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New Reactions of 5-Amino-3-(Cyanomethyl)-1*H*-Pyrazole-4-Carbonitrile †

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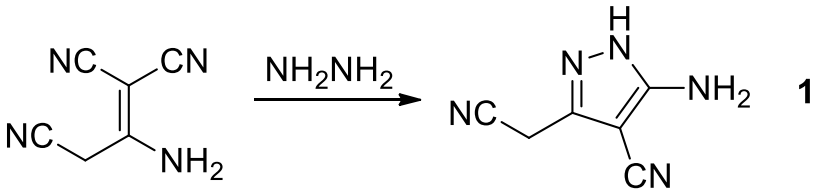
Abstract: 5-Amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile, prepared by reaction of malononitrile dimer with hydrazine, smoothly react with chloroacetyl chloride to afford 2-chloro-*N*-(4-cyano-3-(cyanomethyl)-1*H*-pyrazol-5-yl)acetamide in good yield. The latter easily react with 3-cyanopyridine-2-thiolates to give hybrid molecules bearing nicotinonitrile and pyrazole units.

Keywords: malononitrile dimer; heterocyclization; cyanomethylpyrazole; S-alkylation; Thorpe-Ziegler reaction

1. Introduction

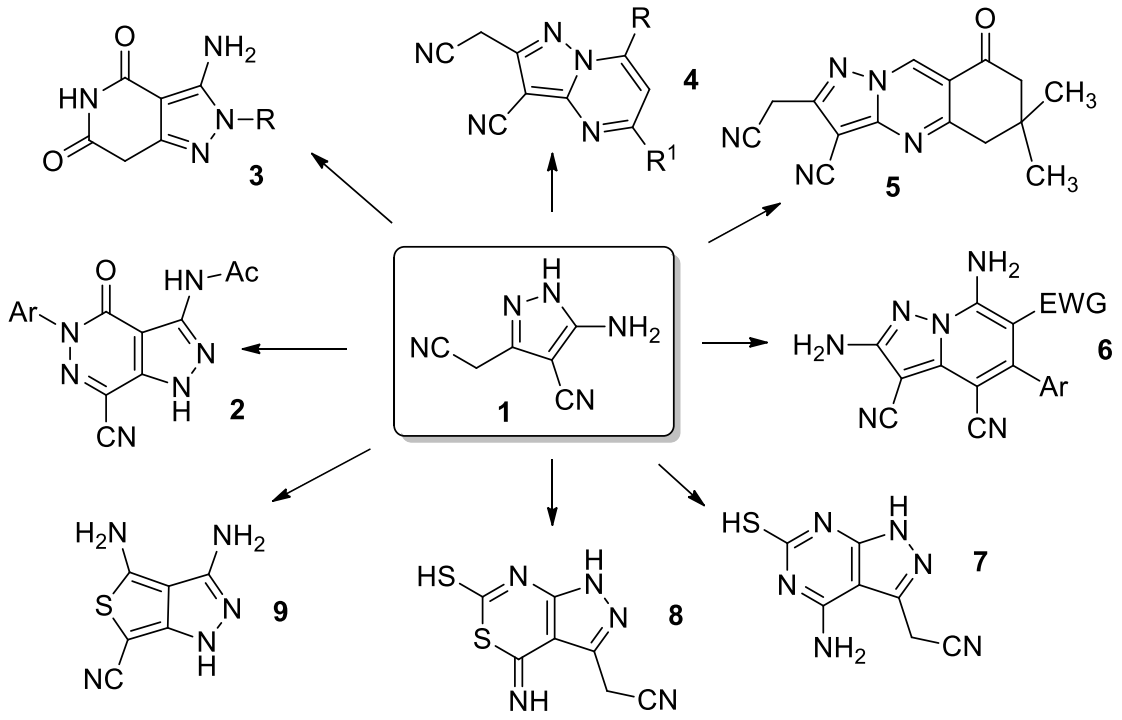
3(5)-Aminopyrazoles have been extensively used as easily accessible reagents in designing and building a number of ring-fused pyrazoles of potential synthetic and medicinal interest such as pyrazolo[3-b]pyridines, pyrazolo[1,5-a]pyrimidines, pyrazolo[3,4-d]pyrimidines, pyrazolo[3,4-b]pyrazines etc. [1–4].

In 1959, Taylor and Hartke reported [5] the synthesis of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **1** by reaction of malononitrile dimer with hydrazine (Scheme 1).



Scheme 1. Synthesis of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **1**.

