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Mendeleev Commun., 2022, **32**, 393–394

Mendeleev Communications

Synthesis of new heterocyclic systems fused at pyrazolo[3,4-*c*]-2,7-naphthyridine core

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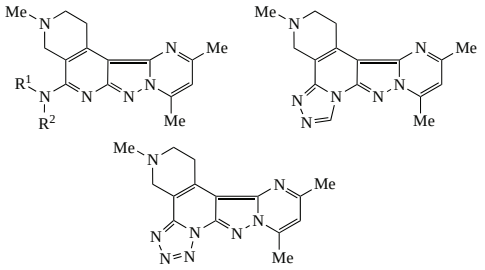
DOI: 10.1016/j.mencom.2022.05.034

Efficient syntheses of new heterocyclic systems comprising pyrimido[1′,2′:1,5]pyrazolo[3,4-*c*]-2,7-naphthyridine, pyrazolo[3,4-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine and pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine cores were performed in two simple steps. In the first step, pyrazole ring was fused at the 2-chloro-3-cyanopyridine moiety by treatment with hydrazine. In the second step, pyrimidine part was fused at the thus formed 3-aminopyrazole moiety by heterocyclization with acetylacetone.



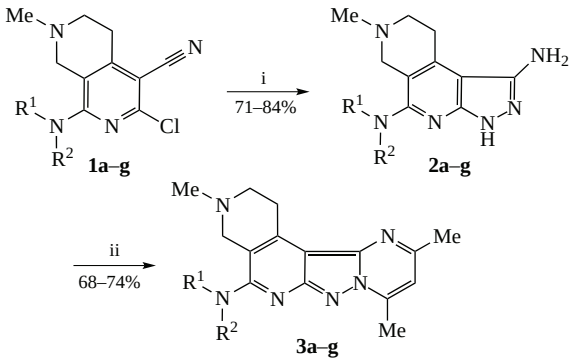
Keywords: 2,7-naphthyridines, pyrimido[1′,2′:1,5]pyrazolo[3,4-*c*]-2,7-naphthyridine, pyrazolo[3,4-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridines, pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine, heterocyclization, hydrazine, acetylacetone.

Pyrazole and pyridine moieties are present in many biologically active natural and synthetic compounds.[1] Pyrazolopyridines are the privileged scaffolds in the developing new drugs. Pyrazolo[3,4-*b*]pyridine derivatives exhibit anticonvulsant,[2] antimicrobial,[3] cardiovascular,[4] antiviral,[5] antileishmanial,[6] anti-PAH (pulmonary arterial hypertension)[7] activities. They are also potent inhibitors of EPHA4 receptor tyrosine kinase,[8] cyclin dependent kinase 1 (CDK1),[9] ALK-L1196M (anaplastic lymphoma kinase)[10] and DYRK 1A/1B (dual-specificity tyrosine phosphorylation-regulated kinases).[11] On the other hand, 2,7-naphthyridine derivatives are relatively less explored. In our research we consider their high biological activity[12–14] along with interesting features for the syntheses.[15–17] Recently we have synthesized some pyrazolo[3,4-*c*]pyridine-2,7-naphthyridines possessing high neurotropic activity.[14]

Taking into account the above and in continuation of our studies searching new potentially bioactive compounds, herein we describe the synthesis of new heterocyclic compounds comprising both pyrazolo[3,4-*c*]pyridine and 2,7-naphthyridine cores. For the starting compounds, we employed previously[15] obtained 1-amino-7-methyl-3-chloro-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitriles **1a**–**g**. Compounds **1** react with hydrazine hydrate giving products of the nucleophilic substitution of the chlorine atom at the pyridine ring followed by an intramolecular cyclization thus furnishing the corresponding 5-amino-7-methyl-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*]-2,7-naphthyridine-1-amines **2a**–**g** (Scheme 1). Compounds **2**, in turn**,** were refluxed in an excess of acetylacetone leading to tetracyclic pyrimido[1′,2′:1,5]pyrazolo[3,4-*c*]-2,7-naphthyridines **3a**–**g**. Apparently, the second step proceeded *via* a condensation/cyclization reaction sequence. All the steps occurred with high yields (see Scheme 1).

