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A new general synthesis of functionally substituted pyrazolo[1,5-*a*]pyrimidines

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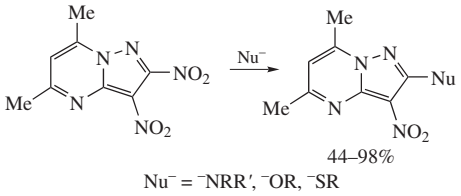
5,7-Dimethyl-2,3-dinitropyrazolo[1,5-*a*]pyrimidine in reaction with N-, S- and O-nucleophiles under mild conditions undergoes regioselective nucleophilic substitution of the 2-positioned nitro group, which provides an access to a library of 2-R-3-nitropyrazolo[1,5-*a*]pyrimidines.



Pyrazolo[1,5-*a*]pyrimidine derivatives are privileged compounds in medicinal chemistry and possess high biological activity such as sedative, antidepressant and antiepileptic,[1] antitumor,[2] antibacterial and antiviral[3] ones. Pyrazolo[1,5-*a*]pyrimidines are investigated as selective inhibitors of numerous enzymes,[4] including, *e.g.* tyrosine kinase (CDK),[5] histone lysine demethylase 4D (KDM4D),[6] COX-2,[7] and glucocerebrosidase.[8] Also, they are antagonists of various receptors,[9] such as the nicotine acid receptor GPR109A[10] and serotonin 5–HT_6 receptor.[11]

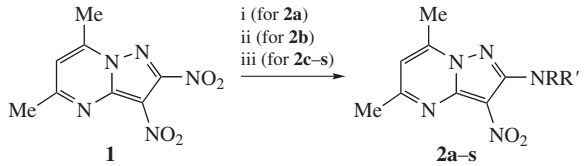
A large number of studies on preparation of pyrazolo[1,5-*a*]-pyrimidines with various substituents and elucidation of their properties has been performed and reviewed.[12] The overwhelming majority of the methods for their synthesis are based on condensation of β-dicarbonyl compounds or their synthetic analogues with N-unsubstituted 3(5)-aminopyrazoles which would already bear a certain set of functional groups. This significantly limits the structural diversity of the pyrazole moiety in pyrazolo[1,5-*a*]-pyrimidines, which can prevent the understanding of structure–property relationship necessary for further development of directed synthesis of biologically active substances. Therefore, it is highly challenging to design new general accesses to pyrazolo[1,5-*a*]-pyrimidines.

One of the known efficient methods of functionalization of pyrazole cycle is selective nucleophilic substitution in di- and trinitropyrazoles.[13] A possibility of independent functionalization of all carbon atoms of pyrazole cycle with the formation of a new $C^{3/4/5}$–XR bond (X = O, N, S) only on the basis of one structural pyrazole type, *viz.* polynitropyrazoles, is an important advantage of this method. Despite a rather facile synthesis of dinitro derivatives of pyrazolo[1,5-*a*]pyrimidines by condensation of 5-amino-3,4-dinitropyrazole with β-diketones,[14] this approach to functionalization of the pyrazole moiety in the pyrazolo[1,5-*a*]-pyrimidines by nucleophilic substitution of nitro group has not been used so far.

In continuation of our research on chemistry of nitropyrazoles,[13–16] this paper reports on nucleophilic substitution in model 5,7-dimethyl-2,3-dinitropyrazolo[1,5-*a*]pyrimidine **1**[14] under the action of various heteroatomic N-, S- and O-nucleophiles.

Amines of various types such as ammonia, methylamine, aliphatic primary and secondary amines, benzylamines, arylamines, and imidazole were used as N-nucleophiles (Scheme 1). Treatment of 5,7-dimethyl-2,3-dinitropyrazolo[1,5-*a*]pyrimidine **1** with a 10-fold excess of ammonia or methylamine aqueous solution at room temperature gave compounds **2a**,**b** in 77 and 84% yields, respectively.† Full conversion was achieved within 18 h. The reaction with the rest of amines was carried out using a 3-fold excess of N-nucleophile in methanol at room temperature for 6–12 h. Yield of compounds **2c**–**s** was 75–77% (see Scheme 1). In all cases substitution proceeded regioselectively, at 2-positioned nitro group.

