Synthesis of 5-alkoxyindolizines from oxazolo[3,2-a]pyridinium salts

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A new route to poorly available 5-alkoxyindolizines has been developed by reaction of oxazolo[3,2-a]pyridinium salts with sodium alkoxides; the structures of three indolizines and one parent salt have been confirmed by X-ray diffraction analysis.

The indolizine ring is isomeric and isostructural to indole, and substituted indolizines are frequently prepared as bioosisters of biologically active indole derivatives. A well-known class of psychotropic indole compounds (e.g., psilocine, psilocybine and pindolole) belongs to the family of 5-hydroxy(alkoxy)indoles. An isostructural class of indolizines bearing 5-OR group (A in Scheme 1) may serve as the biomimetics of such indoles. This class can be designed by a mental rearrangement of the indole ring nitrogen into bridgehead positions.

Scheme 1

The entire class of 5-alkoxy(hydroxy)indolizines is poorly investigated since there is lack of synthetic methodologies leading to this scaffold. Rare examples of preparation of the members of class A include their synthesis from pyrrole derivatives1–3 and by means of photolytic C-5 oxidation of indolizines. We found that the reactions of salts 1a–g with alkoxides to test the synthesis of 5-alkoxyindolizines A.

Variation of the nature of alcohol was performed for salt 1a to annelate the pyrrole ring to pyridine by condensation of the indolizine ring. Rare examples of preparation of the indolizine ring. 4 Structure A with the desired motif was prepared via 1,3-dipolar cycloaddition.5 The most common strategy to indolizine ring (the Chichibabin cyclization) failed for the case of 6-methoxy-2-picoline.6 It is, however, possible to anelate the pyrrole ring to pyridine by condensation of the Guresci pyrdone with α-bromoketones7,8 leading to 5-indoliziones C, which are stable tautomers of desired 5-hydroxy-indolizines D. We found that pyridine-like derivatives C can be converted into 5-chloroindolizines E, which react with MeONa leading to 5-methoxy-6-cyanoindolizines F. However, simple 5-alkoxyindolizines A (without other substituents in the pyridine ring) remain unknown.

We reported an efficient strategy9–12 to build the indolizine ring by a somewhat unusual conversion of oxazolo[3,2-a]-pyridinium salts G (route a in Scheme 2). This reaction allowed us to prepare 5-dialkyaminoindolizines H. Recently,13 this methodology has attracted attention in industrial chemistry as a source of a library of 5-substituted indolizines with potential bioactivity. However, only secondary amines are suitable for such a transformation, and with primary amines (route b) salts I were formed instead of indolizines.

Therefore, it is unclear which other nucleophiles are suitable for this new strategy of indolizine synthesis from oxazolo-pyridines. Furthermore, the ring system of salts G may undergo alternative modes of ring opening depending on the group R and the nature of the nucleophile. Thus, salts G with R = H react with secondary amines with pyridine ring opening (route c11), whereas with alkoxide the C(2)-O bond cleavage was observed (route d14). In this paper, we studied the direction of the reaction of salts G (R = Me) with alkoxides to test the synthesis of 5-alkoxyindolizines A.

We found that the reactions of salts 1a-c with sodium methoxide smoothly led to previously unknown 5-methoxyindolizines 2a–c. Variation of the nature of alcohol was performed for salt 1a, and its reactions with sodium ethoxide and sodium isopropoxide led to corresponding 5-alkoxyindolizines 3, 4. All reactions were usually complete in one or two days at room temperature (additional heating decreased the yields and purity of the products).

Compounds 2–4 gave a positive Erlich test with p-dimethylamino benzaldehyde (deep blue colour typical of indolizines). In the 1H NMR spectra of indolizines (Table 1), two new aromatic singlets of the formed pyrrole ring and the peaks of the RO group were observed (whereas the methyl group, which was initially present in salts I, disappeared), thus clearly confirming

