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Regiospecific cleavage of a triazole or pyrimidine ring in nitrotriazolo[1,5-*a*]pyrimidones

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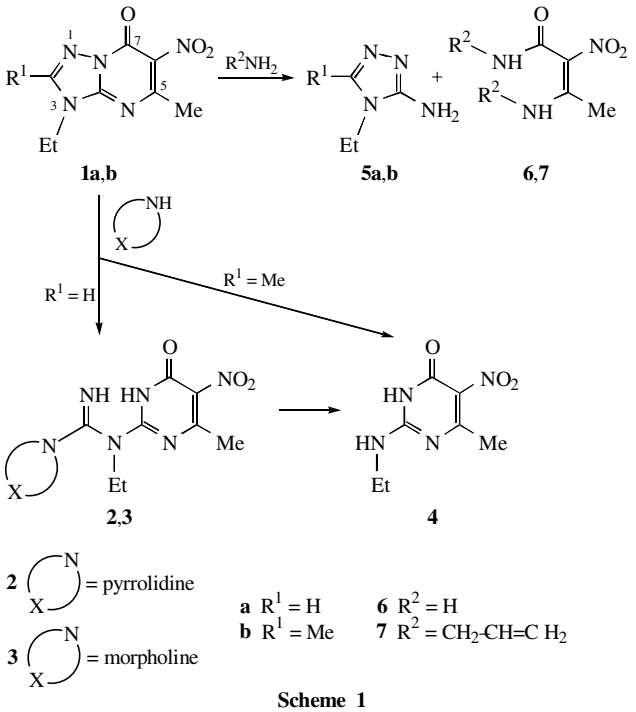
The reaction of nitrotriazolo[1,5-*a*]pyrimidines **1** with primary amines leads to cleavage of the pyrimidine ring, whereas triazole ring opening takes place in the reaction of **1** with secondary amines.

One of the reasons of our continuous interest in condensed azoloazine derivatives bearing a bridgehead nitrogen is their potential biological activity due to the structural similarity to purines. Indeed, a number of compounds possessing antitumor and antiviral activities[1] have been found in this series. Recently, we became interested in nitrotriazolo[5,1-*a*]pyrimidones **1** because of their structural similarity to guanine and of the high antiviral activity of antimetabolites of guanosine and its precursors.[2]

A characteristic chemical property of azaindolizines is an enhanced tendency to ring cleavage by the action of nucleophiles and bases. Depending on the nature of reagents and on the reaction conditions, either azole or azine ring opening reaction can take place. However, the classification of the ring opening reactions of azaindolizines suggested recently on the basis of the molecular design approach[3,4] cannot explain different reaction pathways for aza heterocycles with similar reagents. At the same time, these data are important for the comprehension of the reactivity of azoindolizines and the nature of their metabolism.

In case of triazolo[1,5-*a*]pyrimidones,[3,5] degradation of the pyrimidine ring by the action of nucleophiles appears to be a typical reaction; however, a single example of the triazole ring opening has been reported.[6] Thus, the interaction of 3- -D-ribofuranosyl-5-chloro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one with liquid ammonia was found to yield 4-amino-2-*N*-cyano- -D-ribofuranosylaminopyrimidin-6-one. It was found that the presence of an alkyl substituent in a triazole prevents azole ring opening in triazolo[1,5-*a*]pyrimidinone.[6]



Scheme 1

We have found that nitrotriazolo[1,5-*a*]pyrimidine **1a** reacts easily with pyrrolidine or morpholine to yield hetarylguanidines **2** and **3**† (Scheme 1) after refluxing, instead of the expected cyanamide. An increase in the reaction time leads to the further transformation product, *viz.*, 6-methyl-5-nitro-2-ethylaminopyrimidin-4-one **4**. In contrast to the literature data,[6] we have found that 2-methylpyrimidin-7-one **1b** is transformed only into the same compound **4**‡ on refluxing in an excess of pyrrolidine.

Opening of the pyrimidine ring *via* cleavage of the C_7–N bond in triazolopyrimidones **1a**,**b** was found to take place in the reaction with ammonia to form two products, *viz*., 3-R^2-5-amino-4-ethyl-1,2,4-triazole **5a**,**b** and 3-amino-2-nitrocrotonamide **6**.§ The use of a primary allylamine leads to the allylamide of 3-allylamino-2-nitrocrotonic acid **7**¶ in addition to corresponding aminotriazoles **5a**,**b**. The structure of triazole **5a** is in good agreement with the literature data.[7]

Changes in the temperature conditions changed the reaction time rather than the reaction pathway. The times of full conversion of compound **1a** by the action of corresponding amines are summarised in Table 1.

