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Mendeleev Commun., 2020, **30**, 500–501

Mendeleev Communications

A convenient synthesis of new (1,2,4-triazolylamino)pyrimidines from cyanamide precursor

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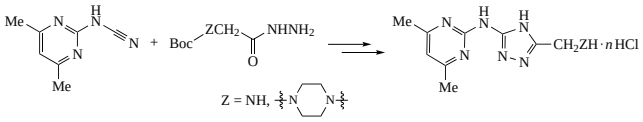
DOI: 10.1016/j.mencom.2020.07.032

The Ni(acac)$_2$-catalyzed 1,2,4-triazole formation from cyanamides and carbohydrazides was extended onto *N*-(4,6-dimethylpyrimidin-2-yl)cyanamide and glycine hydrazides. The obtained *N*-(5-aminomethyl-4*H*-1,2,4-triazol-3-yl)-4,6-dimethylpyrimidin-2-amines may be attractive for the estimation of their biological activity.



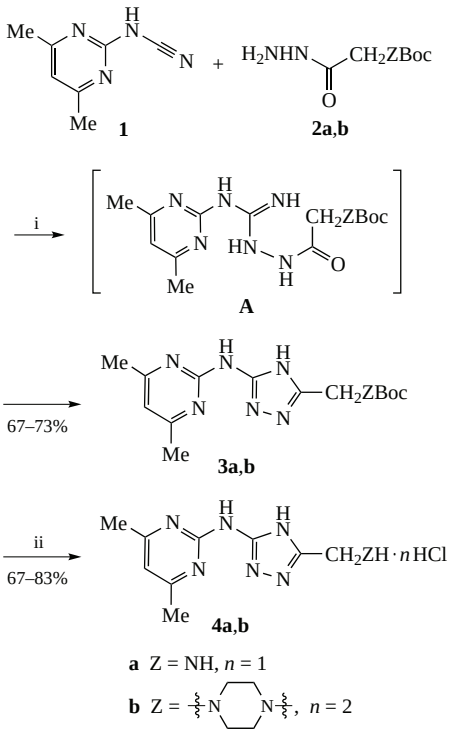
Keywords: Boc-deprotection, amino acids, hydrazides, pyrimidines, cyanamides, piperazines, 1,2,4-triazoles, heterocyclization.

In the last few decades, one of the main trends in the design of potential drugs with improved pharmacological properties is the preparation of new hybrid compounds based on the diverse heterocycles with known biological activity.[1–6] Among them are 1,2,4-triazole and its derivatives which possess a broad spectrum of pharmacological activities, in particular antiviral (ribavirin, taribavirin),[7,8] antifungal (fluconazole),[6] and soporific (triazolam).[9,10] 5-Alkyl-3-amino-1,2,4-triazoles were found to exhibit herbicidal activity[11] and showed positive results in clinical trials for the treatment of the Alzheimer's disease.[12] Some 3-amino substituted 1,2,4-triazoles possess anti-inflammatory[13] and analgesic[14] effects in the human body. Recently, a new convenient access to the novel type of ionic liquids based on one-pot reaction of 1,2,4-triazole-3-thione and 1-iodopropan-2-one was developed.[15]

No less interesting are derivatives of 2-aminopyrimidine which possess cardioprotective,[16] antipsychotic,[17] antitubercular,[18] antimalarial,[19,20] antibacterial[21] and antitumor[22,23] activities, so the synthesis of such compounds is of great interest.[24,25]

Earlier, we successfully used nickel(II) acetylacetonate as a catalyst in the addition of *N*-(benzoyl)cyanamide[26–28] and *N*-(4,6-dimethylpyrimidin-2-yl)cyanamide[26] to methylene active compounds. Recently, we obtained a number of 3-amino substituted 1,2,4-triazoles by addition of *N*-(benzoyl)cyanamide to the amino group of Boc-protected amino acid hydrazides in the presence of Ni(acac)$_2$ as a catalyst.[29] This was the first reported use of Ni(acac)$_2$ to promote the addition of nitriles to amino group. In the absence of Ni(acac)$_2$, the reaction did not proceed. Also we reported[30] that the reaction of 4-amino-1,2,5-oxadiazole-3-carbohydrazide with *N*-(benzoyl)cyanamide under similar conditions resulted in guanidine derivative of type **A** (Scheme 1), which was isolated, and then, upon reflux in AcOH, was cyclized into the corresponding triazole. Further, 3-aminotriazoles were successfully used as convenient building blocks for the construction of 1,2,4-triazolo[1,5-*a*]pyrimidines.[30–32]

In continuation of this work, here new 1,2,4-triazole derivatives were obtained from known[33–35] *N*-(4,6-dimethylpyrimidin-2-yl)-cyanamide **1** and Boc-protected amino acid hydrazides **2a**,**b** (see Scheme 1). Note that this is the first reported use of heteryl cyanamide in the addition reaction of nitriles to amino group.



