Heterocycles with the bridgehead N atom
17.* Recyclization of 2,3,5,7-tetramethyloxazolo[3,2-*a*]pyrimidinium perchlorate in reactions with the simplest nucleophiles

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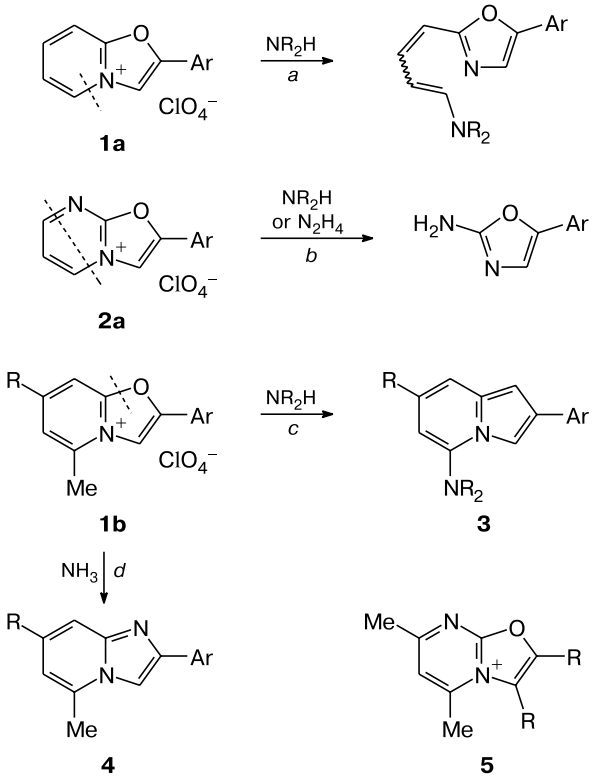
2,3,5,7-Tetramethyloxazolo[3,2-*a*]pyrimidinium perchlorate in reactions with sodium hydroxide, sodium ethoxide, and pyrrolidine undergoes earlier unknown recyclization into 1-substituted pyrrolo[1,2-*c*]pyrimidines. Recyclization of the same salt under the action of ammonia gives 2,3,5,7-tetramethylimidazo[1,2-*a*]pyrimidine.

Key words: recyclization, pyrimidine, oxazole, pyrrole, azaindolizine.

It is known[2,3] that oxazolo[3,2-*a*]pyridinium salts **1a** in reactions with secondary amines undergo opening of the pyridine ring (Scheme 1, route *a*). Recently,[4] we have found that salts **2a** (aza analogs of salts **1a**) undergo analogous opening of the six-membered fragment with complete decomposition of the pyrimidine ring (Scheme 1, route *b*).

Compounds **1b**, which are homologous to salts **1a**, react with secondary amines in a different manner: the oxazole ring undergoes opening followed by recyclization into the pyrrole ring and the formation of an unknown subclass of 5-aminoindolizines **3** (Scheme 1, route *c*).[2,5,6] Recently, this synthetic approach has been tested at pharmaceutical laboratories in the synthesis of combinatorial libraries of this not easily accessible subclass of indolizines.[7] In reactions of salts **1b** with ammonia, the oxazole fragment becomes transformed into an imidazole fragment to give imidazo[3,2-*a*]pyridine derivatives **4** (Scheme 1, route *d*).[8] (Analogous recyclization has been observed[9] for salts **1a**.) Thus, the direction of the transformation of oxazolo[3,2-*a*]pyridinium (**1**) and oxazolo[3,2-*a*]pyrimidinium salts (**2**) depends on both the nature of the nucleophile and the presence of the methyl group in position 5. The direction of reactions of nucleophiles with salts **5**, which are aza analogs of salts **1b** and homologs of salts **2a**, remains unclear. The solution of this problem was a subject of the present work. The published[10] procedure for the synthesis of salts **5a** (R = Me) and **5b** (R = Ph) involves condensation of 4,5-disubstituted 2-aminooxazoles with acetylacetone; however, their reactivities have not been studied.

Scheme 1



We synthesized perchlorate **5a** according to the aforesaid procedure[10] and studied its reactions with sodium hydroxide, sodium ethoxide, pyrrolidine, and ammonia (Scheme 2).

It turned out that salt **5a** reacts with aqueous NaOH at room temperature to give a novel covalent compound.