† *The general synthesis of 1-ethyl-1-(4-methyl-5-nitropyrimidin-6-on-2-yl)-3-tetramethylene guanidine* **2** *and 1-ethyl-1-(4-methyl-5-nitropyrimidin-6-on-2-yl)-3-(3-oxapentamethylene) guanidine* **3**. 500 mg (2.24 mmol) of compound **1a** was refluxed in 3 ml of pyrrolidine (10 min) or morpholine (20 min). The mixture was evaporated and treated with 50% isopropanol. The precipitate was filtered off.

2: yield 55%, mp 270 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.17 (t, 3H), 1.80–2.00 (m, 4H), 2.08 (s, 3H), 3.30–3.50 (m, 4H), 3.78 (q, 2H), 8.78 (br. s, 2H). IR, ν/cm^{-1} : 1330, 1530 (NO_2), 1680 (C=O), 1580 (C=NH); MS, *m*/*z* (%): 294 (3.15).

3: yield 73%, mp 180 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.09 (t, 3H), 2.22 (s, 3H), 3.30–3.40 (m, 4H), 3.60–3.70 (m, 4H), 3.80 (q, 2H), 8.41 (br. s, 1H), 9.81 (br. s, 1H). IR, ν/cm^{-1} : 1310, 1530 (NO_2), 1670 (C=O), 1580 (C=NH).

‡ *The synthesis of 2-ethyl-4-methyl-5-nitropyrimidin-6-one* **4**. 500 mg (2.11 mmol) of compound **1b** was refluxed in 3 ml of pyrrolidine for 40 min. Pyrrolidine was evaporated. The residue was recrystallised from 20% acetic acid. Yield 83%, mp 285 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.18 (t, 3H), 2.28 (s, 3H), 3.20–3.50 (m, 2H), 7.33 (br. s, 1H), 11.43 (br. s, 1H). IR, ν/cm^{-1} : 1510, 1320 (NO_2), 1680 (C=O), 3280, 1250 (NH).

§ *The synthesis of 3-amino-2-nitrocrotonamide* **6**. 500 mg (2.24 mmol) of compound **1a** was added to 5 ml of a methanolic ammonia solution. The mixture was kept at room temperature for a week. The solvent was evaporated. The residue was recrystallised from water. Yield 77%, mp 202 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.14 (s, 3H), 7.35 (br. s, 1H), 7.75 (br. s, 1H), 8.90 (br. s, 1H), 9.80 (br. s, 1H). IR, ν/cm^{-1} : 1510, 1370 (NO_2), 1650 (C=O), 3300, 3150, 1270 (NH_2). MS, *m*/*z* (%): 145 (48.34).

¶ *General synthesis of 3-R-5-amino-4-ethyl-1,2,4-triazoles* **5a**,**b** *and allylamide of 3-allylamino-2-nitrocrotonic acid* **7**. Compound **1** (2 mmol) was refluxed in 5 ml of allylamine for approximately 5–10 min. Allylamine was evaporated *in vacuo*. The residue was dissolved in 10 ml of hot chloroform. After cooling white crystals of triazole **5** were filtered off. The filtrate was evaporated. The residue was recrystallised from octane to give allylamide **7**.

5a: yield 82%, mp 195 °C (lit.,[7] mp 200–201 °C). ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.23 (t, 3H), 3.74 (q, 2H), 5.66 (br. s, 2H), 7.89 (s, 1H). IR, ν/cm^{-1} : 3300, 3400 (NH_2), 1380, 2920 (CH). MS, *m*/*z* (%): 112 (100.00).

5b: yield 79%, mp 247 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.14 (t, 3H), 2.17 (s, 3H), 3.71 (q, 2H), 5.53 (br. s, 2H). IR, ν/cm^{-1} : 1120, 1680, 3300 (NH_2), 1370, 2980 (CH). MS, *m*/*z* (%): 126 (100.00).

7: yield 62%, mp 65 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.07 (s, 3H), 3.72–3.82 (m, 2H), 4.10–4.18 (m, 2H), 5.00–5.30 (m, 4H), 5.75–6.05 (m, 2H), 8.56 (t, 1H), 10.79 (t, 1H). IR, ν/cm^{-1} : 1250, 3450 (NH), 1650 (C=O), 1350, 1550 (NO_2). MS, *m*/*z* (%): 225 (46.32).

Table 1 Times of full conversion of **1a**.

Amine	*t*/min	Products	pK_a
Ammonium hydroxide	10	**5a** and **6**	9.25
Allylamine	25	**5a** and **7**	9.69
Pyrrolidine	30	**2**	11.27
Morpholine	60	**3**	8.33

Thus, 6-nitrotriazolo[1,5-*a*]pyrimidines **1**, which are heterocyclic systems prone to azole and azine ring opening reactions, exhibit an ambident character. The type of bicyclic system cleavage does not depend on the amine basicity but depends on the reagent structure. Thus, ammonia and primary amines open an azine ring, whereas cycloalkyl imines open an azole ring. A plausible explanation of the observed reactivity of triazolo-[1,5-*a*]pyrimidines **1** consists in lower steric hindrances of primary amines in the course of the attack on the pyrimidine carbonyl.

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