A NEW REAGENT FOR THE SYNTHESIS OF PYRAZOLO[4,3-*e*][1,2,4]TRIAZOLO[1,5-*c*]PYRIMIDINES

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Tandem reaction of N'-(4-cyano-1-phenyl-1*H*-pyrazol-5-yl)-N,N-dimethylimidoformamide (**6**) with acylhydrazines in N,N-dimethylacetamide leads to the formation of 2-*R*-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-c]pyrimidines (**10a-f**).

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Introduction

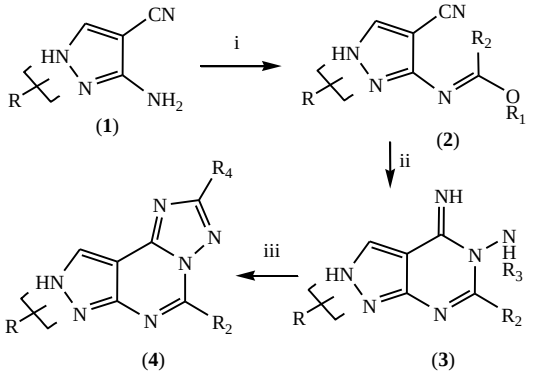
The adenosine receptors ligands considered as prospective and promising candidates for treatment of diseases pathogenesis of which is connected with infringement the regulatory processes with involvement of adenosine (neurodegenerative, psychiatric, inflammatory disorders, diabetes, cancer, etc.). Derivatives of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines attract much attention among the nonpurine heterocyclic antagonists of that receptors, for which the affinity to three subtypes (A_{2A}, A_{2B}, A_3) was revealed.[1-11] Also [^{11}C] - and [^{18}F] – radio-labeled pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines have been developed as positron emission tomography tracers for the imaging of cerebral adenosine A_{2A} receptors.[12,13]

A known synthetic approach to the heterocyclic system pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine is sequential annelation of pyrimidine and triazole moieties to the pyrazole cycle (Scheme 1).[2-4,7,14,15]

The imidoformates (**2**), which were obtained by reaction of aminopyrazoles (**1**) with orthoethers $R_2C(OR_1)_3$ (step i), give pyrazolo[3,4-*d*]pyrimidines (**3**) on interaction with hydrazines R_3NHNH_2 (step ii). An annelated triazole cycle formation takes place as a result of condensation of (**3**) with aromatic aldehydes (step iii, R_3 = H, R_4 = Ar).[15] The desired product can also be obtained by directly treating (**2**) with monoacylhydrazines. In such case intermediate (**3**) is usually are not isolated (step ii+iii, R_3 = R_4CO).[2-4,7,14] Despite the relative simplicity of the preparation of (**2**), this compound does not have thermal stability.

Moreover, fairly drastic conditions of heterocyclisation with acylhydrazides (high reaction temperature and long reaction time, on an average 10 h) and chromatographic purification of desired product are disadvantages of synthesis the method above.

It is, however, known that the corresponding dimethylaminomethylene(imido) derivatives are easily formed on the interaction of N,N-dimethylformamide dimethylacetal (DMFDMA, **5**) with compounds having substituents with labile hydrogen atoms (methyl, methylene, amino groups). These compounds eliminate dimethylamine on reacting with nucleophilic reagents resulting in a growth of carbon and heteroatom chain including in synthesis of heterocyclic compounds.[16]



Scheme 1. Known synthetic route to pyrazolo [4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine scaffold.

The aim of the work is to investigate the possibility reacting *N*'-(4-cyano-1-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylimidoformamide (**6**), a synthetic analog of imidoformates (**2**), with acylhydrazines in a one-pot synthesis of pyrazolo[4,3-*e*]]1,2,4]triazolo[1,5-*c*]-pyrimidines.

Experimental

Instrumentation

^{1}H NMR spectra were recorded on the spectrometer Bruker DRX-500 (500.13 MHz) in ДМСО-d_6 as solvent and with TMS as an internal standard. Elemental analysis was performed on the elemental analyzer Perkin Elmer 2400. The melting points were determined on SMP-30.

The control reaction and compound purity were carried out by TLC on Merck TLC Silica gel 60 F_{254} plates with UV - light 254 nm for visualization and $CHCl_3$, i-PrOH, or $CHCl_3$/EtOAc (5:1) as eluents.

Synthesis of *N*'-(4-cyano-1-phenyl-1*H*-pyrazol-3-yl)-*N*,*N*-dimethylimidoformamide (6).

