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SYNTHESES OF SUBSTITUTED AND FUSED FURO-[3,2-c]PYRIDINES

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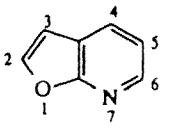
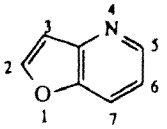
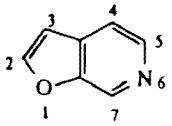
Furopyridines are of chemical interest due to their similarity to benzofuran, quinoline, and isoquinoline, which are important nuclei present in many biologically active compounds. In addition, new pharmacophores with potential antipsychotic activity possess thieno- and furo[3,2-c]pyridine ring system [1]. The fusion of furan nucleus to the pyridine ring gives rise to six isomeric furopyridines **1-6** [2].



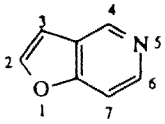
1 [2,3-*b*]



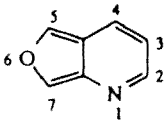
2 [3,2-*b*]



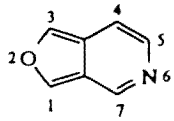
3 [2,3-*c*]



4 [3,2-*c*]



5 [3,4-*b*]

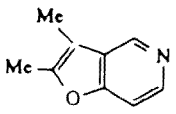


6 [3,4-*c*]

Furopyridines consist of an electron-rich five-membered furan ring fused to an electron-poor six-membered pyridine ring. Five of the parent structures are known, i.e., furo[2,3-b]pyridine (**1**) [3, 4], furo[3,2-b]pyridine (**2**) [5, 6], furo[2,3-c]pyridine (**3**) [7], furo[3,2-c]pyridine (**4**) [8, 9], and furo[3,4-c]pyridine (**6**) [10].

Synthetic approaches to furo[3,2-c]pyridines start either from furans [11, 12] or from pyridines [9, 13, 14].

In continuation of our previous efforts towards the synthesis of 2,3-dimethylfuro[3,2-c]pyridines (**7**) [15] and fused derivatives of furo[3,2-c]pyridines (**8**, **9**) [16] we report here new results concerning syntheses of substituted furo[3,2-c]pyridines.



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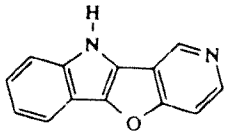

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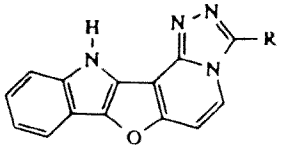

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The procedure we have used for the synthesis of 2-arylfuro[3,2-c]pyridines [17] is a modification of that by Eloy and Derickere [8] in which 5-aryl-2-furancarbaldehydes **10** were the starting materials (Scheme 1).

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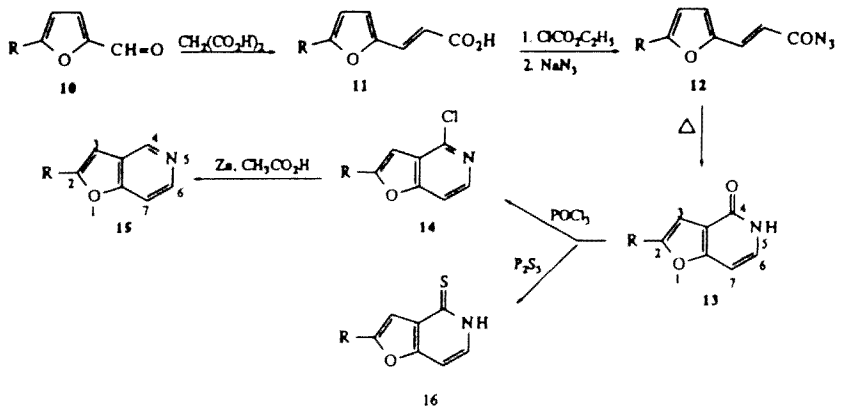
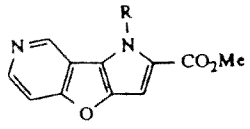
Scheme 1



R = C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$

Starting from 5-aryl-2-furancarbaldehydes **10** via the Doebner condensation, we synthesized the corresponding substituted propenoic acids **11**. The acyl azides **12** were prepared by treatment of the propenoic acids **11** with ethyl chloroformate and sodium azide in a one pot reaction. The compounds **12** were transformed by thermal cyclization in the presence of tributylamine in Dowtherm to 2-aryl-4,5-dihydrofuro[3,2-c]pyridin-4-ones (**13**). Refluxing of **13** with phosphorus oxychloride gave the chloroderivatives **14**. The reduction of the latter with zinc in boiling acetic acid afforded the 2-arylfuro[3,2-c]pyridines (**15**). Treatment of **13** with phosphorus pentasulfide led to the corresponding 2-aryl-4,5-dihydrofuro[3,2-c]pyridin-4-thiones **16**.

Analogously, starting from methyl 2-formyl-4-methyl- or 2-formyl-4-benzylfuro[3,2-b]pyrrole-5-carboxylates, compounds **17** were prepared [18].



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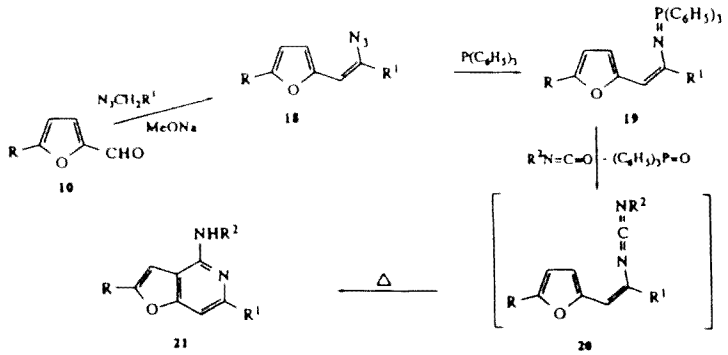
R = Me, Bz

The second method we have used for the synthesis of substituted furo[3,2-c]pyridines is a modification of that by Molina et al. [19, 20] used as *aza* Wittig reaction of iminophosphoranes with isocyanates in which, instead of 4,5-dimethyl-2-furancarbaldehyde, in our case 5-aryl-2-furancarbaldehydes (10) were the starting materials (Scheme 2).

Previously we described the preparation of methyl or ethyl 2-azido-3-(2-furyl)propenoates and their 5-substituted derivatives **18**. Substituted vinyl azides **18** reacted further with triphenylphosphine in dry dichloromethane under nitrogen to give iminophosphoranes **19** in good yields. The aza Wittig reaction of **19** with phenyl or 3-chlorophenyl isocyanate in dry toluene under reflux leads to triphenylphosphine oxide and the corresponding substituted furo[3,2-c]pyridines (**21**) via appropriate carbodiimides **20** which were not isolated.

Scheme 2



R = H, aryl; R^1 = CO_2Me, CO_2Et; R^2 = C_6H_5, 3-ClC_6H_4

Analogously, starting from methyl 2-formyl-4-methyl or 2-formyl-4-benzylfuro[3,2-b]pyrrole-5-carboxylates, compounds **22** were prepared [22, 23].

22

R = Me, Bz; R^1 = CO_2Me, CO_2Et; R^2 = C_6H_5, 3-ClC_6H_4

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