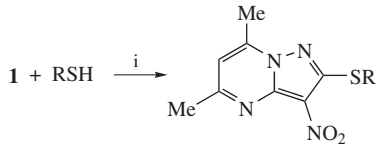
Under similar mild conditions, pyrazolopyrimidine **1** reacted with S-nucleophiles, phenols and sodium methoxide. The reaction with S-nucleophiles was performed in acetonitrile at room temperature in the presence of K_2CO_3 as a base to give sulfides **3a**–**d** in high (88–90%) yields. Note that the products began to



2a R = R′ = H
2b R = H, R′ = Me
2c R = H, R′ = Bu
2d R = H, R′ = $(CH_2)_2OH$
2e R = H, R′ = 3-morpholinopropyl
2f R = H, R′ = 2-pyrrolidinoethyl
2g R + R′ = $(CH_2)_2CHMe(CH_2)_2$
2h R + R′ = $(CH_2)_5$
2i R + R′ = $(CH_2)_6$
2j R + R′ = $(CH_2)_4$
2k R + R′ = $(CH_2)_2N(Bn)(CH_2)_2$
2l R + R′ = $(CH_2)_2NEt(CH_2)_2$
2m R + R′ = $(CH_2)_2S(CH_2)_2$
2n R + R′ = $(CH_2)_2O(CH_2)_2$
2o R = H, R′ = 4-$FC_6H_4CH_2$
2p R = H, R′ = (2-furyl)methyl
2q R = H, R′ = 3-$F_3CC_6H_4$
2r R = H, R′ = 4-$MeO_2CC_6H_4$
2s R = H, R′ = 1-imidazolyl

Scheme 1 *Reagents and conditions*: i, aq. NH_3 (25%); ii, aq. $MeNH_2$ (40%) (10 equiv.), room temperature, 18 h; iii, HNRR′ (3 equiv.), MeOH, room temperature, 6–12 h.

† *Preparation of 2-NRR′-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidines* **2** *(general procedure)*. The appropriate amine (10 equiv. for **2a**,**b** and 3 equiv. for **2c**–**s**) was added to the solution of pyrazolopyrimidine **1**[14] (0.24 g, 1 mmol) in MeOH (6 ml). The mixture was stirred for 18 h (for **2a**,**b**) or 6–12 h (for **2c**–**s**) at ambient temperature. The precipitate formed was filtered off, washed with cold MeOH, dried and crystallized from H_2O–EtOH (1:1).

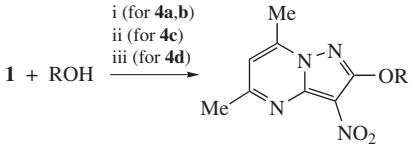


3a R = Et, 79%
3b R = Ph, 88%
3c R = 4-BrC_6H_4, 97%
3d R = 4-$ClC_6H_4CH_2$, 89%

Scheme 2 *Reagents and conditions*: i, RSH (1.2 equiv.), K_2CO_3 (1.2 equiv.), MeCN, room temperature, 7 h.

precipitate from the reaction mixture after 15–20 min, while full conversion was achieved within 7 h (Scheme 2).‡

In the case of phenols, under the same conditions, the reaction time was somewhat longer (10–12 h), and yield of products **4a**,**b** was 44–98% (Scheme 3).§ The reaction with sodium methoxide in methanol resulted in product **4c** after 5 h (see Scheme 3).¶ The reaction with trifluoroethanol proceeded much slower and, even after 16 h of stirring at room temperature, initial pyrazolopyrimidine **1** was still present in the mixture. Even when the reaction mixture was boiled for 8 h, the yield of ether **4d** was as moderate as 51% (see Scheme 3).



4a R = 4-$F_3CC_6H_4$, 44%
4b R = 3-$MeOC_6H_4$, 98%
4c R = Me, 52%
4d R = CF_3CH_2, 51%

Scheme 3 *Reagents and conditions*: i, ArOH (1 equiv.), K_2CO_3 (1 equiv.), MeCN, room temperature, 10–12 h; ii, NaOH (1 equiv.), MeOH, room temperature, 5 h; iii, CF_3CH_2OH (1 equiv.), K_2CO_3 (1 equiv.), MeCN, Δ, 8 h.

The structures of all products **2**–**4** were derived from ^1H and ^{13}C NMR spectra and confirmed by IR spectroscopy, mass spectrometry and elemental analysis data. All compounds in the IR spectra have absorption bands in 1560–1490 and 1360–1310 cm^{-1} regions, corresponding to the NO_2 group, and exhibit a peak of the molecular ion $[M]^+$ in the mass spectra.

The direction of nucleophilic substitution in compound **1**, *viz*. the formation of 2-substituted 3-nitropyrazolo[1,5-*a*]pyrimidines **2**–**4**, was unequivocally established on the basis of the ^{13}C NMR spectra. It is known[16] that chemical shifts of carbon atoms in ^{13}C NMR spectra of nitropyrazoles are usually arranged in the following sequence: $\delta[C^3{=}N(sp^2)] > \delta[C^5{-}N(sp^3)] \gg \delta(C^4)$. In the pyrazolo[1,5-*a*]pyrimidine system, this regularity is expressed as $\delta[C^2{=}N(sp^2)] > \delta[C^{3a}{-}N(sp^3)] \gg \delta(C^3)$, meanwhile the signals of carbon atoms bound to the nitro group are broadened due to quadrupole relaxation $^{13}C{-}^{14}N$ and, therefore, are easily assigned. The ^{13}C NMR spectra of mononitro derivatives **2**–**4** show only one broadened signal at 108–112 ppm that corresponds to the atom C^3 (*cf.* 112.3 ppm for signal in **1**), whereas the broadening of the C^2 signal at 158.2–150.0 ppm disappears, which indicates substitution of the nitro group at this carbon atom (Figure 1).