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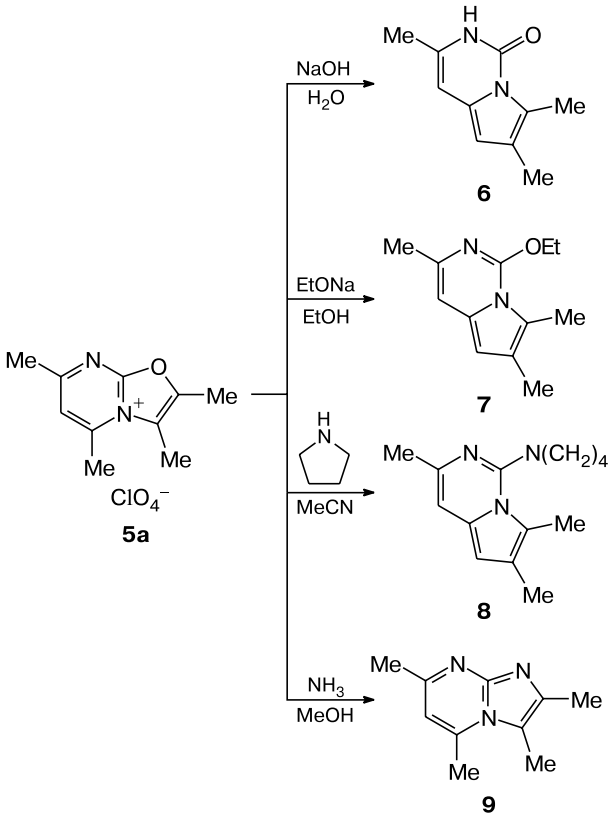
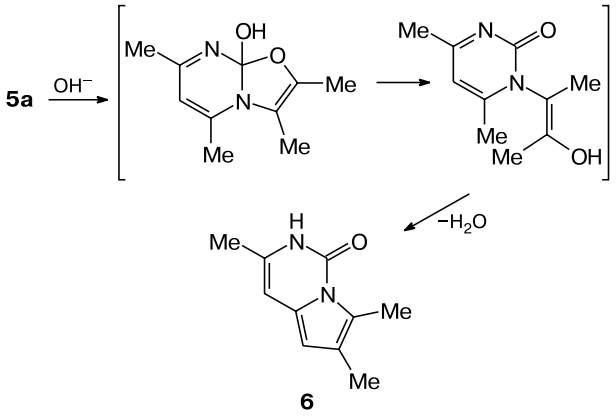
Scheme 2



According to elemental analysis data and mass spectra, the compound obtained is identical in composition with salt **5a** minus a $HClO_4$ molecule. In contrast to the ^1H NMR spectrum of salt **5a**, the spectrum of the product does not show the signal for one of the methyl groups and contains three singlets (at δ 5.70, 5.79 and 10.11) instead of one aromatic singlet for the pyrimidine ring (at δ 7.8). The signal for one of the methyl groups also disappears from the ^{13}C NMR spectrum of the product and seven (instead of six) signals appear in the aromatic range. All these data unambiguously suggest that the oxazole ring is transformed into a pyrrole ring to give 3,6,7-trimethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one (**6**). (Note that amide-type tautomerism has been proved for the sole documented[11] representative of pyrrolo[1,2-*c*]pyrimidin-1-ones.) Apparently, this rearrangement follows the ANRORC mechanism (Scheme 3).

Scheme 3



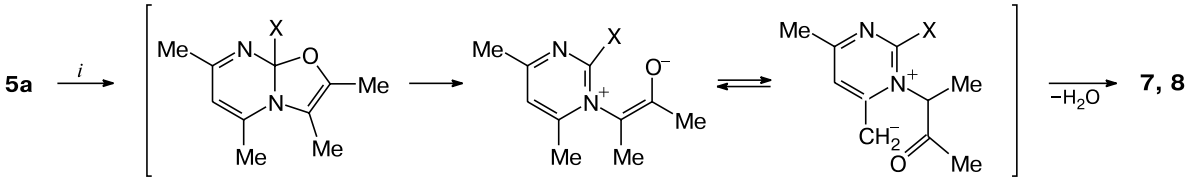
Reactions of perchlorate **5a** with sodium ethoxide and pyrrolidine also yielded novel compounds. According to elemental analysis data and mass spectra, the molecular masses of compounds **7** and **8** correspond to the following formulas:

$$M(\mathbf{7}) = M(\mathbf{5a}) - M(ClO_4) - M(H_2O) + M(OEt),$$

$$M(\mathbf{8}) = M(\mathbf{5a}) - M(ClO_4) - M(H_2O) + M(N(CH_2)_4)$$

The ^1H and ^{13}C NMR spectra of the products obtained do not contain, in contrast to the spectra of the starting salt **5a**, the signal for one of the methyl groups but show signals for the coming ethoxy group or the pyrrolidine fragment. The ^1H NMR spectra contain a new singlet at δ 5.9 and the sole low-field singlet for the pyrimidine ring of salt **5a** is shifted upfield to δ 6.4—6.5. Therefore, like the reaction of salt **5a** with NaOH, its reactions with sodium alkoxide and the secondary amine involve opening of the oxazole ring followed by recyclization into a pyrrole ring. The reaction is accompanied by introduction of the ethanol (amine) residue and loss of a water molecule during cyclocondensation. Therefore, the recyclization products are 1-ethoxy(pyrrolidino)pyrrolo[1,2-*c*]pyrimidines **7** and **8** (Scheme 4).

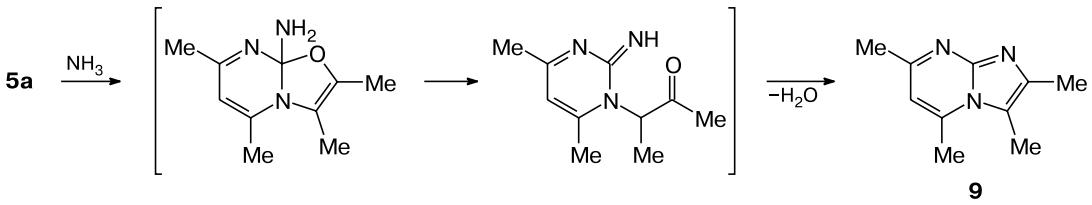
Scheme 4



i. NR_2H or RO^-.

X = NR_2, RO^-

Scheme 5



The compounds obtained demonstrate a positive Ehrlich color probe typical of fused pyrroles.[12]

A reaction of salt **5a** with ammonia gives a product in the ^{1}H and ^{13}C NMR spectra of which all the characteristic signals of the starting salt **5a** are retained with a general upfield shift. The physical properties of the product are identical with the literature[13] data for 2,3,5,7-tetramethylimidazo[1,2-*a*]pyrimidine (**9**). In this case, recyclization probably involves the coming amino group (Scheme 5).

In conclusion, we discovered with salt **5a** as examples that 5-methyloxazolo[3,2-*a*]pyrimidinium cations **5** react with nucleophiles with opening and transformation of the oxazole rather than pyrimidine ring to give, *via* earlier unknown recyclization, not easily accessible azaindolizines **6**—**8**. Such a type of the reactivity of fused pyrimidines **5** differs from the behavior of lower homologs **2a** and resembles the conversion of salts **1b** of the pyridine series.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument (350 (^{1}H) and 100 MHz (^{13}C)) in DMSO-d_6. Chemical shifts were measured using the δ scale with $SiMe_4$ as the internal standard. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV). Thin-layer chromatography was carried out on Silufol F_{254} plates (Merck); spots were visualized under UV light (λ = 254 and 365 nm).

2-Amino-4,5-dimethyloxazole was prepared from cyanamide and acetoin according to a known procedure.[14] 2,3,5,7-Tetramethyloxazolo[3,2-*a*]pyrimidinium perchlorate (**5a**) was prepared by condensation of 2-amino-4,5-dimethyloxazole with acetylacetone as described earlier.[10] The yield was 60%, m.p. 227—228 °C (ethanol) (*cf.* Ref. 10: 227—228 °C). ^{1}H NMR, δ: 2.59 (s, 3 H, C(7)H_3); 2.72 (s, 3 H, C(3)H_3); 2.77 (s, 3 H, C(2)H_3); 3.06 (s, 3 H, C(5)H_3); 7.80 (s, 1 H, H(6)). ^{13}C NMR, δ: 9.8; 10.0; 18.6; 24.3; 118.9; 121.3; 146.7; 153.1; 153.9; 172.4.

3,6,7-Trimethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one (6). A 20% solution of NaOH (100 mL) was added to salt **5a** (2.765 g, 0.01 mol). The reaction mixture was stirred at room temperature for 5 h and then kept for 16 h. The precipitate that formed was filtered off, washed with water, and recrystallized from ethanol. The yield of compound **6** was 1.58 g (90%), m.p. 179—181 °C. Found (%): C, 67.93; H, 6.88; N, 15.68. $C_{10}H_{12}N_2O$. Calculated (%): C, 68.16; H, 6.86; N, 15.90. ^{1}H NMR, δ: 1.99, 2.02 (both s, 3 H each, C(6)Me, C(7)Me); 2.55 (s, 3 H, C(3)H_3); 5.70 (s, 1 H, H(5)); 5.79 (s, 1 H, H(4)); 10.11 (br.s, 1 H, NH). ^{13}C NMR, δ: 10.9; 12.2; 17.6; 96.2; 102.5; 120.7; 121.4; 130.1; 130.7; 148.3. MS, *m/z* (I_{rel} (%)): 176 $[M]^+$ (100%).