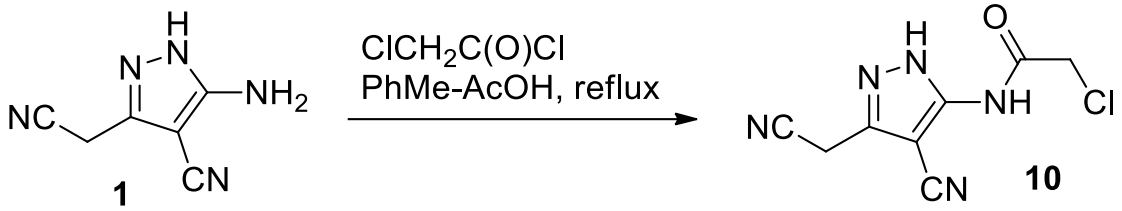
This polyfunctionalized pyrazole have been reported to be widely used on organic synthesis for preparation of pyrazolo[3,4-d]pyridazines **2** [6], pyrazolo[4,3-c]pyridines **3** [7], pyrazolo[1,5-a]pyrimidines **4** [8], pyrazolo[1,5-a]quinazolines **5** [9], pyrazolo[1,5-a]pyridine **6** [10,11], pyrazolo[3,4-dlpyrimidines **7** [12], pyrazolo-1,3-thiazine **8** [13], 3,4-diamino-1H-thieno[3,4-c]pyrazole-6-carbonitrile **9** [14], etc.



Scheme 1. The diversity of heterocyclic products derived from 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **1**.

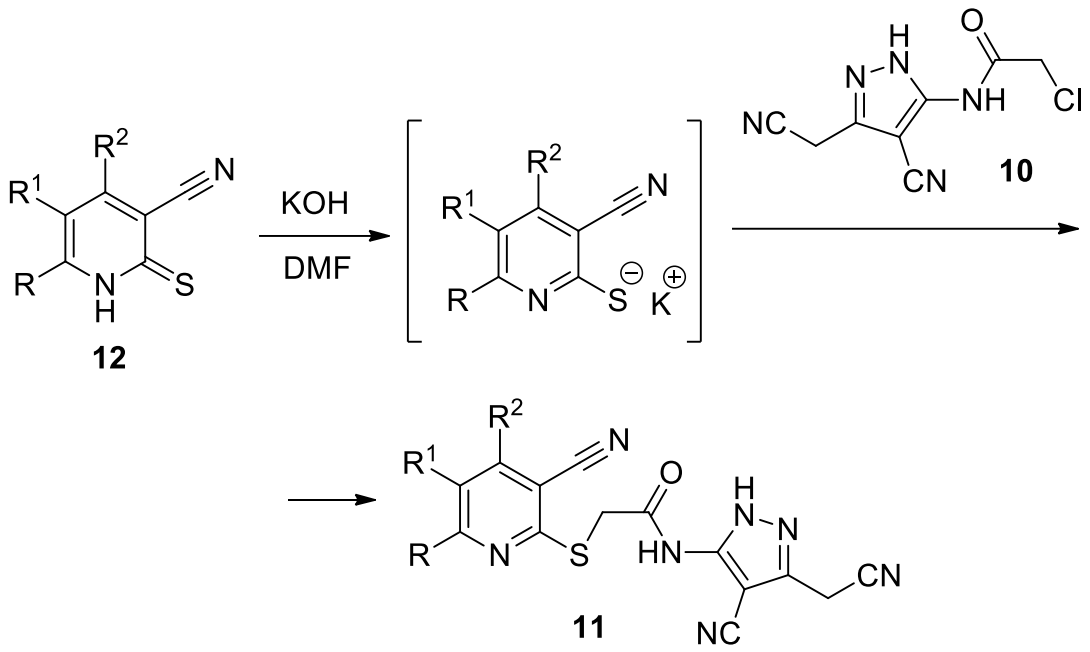
2. Results and Discussion

In continuation of our studies on the chemistry of functionalized pyridines [15–18], we decided to prepare hybrid molecules bearing both nicotinonitrile and 3(50-aminopyrazole moieties. First, we prepared chloroacetamide **10** through reaction of 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **1** with chloroacetyl chloride (Scheme 2).



Scheme 2. Synthesis of chloroacetamide **10**.

2-chloro-N-(4-cyano-3-(cyanomethyl)-1*H*-pyrazol-5-yl)acetamide **10** was found to be reactive molecule towards various S-nucleophiles such as 3-cyanopyridine-2-thiolates, easily available from corresponding 3-cyanopyridine-2(1*H*)-thiones **12** (Scheme 3). The compounds **11** are useful intermediates for preparation of thieno[2,3-b]pyridines by Thorpe-Ziegler reaction.



Scheme 3. Synthesis of compounds **11**.

3. Experimental

3.1. Preparation of 2-chloro-N-(4-cyano-3-(cyanomethyl)-1H-pyrazol-5-yl)acetamide 10

Equimolar amounts of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **1** and chloroacetyl chloride were dissolved in PhMe and refluxed for 5–7 h. The reaction mixture was left to stand at r.t. for 24–72 h, the precipitate was filtered off and to give **10** in 65–70% yields.

3.2. Preparation of compounds 11

3-Cyanopyridine-2(1*H*)-thiones **12** (0.01 mol) was suspended or dissolved in 15 mL of DMF, the mixture was treated with 10% aq. KOH (0.01 mol). After 10 min, the reaction mixture was treated with 2-chloro-*N*-(4-cyano-3-(cyanomethyl)-1*H*-pyrazol-5-yl)acetamide **10** (0.01 mol). The mixture was stirred for 2 h, the precipitated solid was filtered off and washed with EtOH to afford compounds **11** in 75–90% yields.

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