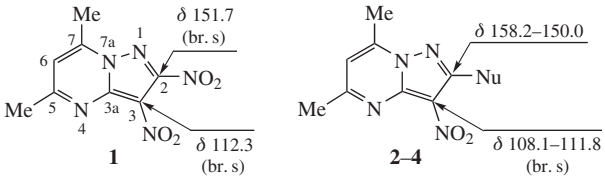


Figure 1 The ^{13}C NMR data for compounds **1**–**4**.

For compounds **2m** and **3d**, the assignment was additionally ascertained using 2D correlation spectroscopy $^1H{-}^{13}C$ HMBC (Figure 2). In the case of compound **2m**, the HMBC spectrum showed correlation of hydrogen atoms of the methylene group of thiomorpholine with the C^2 atom (δ 156.3 ppm) of the pyrazole cycle. A similar pattern was observed in the HMBC spectrum of compound **3d**.

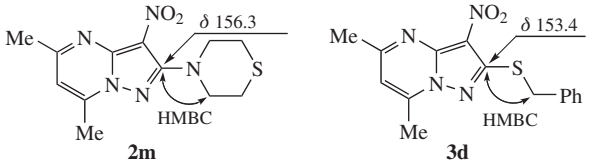
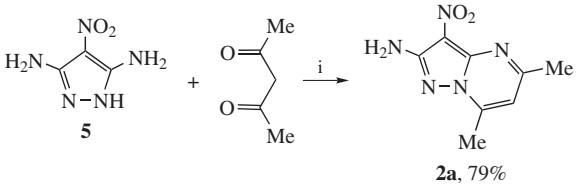


Figure 2 The main correlation pattern in $^1H{-}^{13}C$ HMBC spectra of compounds **2m** and **3d**.

Additional evidence of the nucleophilic substitution direction was obtained from a counter synthesis of known 2-amino-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine[17] **2a** by cyclization of diaminonitropyrazole **5**[18] with acetylacetone (Scheme 4). The spectral and other physicochemical characteristics of compound **2a** prepared by this method completely coincide with the characteristics of the product synthesized from compound **1** by nucleophilic substitution.



Scheme 4 *Reagents and conditions*: i, 2 N HCl, 50–60 °C, 10 h.

In summary, we have proposed a reliable procedure based on regioselective nucleophilic substitution of the nitro group in 2,3-dinitropyrazolo[1,5-*a*]pyrimidines, which can substantially enhance possibilities of heteroatomic functionalization of compounds of this heterocyclic system.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.025.

‡ *Preparation of 2-SR-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidines* **3a**–**d** *(general procedure)*. Pyrazolopyrimidine **1**[14] (0.47 g, 2 mmol) was added to a solution of K_2CO_3 (0.30 g, 2.2 mmol) and appropriate thiol (2.2 mmol) in MeCN (5 ml). The mixture was stirred at ambient temperature for 7 h. The precipitate formed was filtered off, washed with cold MeCN, cold H_2O, dried and crystallized from H_2O–EtOH (1:1).

§ *Preparation of 2-OR-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidines* **4a**,**b**,**d** *(general procedure)*. Pyrazolopyrimidine **1**[14] (0.47 g, 2 mmol) was added to a solution of K_2CO_3 (0.28 g, 2 mmol) and appropriate phenol (2 mmol) or 2,2,2-trifluoroethanol (2 mmol) in MeCN (5 ml). The mixture was stirred at ambient temperature for 10–12 h in case of phenols or refluxed for 8 h in case of 2,2,2-trifluoroethanol. The precipitate formed was filtered off, washed with cold MeCN, cold H_2O, dried and crystallized from H_2O–EtOH (1:1).

¶ *5,7-Dimethyl-2-methoxy-3-nitropyrazolo[1,5-*a*]pyrimidine* **4c**. Pyrazolopyrimidine **1**[14] (0.24 g, 1 mmol) was added to a solution of NaOH (0.04 g, 1.1 mmol) in MeOH (4 ml). The mixture was stirred at ambient temperature for 5 h. The precipitate formed was filtered off, washed with cold MeOH, dried and crystallized from H_2O–EtOH (1:1). Yield 0.12 g (52%), white solid, mp 271 °C.

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