Scheme 1 *Reagents and conditions*: i, Ni(acac)$_2$ (10 mol%), dioxane, Δ; ii, HCl (14%, dioxane), room temperature.

Heating the mixture of compounds **1** and **2** in dioxane in the presence of 10 mol% nickel(II) acetylacetonate afforded (4,6-dimethylpyrimidin-2-yl)amino substituted triazoles **3**.† In the absence of Ni(acac)$_2$ the reaction does not proceed.

† *5-(4,6-Dimethylpyrimidin-2-ylamino)-4*H*-1,2,4-triazole carbamate derivatives* **3a**,**b** (*general procedure*). A mixture of *N*-(4,6-dimethylpyrimidin-2-yl)cyanamide, glycine hydrazide **2** (10 mmol each), and nickel(II) acetylacetonate (1 mmol) in anhydrous dioxane (20 ml) was refluxed with stirring for 6 h. The mixture was cooled, the precipitate formed was filtered off, washed with water, and dried in air.

Apparently, the reaction of Boc-protected amino acids hydrazides **2a**,**b** with *N*-(pyrimidinyl)cyanamide **1** occurred *via* the formation of the corresponding intermediate guanidine derivatives **A** (see Scheme 1). However, in this study their cyclization into triazoles **3a**,**b** proceeded too rapidly, which differed from the case with *N*-(benzoyl)cyanamide[29] when analogous guanidines were isolated.

Compounds **3a**,**b** are white crystalline substances well soluble in chloroform and THF, but poorly soluble in diethyl ether, ethanol and water. Their mass spectra contain the molecular ion $[M+H]^+$ peaks, and IR spectra exhibit absorption bands in the region of 3450–3308 cm^{-1} characteristic of amino groups and in the region of ~1700 cm^{-1} corresponding to the C=O groups of the *tert*-butoxycarbonyl fragments. ^1H NMR spectra of compounds **3a**,**b** indicate the presence of *tert*-butyl and NH groups protons, the protons for two methyl groups and signal for H^5 (7.20 ppm) of the pyrimidine ring.

Carbamates **3a**,**b** on treatment with HCl solution in dioxane at room temperature are converted into amine hydrochlorides **4a**,**b**‡ being new derivatives of 2-aminopyrimidine with the 1,2,4-triazole fragment at 2-amino group. Hydrochlorides **4a**,**b** are white crystalline substances well soluble in water, moderately soluble in ethanol and poorly in THF, diethyl ether and $CHCl_3$. Their mass spectra contain the molecular ion $[(M–n\,HCl) + H]^+$ peaks. Their IR spectra reveal absorption bands in the region of 3450–3308 cm^{-1} characteristic of amino groups and no absorption in the region of ~1700 cm^{-1} corresponding to the C=O groups. ^1H NMR spectra of compounds **4a**,**b** indicate the presence of NH and NH_3^+, pyrimidine H^5 and two methyl groups. The singlets of piperazine CH_2 protons in the region 3.05–3.20 ppm are observed in the ^1H NMR spectrum of dihydrochloride **4b**. The structure of hydrochlorides **4a**,**b** was also confirmed by ^{13}C NMR spectra and elemental analysis.

In conclusion, a convenient synthesis of 2-aminopyrimidine derivatives with the 5-aminoalkyl-1,2,4-triazole substituent at 2-amino group of pyrimidine ring from available reagents has been developed. The obtained compounds **4a**,**b** may be attractive for the investigation of their biological activity.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.07.032.

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‡ *5-(4,6-Dimethylpyrimidin-2-ylamino)-4*H*-1,2,4-triazole amine derivatives* **4a**,**b** (*general procedure*). A solution of the corresponding *tert*-butyl carbamate **3a**,**b** (10 mmol) in 14% dioxane HCl (20 ml) was stirred for 5 h. The precipitate formed was filtered off, washed with acetone and then with diethyl ether, and dried in air.

Physico-chemical and spectral data of compounds obtained are available in Online Supplementary Materials.

Received: 19th March 2020; Com. 20/6167