Oxazolo[3,2-*a*]pyridinium and oxazolo[3,2-*a*]pyrimidinium salts in organic synthesis

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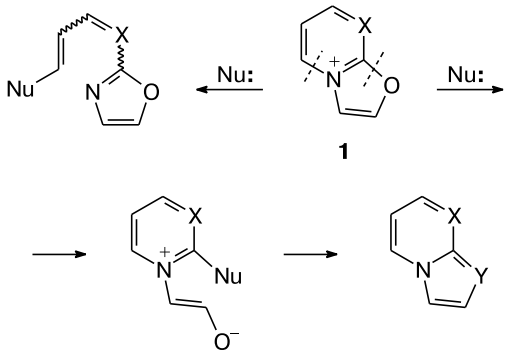
The methods for the synthesis of oxazolo[3,2-*a*]pyridinium and oxazolo[3,2-*a*]pyrimidinium salts and their reactivities are reviewed. Both systems exhibit ambident properties in reactions with nucleophiles; depending on the substituents and the reagents, both the oxazole and azine rings can undergo opening and transformations. A number of new methodologies involving oxazolopyridinium and oxazolopyrimidinium salts for the design of functionalized oxazoles, imidazoles, fused pyrroles, and other heterocyclic systems are generalized.

Key words: recyclization, oxazole, pyridine, pyrimidine, pyrrole, indolizine, fused rings.

One of the main features of aromatic heterocycles is their tendency (in contrast to carbocycles) toward heterolytic ring opening *via* cleavage of a carbon—heteroatom bond. The resulting acyclic fragment is often capable of undergoing cyclization into a new ring. As a rule, such a recyclization of one heterocycle into another is a single-step process leading to otherwise inaccessible structures with unusually arranged functional groups. The well-known examples of recyclization include the Yur´ev reaction, the Hafner reaction, and the Dimroth, Kost—Sagitullin, and Boulton—Katritzky rearrangements.[1] A number of our reviews[2—4] have been devoted to the general structural classification of recyclization reactions. Recyclization is widely used in modern organic synthesis as a nontrivial strategy for the targeted preparation of biologically active compounds, dyes, and compounds with other valuable properties. A search for new recyclization examples is still of current interest for organic chemists.

In the general case, bond cleavage in a monocyclic heterocycle can involve different positions of the ring to give various acyclic compounds (or recyclization products). Opening of fused rings consisting of at least two fused heterocycles can follow a more complicated pattern. In this case, any of the annulated heterocycles can undergo opening and recyclization so that the opening pathway is difficult to predict. An interesting model system with dissimilar rings capable of opening and recyclization is the class of cationoid heteroaromatic systems **1** with the bridgehead nitrogen atom, in which the oxazole fragment is fused with the pyridine (X = CH) or pyrimidine ring (X = N). It is well known that monocyclic oxazolium, pyridinium, and pyrimidinium cations readily undergo ring opening under the action of various nucleophiles; in bicyclic salts **1**, competitive opening of the azole and azine rings seems to be possible (Scheme 1, also see the reviews[5—7]).

Scheme 1



Potentially ambident cations **1** could serve as promising reagents for the synthesis of various classes of heterocycles (substituted azoles, azines, and azoloazines). The present review is devoted to development of synthetic routes to fused systems **1**, study of the regularities and the factors that influence the regioselectivity of ring opening, and ways of controlling such processes.

1. Methods for the synthesis of oxazolo[3,2-*a*]pyridinium salts

1.1. Known strategies

Oxazolo[3,2-*a*]pyridinium salts **2** were first obtained from *N*-phenacyl-2-pyridones **3** in the presence of conc. H_2SO_4 according to reaction *2a* (Scheme 2).[8,9]

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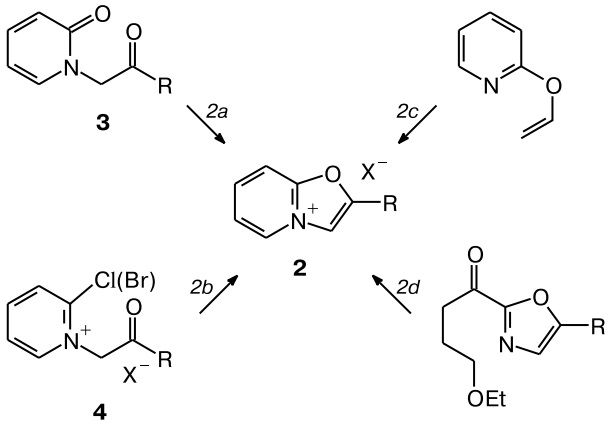
Scheme 2



X = Cl, Br

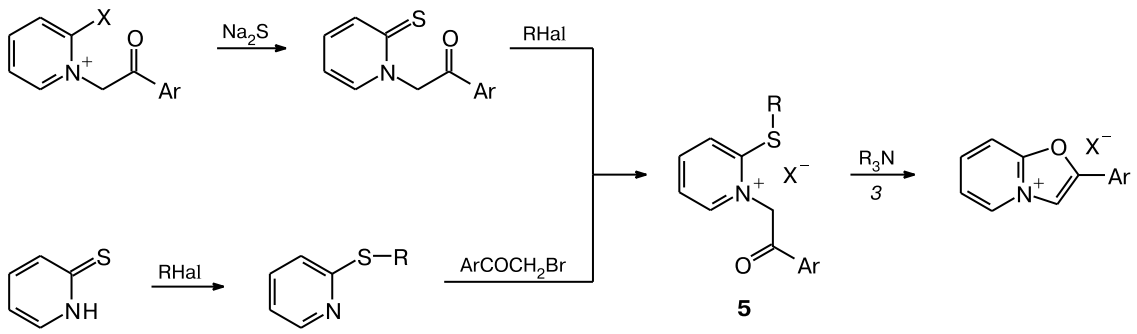
Reagents and conditions: (*2a*) H_2SO_4, $HClO_4$; (*2b*) R'_3N or picoline; (*2c*) Br_2, Δ, R = H; (*2d*) HBr, Ac_2O.