A mixture of 1.84 g (10 mmol) 5-amino-4-cyano-1-phenylpyrazole (**1**) and 2.0 ml (1.78 g, 15 mmol) (**5**) in 1 ml *N*,*N*-dimethylacetamide (DMAA) was heated under reflux for 3 h. The residue, precipitated on cooling, was filtered and recrystallized from i-PrOH. The product was obtainted as a beige powdery substance, yield 2.15 g (90 %). m.p. 94-95 °C. ^{1}H NMR δ: 2.97 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 7.33 -7.36 (m, 1H, Ph), 7.46-7.50 (m, 2H, Ph), 7.74-7.77 (m, 2H, Ph), 7.98 (s, 1H, Me_2NCH=N), 8.25 (s, 1H, pyrazole ring). Anal. calcd. for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27 %; Found: C, 65.31; H, 5.41; N, 29.34 %.

General procedure for the synthesis of 2-R-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines (10a-f)

The mixture of 10 mmol (**6**) and 10 mmol of the carboxylic acid hydrazide (**7**) were refluxed for 2-3 h in DMAA (5 ml). The precipitate, obtained on cooling, was filtered and recrystallized from mixture of i-PrOH-DMF (5:1). The resulted pyrazolotriazolopyrimidines (**10**) are white powdery substances.

2,7-Diphenyl-7*H*-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (10a).

Yield = 76 %. m.p. 219-220 °C. ^{1}H NMR δ: 7.53-7.66 (m, 6H, benzene rings), 8.13-8.16 (m, 2H, benzene rings), 8.26-8.30 (m, 2H, benzene rings), 8.80 (s, 1H, pyrazole ring), 9.72 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{18}H_{12}N_6$: C, 69.22; H, 26,91; N, 3,87 %; Found: C, 69.15; H, 26.86; N, 3.93 %.

2-(4-Methoxyphenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (10b).

Yield = 72 %. m.p. 231 - 232 °C, (lit. 232 - 233 °C[14]). ^{1}H NMR δ: 3.85 (s, 3H, MeO), 7.13 (d, 2H, *J* = 8.7 Hz, p-$MeOC_6H_4$), 7.48 (t, 1H, *J* = 7.4 Hz, Ph), 7.62-7.65 (m, 2H, Ph), 8.15 (d, 2H, *J* = 8.0 Hz, Ph), 8.21 (d, 2H, *J* = 8.7 Hz, p-$MeOC_6H_4$), 8.80 (s, 1H, pyrazole ring), 9.70 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 24.55 ; N, 4.12 %; Found: C, 66.56; H, 24.51; N, 4.23 %.

2-(3-Chlorophenyl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (10c).

Yield = 81 %. m.p. 246 - 247 °C. ^{1}H NMR δ: 7.49 (t, 2H, *J* = 7.3 Hz, benzene rings), 7.63-7.67 (m, 3H, benzene rings), 8.15 (d, 2H, *J* = 7.9 Hz, benzene rings), 8.22-8.25 (m, 2H, benzene rings), 8.85 (s, 1H, pyrazole ring), 9.78 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{18}H_{11}ClN_6$: C, 62.34; H, 24.23; N, 3.20 %; Found: C, 62.24; H, 24.28 ; N, 3.25 %.

7-Phenyl-2-pyridin-4-yl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (10d).

Yield = 67 %. m.p. 268 - 269 °C. ^{1}H NMR δ: 7.48-7.52 (m, 1H, benzene or pyridine ring), 7.66 (t, 2H, *J* = 7.9 Hz, benzene or pyridine ring), 8.15 (d, 2H, *J* = 7.9 Hz, benzene or pyridine ring), 8.19 (d, 2H, *J* = 5.9 Hz, benzene or pyridine ring), 8.83 (d, 2H, *J* = 5.9 Hz, benzene or pyridine ring), 8.88 (s, 1H, pyrazole ring), 9.84 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{17}H_{11}N_7$: C, 65.17, H, 31.29, N, 3.54 %. Found: C, 65.22, H, 31.34, N, 3.48 %.

7-Phenyl-2-pyridin-3-yl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (10e).

Yield = 78 %, m.p. 220-221 °C. ^{1}H NMR δ: 7.49-7.53 (m, 1H, benzene or pyridine ring), 7.64-7.66 (m, 2H, benzene or pyridine ring), 8.14-8.16 (m, 4H, benzene or pyridine ring), 8.60-8.62 (m, 1H, benzene or pyridine ring), 8.77-8.79 (m, 2H, benzene or pyridine ring), 8.88 (s, 1H, pyrazole ring), 9.82 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{17}H_{11}N_7$: C 65.17, H 31.29, N 3.54 %. Found: C 65.23, H 31.37, N 3.45 %.

2-[(4-Chlorophenoxy)methyl]-7-phenyl-7*H*-pyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (10f).

