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A new approach to condensed pyridines

Mikhail M. Krayushkin,[a] Vladimir N. Yarovenko,[a] Igor P. Sedishev,[a] Anatoly A. Andreiko,[b] Nataliya N. Mochulskaya[c] and Valery N. Charushin*[b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 137 6939; e-mail: mkray@ioc.ac.ru*
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Urals Branch of the Russian Academy of Sciences, 620219 Ekaterinburg, Russian Federation. Fax: +7 3433 74 1189; e-mail: charushin@ios.uran.ru*
[c] *Department of Organic Chemistry, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3433 74 0458; e-mail: 7708@mail.ur.ru*

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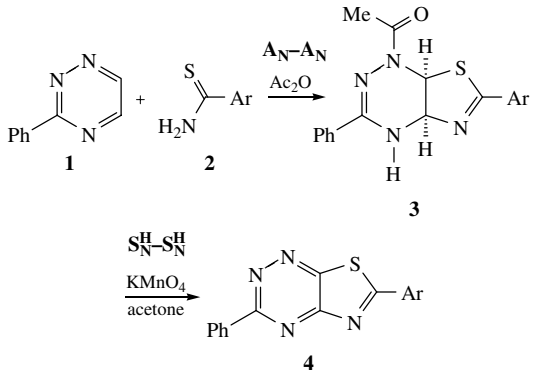
The interaction of thiazolo[4,5-*e*][1,2,4]triazines with bicyclo[2.2.1]heptadiene at a high pressure (up to 15 kbar) results in the corresponding thiazolo[4,5-*b*]pyridines, and this is the key step of a new approach to fused pyridines based on the tandem $S_N^H - S_N^H$ reactions on the 1,2,4-triazine ring.

Pyridines and condensed systems bearing the pyridine ring are of considerable interest to chemists and biologists.[1–5] These molecules are very important for medicinal chemistry, pharmaceutical industry, *etc.*[1,2] Condensed systems, such as thieno-[3] and thiazolopyridines,[4,5] are of interest as biologically active compounds.

In this paper, we describe a new methodology for the synthesis of condensed pyridines, which is based on the tandem $S_N^H - S_N^H$ reactions on the 1,2,4-triazine ring followed by the triazine-to-pyridine ring transformation reaction.

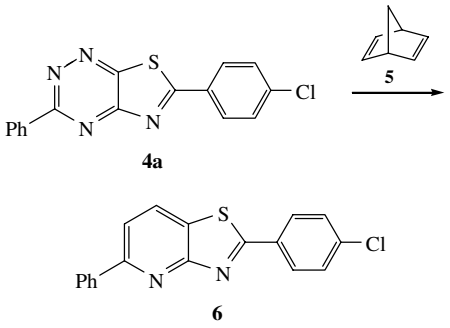
We have recently reported that the tandem nucleophilic addition (A_N–A_N) reactions of 3-aryl-1,2,4-triazines **1** with thioarylamides **2** in acetic anhydride proceed smoothly at room temperature resulting in the formation of 1,4,4a,7a-tetrahydrothiazolo[4,5-*e*][1,2,4]triazines **3** in good yields. Oxidation of adducts **3** with potassium permanganate in acetone gave aromatic thiazolo[4,5-*e*][1,2,4]triazines **4** as a result of the tandem $S_N^H - S_N^H$ reaction (Scheme 1).[6,7]



Scheme 1

1,2,4-Triazines are known to undergo inverse electron-demand Diels–Alder cycloaddition reactions with electron-rich dienophiles, thus being transformed into pyridines or pyrimidines.[8–12] In continuation of our studies on the chemistry of 1,2,4-triazines, we studied the conversion of thiazolo[4,5-*e*][1,2,4]-triazine **4a** into thiazolopyridine **6** by the action of bicyclo-[2.2.1]hepta-2,5-diene **5** (Scheme 2). The behaviour of 3-phenyl-1,2,4-triaizine **1** towards dienophile **5** was studied for comparison.

