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

Compounds 1\textsubscript{b}, which are homologous to salts 1\textsubscript{a}, 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).\textsuperscript{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.\textsuperscript{7} In reactions of salts 1\textsubscript{b} with ammonia, the oxazole fragment becomes transformed into an imidazole fragment to give imidazo[3,2-a]pyridine derivatives 4 (Scheme 1, route d).\textsuperscript{8} (Analogous recyclization has been observed\textsuperscript{9} for salts 1\textsubscript{a}.) 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 1\textsubscript{b} and homologs of salts 2\textsubscript{a}, remains unclear. The solution of this problem was a subject of the present work. The published\textsuperscript{10} procedure for the synthesis of salts 5\textsubscript{a} (R = Me) and 5\textsubscript{b} (R = Ph) involves condensation of 4,5-disubstituted 2-aminooxazoles with acetylacetone; however, their reactivities have not been studied.

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

* For Part 16, see Ref. 1.

 Scheme 1

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According to elemental analysis data and mass spectra, the compound obtained is identical in composition with salt 5a minus a HClO₄ 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 ¹³C 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(2H)-one (6). (Note that amide-type tautomerism has been proved for the sole documented¹¹ representative of pyrrolo[1,2-c]pyrimidin-1-ones.) Apparently, this rearrangement follows the ANRORC mechanism (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:

\[ M(7) = M(5a) - M(\text{ClO}_4) - M(\text{H}_2\text{O}) + M(\text{C}_2\text{H}_5\text{O}) \]
\[ M(8) = M(5a) - M(\text{ClO}_4) - M(\text{H}_2\text{O}) + M(N(C_2H_5)_4) \]

The ¹H and ¹³C 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 recyclocondensation 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 recyclocondensation products are 1-ethoxy(pyrrolidino)pyrrolo[1,2-c]pyrimidines 7 and 8 (Scheme 4).

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\( \text{i. } \text{NR}_2\text{H or RO}^- \)
\( X = \text{NR}_2, \text{RO}^- \)
The compounds obtained demonstrate a positive Ehrlich color probe typical of fused pyroles.\textsuperscript{12}

A reaction of salt 5a with ammonia gives a product in the \textsuperscript{1}H and \textsuperscript{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\textsuperscript{13} data for 2,3,5,7-tetramethylimidazo[1,2-\textalpha]pyrimidine (9). In this case, recrystallization probably involves the coming amino group (Scheme 5).

In conclusion, we discovered with salt 5a as examples that 5-methyloxazolo[3,2-\textalpha]pyrimidinium cations 5 react with nucleophiles with opening and transformation of the oxazole rather than pyrimidine ring to give, via earlier unknown recrystallization, 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**

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker AC 400 instrument (350 (\textsuperscript{1}H) and 100 MHz (\textsuperscript{13}C)) in DMSO-\textdelta. Chemical shifts were measured using the \textdelta scale with SiMe\textsubscript{4} as the internal standard. Mass spectra were recorded on a Kratos MS-150 instrument (350 (\textsuperscript{1}H) and 100 MHz (\textsuperscript{13}C)) in DMSO-d\textsubscript{6}. Chemical shifts were measured using the \textdelta scale with SiMe\textsubscript{4} as the internal standard. Mass spectra were recorded on a Kratos MS-150 instrument (350 (\textsuperscript{1}H) and 100 MHz (\textsuperscript{13}C)) in DMSO-d\textsubscript{6}. Chemiluminescence was detected at 254 and 365 nm). MS, m/z (rel (%)): 9.8; 10.0; 18.6; 24.3; 118.9; 121.3; 146.7; 153.1; 153.9; 172.4.

**Scheme 5**

The yield was 60%, m.p. 179—181 °C. Ref. 10: 227—228 °C. The extract was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated; the residue was dissolved in chloroform and chromatographed on silica gel with chloroform as an eluent. The yield of compound 8 was 0.92 g (40%), a yellow oil. Found (%): C, 73.22; H, 8.37; N, 18.51. C\textsubscript{46}H\textsubscript{19}N\textsubscript{3}I. Calculated (%): C, 73.33; H, 8.35; N, 18.32. \textsuperscript{1}H NMR, \&: 1.91 (m, 3 H, C(1)H\textsubscript{3}); 2.13 (s, 3 H, C(3)H\textsubscript{3}); 2.18 (s, 3 H, C(6)H\textsubscript{3}); 2.59 (s, 3 H, C(3)H\textsubscript{3}); 3.29 (m, 4 H, CH\textsubscript{2}); 5.91 (s, 1 H, H(5)); 6.42 (s, 1 H, H(4)). \textsuperscript{13}C NMR, \&: 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 (rel (%)): 204 [M\textsuperscript{+}] (54%), 175 (100%).

**3,6,7-Trimethyl-1-(pyrrolidino)pyrimidinium perchlorate (2).** 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 residue was dissolved in water. The product was extracted with chloroform (3×20 mL). The extract was dried over Na\textsubscript{2}SO\textsubscript{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\textsubscript{46}H\textsubscript{19}N\textsubscript{3}I. Calculated (%): C, 73.33; H, 8.35; N, 18.32. \textsuperscript{1}H NMR, \&: 1.91 (m, 3 H, C(1)H\textsubscript{3}); 2.13 (s, 3 H, C(3)H\textsubscript{3}); 2.18 (s, 3 H, C(6)H\textsubscript{3}); 2.59 (s, 3 H, C(3)H\textsubscript{3}); 3.29 (m, 4 H, CH\textsubscript{2}); 5.91 (s, 1 H, H(5)); 6.42 (s, 1 H, H(4)). \textsuperscript{13}C NMR, \&: 11.5; 12.5; 176 [M\textsuperscript{+}] (100%).

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References


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