Yield = 77 %. m.p. 255-256 °C. ^{1}H NMR δ: 5.45 (s, 2H, CH_2), 7.13 (d, 2H, *J* = 9.0 Hz, p-ClC_6H_4), 7.37 (d, 2H, *J* = 9.0 Hz, p-ClC_6H_4), 7.48 (t, 1H, *J* = 7.4 Hz, Ph), 7.62-7.66 (m, 2H, Ph), 8.13 (d, 2H, *J* = 7.8 Hz, Ph), 8.79 (s, 1H, pyrazole ring), 9.73 (s, 1H, pyrimidine ring). Anal. calcd. for $C_{19}H_{13}ClN_6O$: C, 60.56; H, 22.30; N, 3.48 . Found: C, 60.62; H, 22.39; N, 3.35.

Table 1. Optimizing of reaction conditions of (**6**) with benzoic acid hydrazide (**7a**).

S.No	Solvent	Time, h	Results
1	Dioxane / TsOH (catalyst)	21	The reaction product is the resinous, chromato-graphically inseparable mixture
2	AcOH	16	The same
3	DMF	14	yield of 10a 52 %
4	DMAA	2.5	yield of 10a 76 %

Results and Discussion

N'-(4-Cyano-1-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylimidoformamide (**6**) was obtained from 5-amino-4-cyano-1-phenylpyrazole (**1**) and (**5**) according to a method that is similar to one proposed for 5-amino-4-cyano pyrazole with dimethylformamide diethylacetal. In this method there is no requirement for chromatographic purification.[17] This compound, unlike imidoformates (**2**), is stable during storage.

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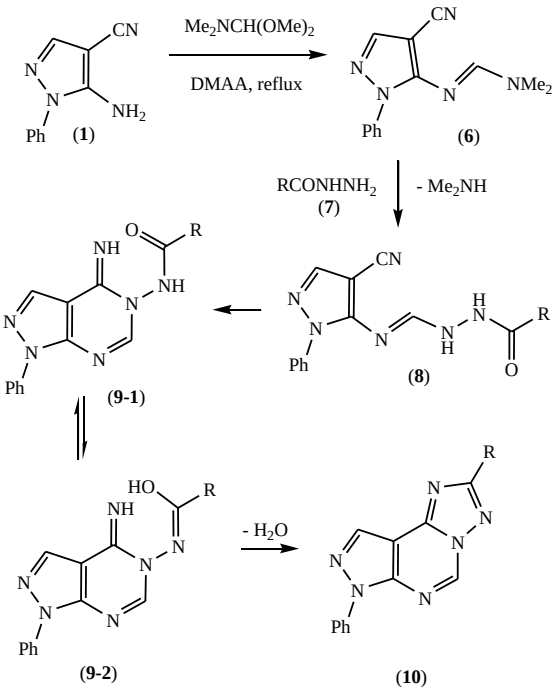
Optimization the reaction conditions of the reaction aromatic heterocyclic and aroxyacetic acids hydrazides (**7**) with (**6**) was carried out by an example of benzoic acid hydrazide (**7a**) (Table 1). The reactants were refluxed in the solvent for the time period mentioned in the table.

DMAA has found as optimal solvent. It provides comparable (or higher) yields of desired products in significantly shorter reaction time in comparison reported synthesis of (**2**).

In the ^{1}H NMR spectra of 2-*R*-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**10a-f**) there are two singlets near 8.8 and 9.7 ppm together with other protons signals of aryl and pyridine moieties (7.1-8.7 ppm), MeO-group (3.85 ppm, **10b**), methylene group (5.45 ppm, **10f**).The first singlet is corresponded to proton of pyrazole cycle (it is shifted to weaker field as compared to similar signal for starting compound (**6**), the second one corresponds to pyrimidine ring).

The interaction of (**6**) with acylhydrazides (**7**) is a tandem process (Scheme 2) that is similar to synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines from (**2**). In the first step there is an elimination of dimethylamine and formation of *N*'-[(4-cyano-1-phenyl-1*H*-pyrazol-5-yl)imino]methylhydrazide carboxylic acids (**8**), whose spontaneous heterocyclization leads to *N*'-(4-imino-1-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl)amides (**9-1**). As a result of further cyclization, with water elimination, annelated triazolic cycle pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**10**) is formed. Compound (**10**) can be also formed from N-substituted carboximidic acids (**9-2**) that are tautomeric forms of amides (**9-1**).



R = (a) Ph, (b) 4-MeOC$_6$H$_4$, (c) 3-ClC$_6$H$_4$
(d) pyridin-4-yl, (e) pyridin-3-yl, (f) 4-ClC$_6$H$_4$OCH$_2$

Scheme 2. Plausible route of the formation of (**10**).

Conclusion

Thus, the interaction of *N*'-(4-cyano-1-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylimidoformamide (**6**) with carboxylic acid hydrazides in *N*,*N*-dimethylacetamide leading to 2-*R*-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**10a-f**) is a tandem process.

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