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Proceeding Paper

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 reacts with chloroacetyl chloride to form 2-chloro-*N*-(4-cyano-3-(cyanomethyl)-1*H*-pyrazol-5-yl)acetamide in good yield. The latter easily reacts with 3-cyanopyridine-2-thiolates to give hybrid molecules bearing nicotinonitrile and pyrazole units.

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

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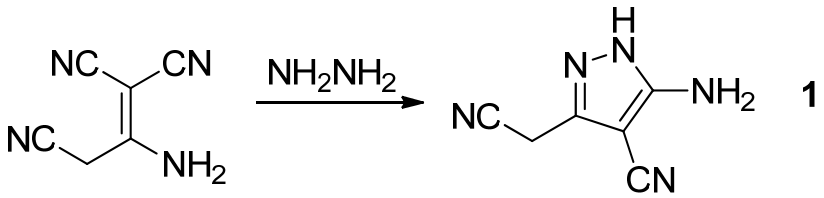
1. Introduction

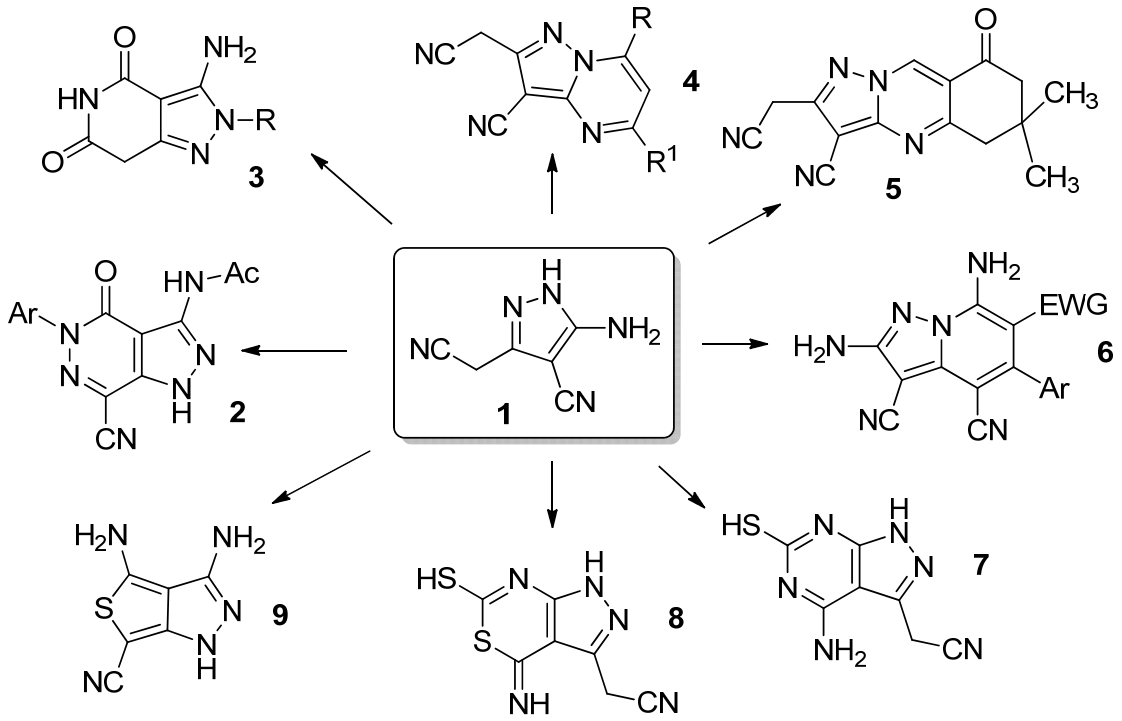
3(5)-Aminopyrazoles have been extensively used as easily accessible reagents in designing and building of a number of ring-fused pyrazoles of potential synthetic and medicinal interest such as pyrazolo[3-b]pyridines, pyrazolo[1,5-a]pyrimidines, pyrazolo[3,4-d]pyrimidines, pyrazolo[3,4-b]pyrazines, etc.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