1-Ethoxy-3,6,7-trimethylpyrrolo[1,2-*c*]pyrimidine (7). Metallic Na (0.05 mol) was dissolved with cooling in anhydrous ethanol (100 mL). The resulting solution of sodium ethoxide was heated to 50 °C and oxazolo[3,2-*a*]pyrimidinium perchlorate **5a** (2.765 g, 0.01 mol) was added. The reaction mixture was refluxed for 3 h. On cooling, the solvent was removed and the residue was poured into water. The precipitate that formed was washed with water, dried, and recrystallized from ether. The yield of compound **7** was 1.63 g (80%), m.p. 38—40 °C. Found (%): C, 70.04; H, 7.60; N, 13.39. $C_{10}H_{12}N_2O$. Calculated (%): C, 70.56; H, 7.89; N, 13.71. ^{1}H NMR, δ: 1.45 (q, 3 H, C(3)H_3, J = 7.1 Hz); 2.10 (s, 3 H, C(7)H_3); 2.17 (s, 3 H, C(6)H_3); 2.56 (s, 3 H, C(3)H_3); 4.49 (t, 2 H, OCH_2, J = 7.1 Hz); 5.85 (s, 1 H, H(5)); 6.42 (s, 1 H, H(4)). ^{13}C NMR, δ: 11.5; 12.5; 14.0; 22.5; 63.2; 99.6; 103.7; 116.5; 122.5; 133.2; 138.0; 147.6. MS, *m/z* (I_{rel} (%)): 204 $[M]^+$ (54%), 175 (100).

3,6,7-Trimethyl-1-(pyrrolidino)pyrrolo[1,2-*c*]pyrimidine (8). Perchlorate **5a** (2.765 g, 0.01 mol) was suspended in anhydrous acetonitrile (50 mL). The solution was heated to 50 °C and refluxed with pyrrolidine (0.05 mol) for 4 h. On cooling, the solvent was removed and the resulting brown oil was dissolved in water. The product was extracted with chloroform (3×20 mL). The extract was dried over Na_2SO_4 and concentrated; the residue was dissolved in chloroform and chromatographed on silica gel with chloroform as an eluent. The first fraction was collected. The yield of compound **8** was 0.92 g (40%), a yellow oil. Found (%): C, 73.22; H, 8.37; N, 18.51. $C_{14}H_{19}N_3$. Calculated (%): C, 73.33; H, 8.35; N, 18.32. ^{1}H NMR, δ: 1.91 (m, 4 H, $(CH_2)_2$); 2.13 (s, 3 H, C(7)H_3); 2.18 (s, 3 H, C(6)H_3); 2.59 (s, 3 H, C(3)H_3); 3.29 (m, 4 H, N$(CH_2)_2$); 5.91 (s, 1 H, H(5)); 6.50 (s, 1 H, H(4)). ^{13}C NMR, δ: 11.5; 11.7; 22.4; 23.4; 50.2; 99.2; 104.9; 116.5; 123.8; 134.0; 137.4; 148.2. MS, *m/z* (I_{rel} (%)): 229 $[M]^+$ (100%).

2,3,5,7-Tetramethylimidazo[1,2-*a*]pyrimidine (9). Perchlorate **5a** (2.765 g, 0.01 mol) was added to a 4 *M* solution of NH_3 in methanol (100 mL). The mixture was stirred for 12 h and then refluxed for 2 h. The solvent was removed and the residue was treated with water. The precipitate that formed was filtered off and recrystallized from ethanol. The yield of compound **9** was 1.5 g (86%), m.p. 201—202 °C (ethanol) (*cf.* Ref. 14: 202 °C). ^{1}H NMR, δ: 2.23 (s, 3 H, C(7)H_3); 2.38 (s, 3 H, C(3)H_3); 2.61 (s, 3 H, C(2)H_3); 2.80 (s, 3 H, C(5)H_3); 6.58 (s, 1 H, H(6)). ^{13}C NMR, δ: 11.4; 13.1; 18.9; 23.7; 109.2; 115.1; 139.6; 144.8; 147.5; 157.1.

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