Our attempts to cause the ring transformation of thiazolo-[4,5-*e*][1,2,4]triazine **4a** by the action of 1-morpholinocyclo-



Scheme 2

hexene or bicyclo[2.2.1]hepta-2,5-diene **5** in refluxing dioxane at ambient pressure were unsuccessful. In all cases, the starting material, *i.e.*, thiazolo[4,5-*e*][1,2,4]triazine **4a**, was isolated. However, we found that the reaction of 6-(4-chlorophenyl)-3-phenyl[1,3]thiazolo[4,5-*e*][1,2,4]triazine **4a** with bicyclo-[2.2.1]hepta-2,5-diene **5** in dichloromethane leads to the formation of thiazolo[4,5-*b*]pyridine **6** under high-pressure conditions (from 250 bar to 15 kbar) (Scheme 2). The yields of **6** are listed in Table 1.

The best yield of thiazolo[4,5-*b*]pyridine **6** (95%) was reached at a pressure of 15 kbar and at 100 °C (Table 1, entry 4). Evidence for the structure of **6** is provided by ^{1}H NMR spectroscopy and mass spectrometry.† The resonance signals of H-6 and H-7 of the pyridine ring are two doublets at 7.83 and 8.32 ppm with vicinal coupling ^3J 8.4 Hz characteristic of *ortho*-protons. The peak of the molecular ion (M^+) observed in the mass spectrum of compound **6** (M^+, *m*/*z* 322) is in full agreement with the structure. For comparison, 3-phenyl-1,2,4-triazine **1** was found to react with **5** to 2-phenylpyridine in dichloromethane at 110 °C and 5 kbar in a nearly quantitative yield (98%).

In conclusion, note that we have found the ability of the 1,2,4-triazine ring annelated with the electron-donating thiazole ring to be transformed into the corresponding thiazolo[4,5-*b*]-pyridine *via* an inverse electron-demand Diels–Alder reaction proceeding under high-pressure conditions (0.25–15 kbar). The reaction is a key step in the new synthesis of condensed pyridines based on the tandem $S_N^H - S_N^H$ reactions on the 1,2,4-triazine ring.

Table 1 Yields of thiazolo[4,5-*b*]pyridine **6** derived from the reaction of **4a** with **5** in CH_2Cl_2 performed under high-pressure conditions (0.25–15 kbar) (the reaction time is 6 h).

Entry	*T*/°C	*P*/kbar	Yield (%)	
			Pyridine **6**	Starting material **4a**
1	100	0.25	—	94
2	100	5	—	91
3	100	10	44	56
4	100	15	95	5
5	150	0.25	—	96
6	150	5	45	55
7	150	10	86	14
8	175	0.25	40	60
9	175	5	75	25

† The ^{1}H NMR spectrum of **6** in $CDCl_3$ was recorded on a Bruker WP-250 instrument (250 MHz for ^{1}H). The mass spectrum was recorded using a Varian MAT 311A spectrometer.

*A typical experimental procedure for the synthesis of 2-(4-chlorophenyl)-5-phenylthiazolo[4,5-*b*]pyridine* **6**. Bicyclo[2.2.1]hepta-2,5-diene **5** (405 mg, 4.4 mmol) was added to 6-(4-chlorophenyl)-3-phenyl[1,3]-thiazolo[4,5-*e*][1,2,4]triazine **4** (100 mg, 0.308 mmol) in 15 ml (19.8 g) of dichloromethane. The reaction mixture was heated in a Teflon ampoule for 6 h under high-pressure conditions (Table 1). The solvent was evaporated to give a precipitate of **6** with mp 234.5–235 °C. MS, *m*/*z* (%): 322 (M^+), 185 (M – CNPhCl), 153 (M – SCNPhCl). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.52 (m, 5H, H_{Ar}), 7.83 (d, 1H, H_{Py}, *J* 8.4 Hz), 8.20 (m, 4H, H_{Ar}), 8.32 (d, 1H, H_{Py}, *J* 8.4 Hz).

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