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Table 1 Characteristics of 5-alkoxyindolizines.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Mp/°C</th>
<th>1H NMR ([D$_6$]DMSO) / Substituents$^*$</th>
<th>m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-H (s) 3-H (s) 6-H (s) 7-H [R] 8-H (s) 5-OR 2-Ar (s)</td>
<td>[M$^+$]</td>
</tr>
<tr>
<td>2a$^b$</td>
<td>66</td>
<td>188–189</td>
<td>6.90 7.96 6.03 [2.64 (m)] 7.10 4.14 8.24 8.03</td>
<td>268 (97)</td>
</tr>
<tr>
<td>2b</td>
<td>39</td>
<td>202–204</td>
<td>6.78 7.95 5.95 [2.28] 6.88 4.07 8.22 8.20, 8.03–8.01</td>
<td>282 (96)</td>
</tr>
<tr>
<td>2c</td>
<td>79</td>
<td>177–179</td>
<td>6.61 7.73 5.77 [2.64 (m)] 7.10 4.03 7.71–7.68, 7.55–7.52</td>
<td>355 (100)</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>196–197</td>
<td>6.80 7.88 5.97 6.75 (m) 7.04 4.37, 1.57 8.21, 7.94</td>
<td>282 (84)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>178–179</td>
<td>6.79 7.86 5.99 6.75 (m) 7.03 4.88, 1.51 8.24, 8.03</td>
<td>298 (20)</td>
</tr>
<tr>
<td>a</td>
<td></td>
<td></td>
<td>2.64 (m)</td>
<td>2.28</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td></td>
<td>2.28</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td></td>
<td></td>
<td>2.64 (m)</td>
<td></td>
</tr>
</tbody>
</table>

$^*$According to the numbering of the indolizine ring. $^\dagger$Solvant (CD$_3$)$_2$CO. $^\ddagger$1.80 ppm (m) for (CH$_2$)$_4$.

Further cleavage of the oxazole ring gave rise to ylide structure K, which undergoes final closure and dehydration to the pyrrole ring. Interestingly, in the reaction of salt 1a with Bu'ONa (or Bu'OK), no indolizine was formed, and the starting material was converted into unidentified tar. Probably, the more basic tert-butoxide ion may cause deprotonation of the potentially acidic 5-Me group of salt 1a followed by side chain reactions. No reaction of salt 1a with PhONa was observed (maybe due to a lower nucleophilicity of the phenolate anion). The nature of the electron-withdrawing group at the phenyl group in the 2-position is crucial to the stability of 5-alkoxyindolizines. Thus, indolizines 2a, 2c, 3, 4 with the 2-(p-nitrophenyl) group were stable, whereas compound 2c with the 2-(p-bromophenyl) residue decomposed on keeping. Attempts to prepare other oxazolopyridinium salts with 2-[p-bromo(chloro)phenyl] substituents in reactions with alkoxides led to very unstable products.

Parent salts 1 were prepared by the phenacylation of methoxypyridines 5a–c followed by the cyclocondensation.
of N-phenacylpyridones 6a–c (using H2SO4 as a dehydrating agent) (Scheme 4) and separated as perchlorates. The spectral changes3 from pyridones 6 to oxazolo[3,2-α]pyridinium salts 1 clearly confirm the closure of an aromatic ring: the singlet of the CH2 group disappeared in salts 1, and a new aromatic singlet (1H) of the oxazole fragment is observed at 9.5–9.7 ppm. The structure of salt 1c was confirmed by X-ray data1 (see Figure 1).

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References

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1 1H NMR spectra were recorded on a Bruker AC 400 instrument. The syntheses of compounds 1a, 5a and 6a were described elsewhere;10,11 compound 5b was obtained according to a published procedure.15 3-Methoxy-1-methyl-5,6,7,8-tetrahydroisoquinoline 5c was prepared by the alkylation of the Ag salt of the corresponding pyridine with Mel using a protocol16 for pyrid-2-one. Yield, 73%; mp 39–40 °C. 1HN M R (1H-DMSO)δ = 8.31 (2H, 5-CH2), 7.62 (2H, 6-CH2), 7.81–7.78 (m, 2H, Ar), 3.05 (t, 2H, 9-CH2), 2.13 (s, 3H, 1-Me), 1.76 [m, 4H, 7,8-(CH2)2]. Compound 5c was involved into the next step without further purification.

Reaction of 2-methoxypyridines 5b,c with phenylacetonitrile. A solution of 2-methoxy pyridine (25 mmol) and phenacyl bromide (20 mmol) in acetonitrile (250 ml) was prepared according to the described procedure11 (using H2SO4 as a dehydrating agent) (Scheme 4), and evaporated to dryness. The reaction mixture was kept for 16 h at room temperature. The precipitate was filtered off and recrystallised from acetonitrile. All compounds gave satisfactory elemental analysis data. Crystal structures of the compounds 5a–c and 6a–c are shown in Figure 1. Other characteristics of 5-alkoxyindolizines 2–4 are given in Table 1.

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