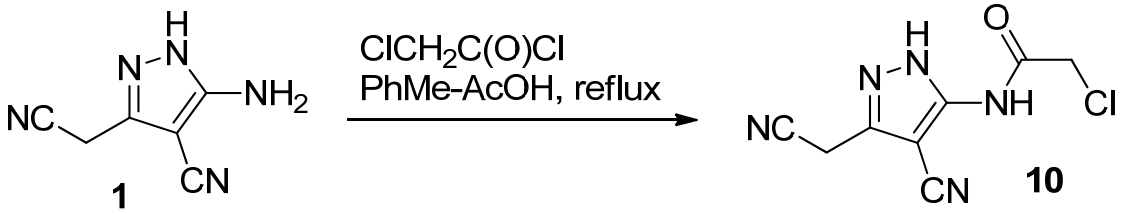
This polyfunctionalized pyrazole have been reported to be widely used in organic synthesis for preparation of pyrazolo[3,4-d]pyridazine **2** [6], pyrazolo[4,3-c]pyridine **3** [7], pyrazolo[1,5-a]pyrimidine **4** [8], pyrazolo[1,5-a]quinazoline **5** [9], pyrazolo[1,5-a]pyridine **6** [10,11], pyrazolo[3,4-dlpyrimidine **7** [12], pyrazolo-1,3-thiazine **8** [13], 3,4-diamino-1*H*-thieno[3,4-c]pyrazole-6-carbonitrile **9** [14], etc. (Scheme 2).



Scheme 2. The diversity of heterocyclic products derived from 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **1**.

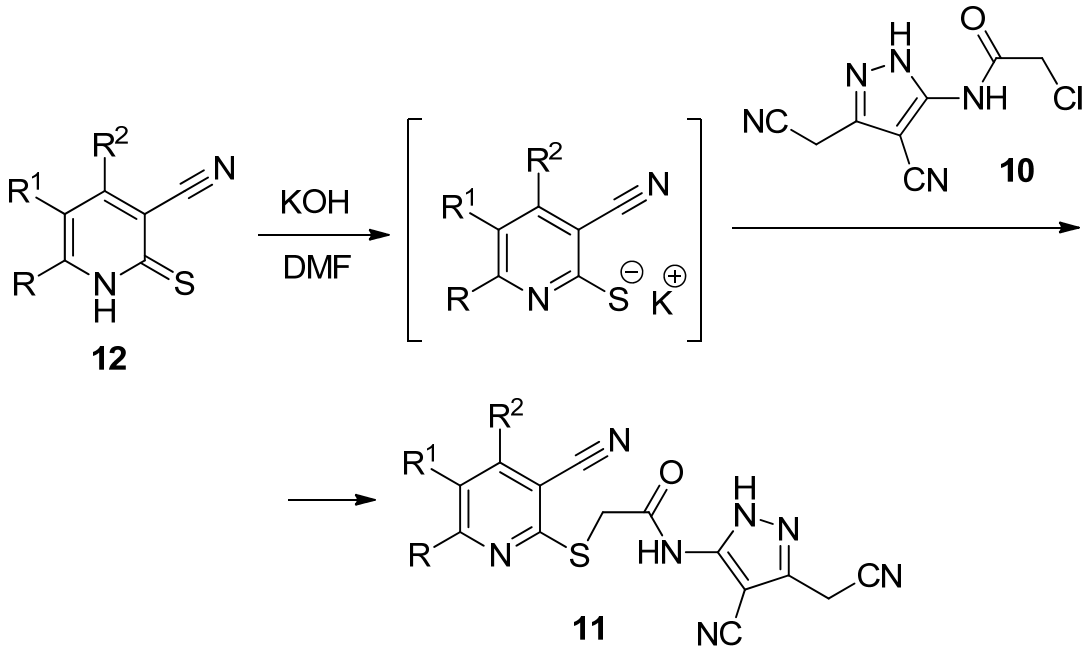
2. Results and Discussion

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 3).



Scheme 3. Synthesis of chloroacetamide **10**.

2-Chloro-*N*-(4-cyano-3-(cyanomethyl)-1*H*-pyrazol-5-yl)acetamide **10** was found to be reactive towards various S-nucleophiles such as 3-cyanopyridine-2-thiolates, easily available from corresponding 3-cyanopyridine-2(1*H*)-thione **12** (Scheme 4). Compound **11** is a useful intermediate for preparation of thieno[2,3-b]pyridines by the Thorpe–Ziegler reaction.



Scheme 4. Synthesis of compound **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)-1*H*-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 and the precipitate was filtered off and to give **10** in 65–70% yield.

3.2. Preparation of Compound **11**

3-Cyanopyridine-2(1*H*)-thione **12** (0.01 mol) was suspended or dissolved in 15 mL of DMF, and 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, and the precipitated solid was filtered off and washed with EtOH to afford compound **11** in 75–90% yields.

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