thienopyridines

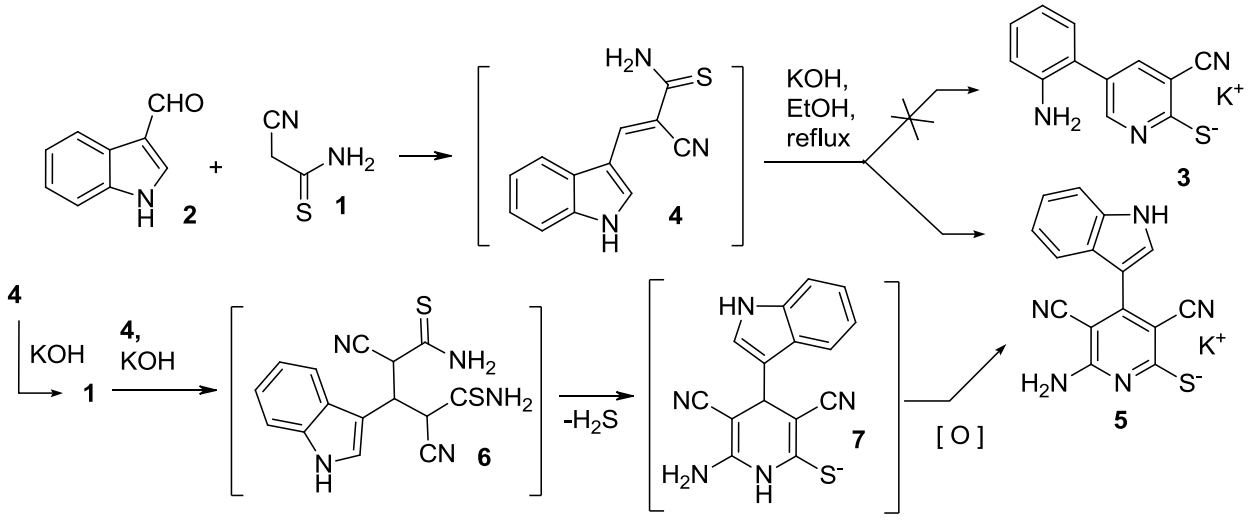
The reaction of active methylene (thio)amides with β-enamino carbonyls have been recognized as a convenient approach to various N-heterocyclic systems. At the outset of our studies we have been focused on the reaction of cyanothioacetamide **1** with indole-3-carbaldehyde **2** that we supposed to be the method for the synthesis of 5-(2-aminophenyl)pyridine-2-thiolates **3**. In this context, indole-3-carbaldehyde **2** could be considered as cyclic β-enamino aldehyde, and the product of Knoevenagel condensation with thioamide **1**, 3-(1H-indol-3-yl)-2-cyanoprop-2-enethioamide **4** could be represented as indole bearing at C-3 position a nucleophilic group which can attack C-2 position to cleave pyrrole ring, as shown in Scheme 1.



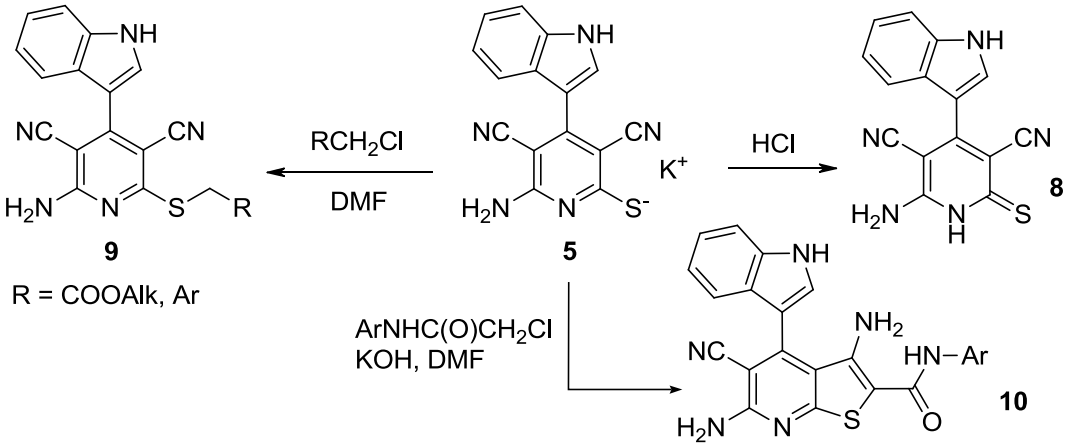
A brief survey of literature revealed that such a cleavage of indole system upon the action of N-nucleophiles is known and have been reported before [1-7]. It have been noted [5, 7] that an electron-withdrawing group at C-3 favors the cleavage, and indoles bearing CHO or acyl group at C-3 position can react as 1,3-CCC-dielectrophiles with (di)nucleophiles to give a variety of recyclization products:



We found that the reaction of thioamide **1** with indole-3-carbaldehyde **2** in the presence of base, followed by the treatment of formed indole **4** with excessive KOH in boiling EtOH leads to the formation of a white precipitate, which we suggested to be potassium salt of 5-(2-aminophenyl)-2-thioxo-1,2-dihydropyridin-3-carbonitrile **3**. The IR spectrum of salt **3** revealed the expected absorption bands corresponding to NH_2- and conjugated N≡C-groups, however, NMR spectra did not match the expected structure. The detailed analysis of spectral data allowed us to conclude that the product in fact is potassium 6-amino-3,5-dicyano-4-(1H-indol-3-yl)pyridine-2-thiolate **5**. The yield of thiolate **5** was 61%. A possible mechanism for the formation of **5** includes retro-Knoevenagel reaction of compound **4** to give thioamide **1**; the reaction of **1** with **4** afforded the Michael adduct **6** which undergo cyclization to give intermediate 1,4-dihydropyridine-2-thiolate **7** followed by *in situ* aromatization:



Upon treatment with acids and alkyl halides in basic media, thiolate **5** gave 2-thioxopyridine **8** and 2-(alkylthio)pyridines **9** or thieno[2,3-b]pyridines **10**, respectively:



In summary, we failed to prepare any indole ring cleavage products in the reaction of cyanothioacetamide with indole-3-carbaldehyde. The product was recognized as potassium 6-amino-3,5-dicyano-4-(1H-indol-3-yl)pyridine-2-thiolate. Though not being neither atom-economic nor preparative, the method we describe here demonstrates a new approach to the synthesis of 6-amino-3,5-dicyanopyridine-2-thiolates and -thiones, which have been reported as bioactive molecules or their precursors. Full experimental details will be reported elsewhere.

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