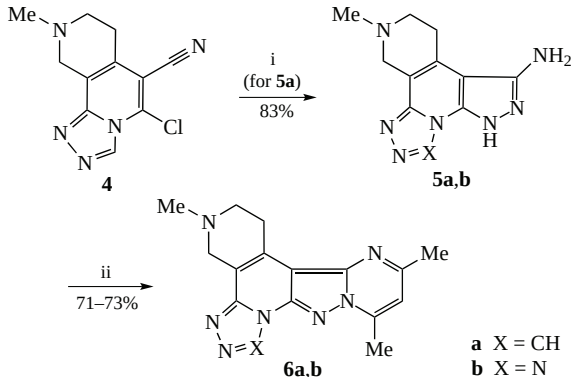
As expected, the IR spectra of compounds **3a**–**g** did not contain absorption bands for NH and NH_2 groups. In their ^{1}H NMR spectra, two singlets for methyl groups at 2.53–2.64 and 2.61–2.85 ppm and one CH singlet proton at 6.89–7.04 ppm were observed.

It seemed interesting to perform similar transformations in a relative tricyclic system, namely, in triazolo[3,4-*a*]-2,7-



a $R^1 + R^2 = (CH_2)_5$
b $R^1 + R^2 = (CH_2)_2CHBn(CH_2)_2$
c $R^1 + R^2 = (CH_2)_2N(CHPh_2)(CH_2)_2$
d R^1 = H, R^2 = 4-MeC_6H_4
e R^1 = H, R^2 = 4-$MeOC_6H_4$
f R^1 = H, R^2 = CH_2Bn
g R^1 = H, R^2 = 3,4-$(MeO)_2C_6H_3(CH_2)_2$

Scheme 1 *Reagents and conditions*: i, $N_2H_4 \cdot H_2O$, EtOH, reflux, 10 h; ii, $CH_2(COMe)_2$, reflux, 5 h.



Scheme 2 *Reagents and conditions*: i, $N_2H_4 \cdot H_2O$, EtOH, reflux, 5 h; ii, $CH_2(COMe)_2$, reflux, 5 h.

naphthyridine **4**[16] (Scheme 2). As expected, compound **4** by refluxing with hydrazine hydrate in ethanol was readily converted into the corresponding 10-methyl-8,9,10,11-tetrahydro-5*H*-pyrazolo[3,4-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine-7-amine **5a**. This compound, in turn, by reaction with acetylacetone afforded 5,9,11-trimethyl-4,5,6,7-tetrahydropyrimido[1′,2′:1,5]-pyrazolo[3,4-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine **6a** *via* a condensation/cyclization process.

We also tried to condense a pyrimidine ring on the hetero-analogous pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine[17] system of compound **5b** (see Scheme 2). Previously, we showed that compound **5b**, both in the crystalline state and in solution, existed exclusively in the tetrazole tautomeric form.[17] We have observed that the closure of the pyrimidine ring resulted in 5,9,11-trimethyl-4,5,6,7-tetrahydropyrimido[1′,2′:1,5]-pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine **6b**, in which the azido-tetrazole tautomerism did not occur. In fact, the ^{1}H NMR spectrum of compound **6b** shows only the single set of signals while its IR spectrum does not contain characteristic band for azido group.

In conclusion, the synthesis of some new original poly-heterocyclic compounds has been accomplished. We have obtained several pyrimido[1′,2′:1,5]pyrazolo[3,4-*c*]-2,7-naphthyridines **3** and three new heterocyclic systems **5a** and **6a**,**b**. All of the obtained compounds may show interesting biological/pharmacological activities and will be tested soon.

The work was supported by the Science Committee of the Republic of Armenia, in the frames of the research project no. 21AG-1D036.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.034.

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Received: 22nd October 2021; Com. 21/6737