Later, this system was alternatively synthesized by a reaction of 2-halo-1-phenacylpyridinium salts **4** with various tertiary amines:[10,11] triethylamine, *N*,*N*-dimethylaniline, diisopropyl(ethyl)amine, or α-picoline (reaction *2b*). Bicyclic compound **2** can also be constructed in two other (less common) ways: closure of an oxazole ring from 2-(vinyloxy)pyridine[12] (reaction *2c*) and closure of a pyridine ring in reaction *2d* (see Ref. 13). It should be noted that reaction *2b* has been recently[14,15] modified by using sulfur-containing pyridinium salts **5** instead of halopyridinium salts **4** (Scheme 3, reaction *3*). A version of this reaction involves immobilization of the above salts on the solid-phase support.

We found another, very unusual example of the formation of an oxazolopyridinium salt in a reaction of a thiazolopyridinium salt with an aromatic amine[16,17] (Scheme 4).

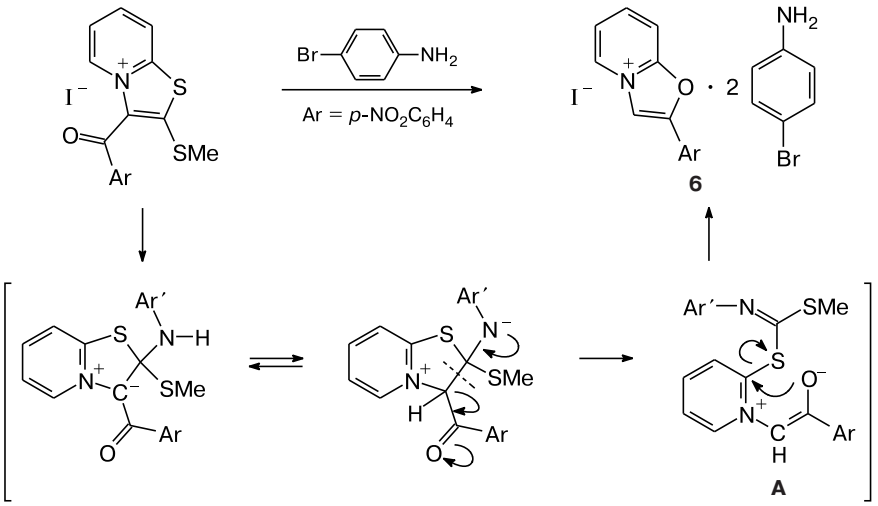
Compound **6** was isolated which turned out to be a complex of an oxazolopyridinium salt with 4-bromoaniline (X-ray diffraction data). During the reaction, the framework of the starting reagent loses the fragment MeSCS. The unexpected formation of the oxazole ring from the thiazole one can be explained only by the formation of intermediate *N*-phenacylpyridinium betaine (*e.g.*, **A**)

Scheme 3



X = Cl, Br
RHal = MeI or the Merrifield resin

Scheme 4



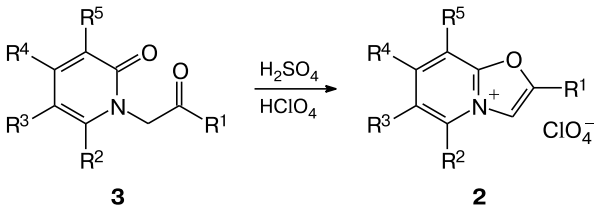
that undergoes cyclization by eliminating a leaving group from the α-position (dithiocarbamate residue).

1.2. Synthesis of oxazolo[3,2-*a*]pyridinium salts by cyclization of *N*-substituted pyridones

Among the aforementioned synthetic strategies leading to oxazolopyridinium salts **2** (see Schemes 2—4), pathway *2a* involving cyclization of *N*-(2-oxoethyl)pyridones **3** should be preferred. As a rule, the residue CH_2COR at the nitrogen atom is the phenacyl group. Closure of the oxazole ring in such pyridones easily occurs in conc. H_2SO_4 (such a cyclization is analogous to the Gabriel synthesis of monocyclic oxazoles) and the resulting salts can be easily isolated as insoluble perchlorates. This cyclization can be complicated by the sulfonating ability of H_2SO_4. For instance, an attempted synthesis of an oxazolopyridinium salt containing a *p*-anisyl residue at the C(2) atom gave a sulfo derivative and in a cyclization of pyridone with a diphenyl residue, sulfonation was prevented only by careful heating of the reaction mixture in conc. $HClO_4$.[9] Analogous cyclizations of benzopyridones proceed smoothly for isoquinolone (Scheme 5, reaction *5a*).[9] In the case of quinolones, they follow usual (reaction *5b*)[9] or anomalous pathways (reaction *5c*),[18] depending on the presence of electron-donating substituents in the phenacyl residue.

We studied the possibility of obtaining in this way various oxazolopyridinium salts containing aromatic, aliphatic, arylaliphatic, and heterocyclic substituents in the five-membered ring and (cyclo)alkyl substituents and/or electron-withdrawing substituents in the six-membered ring (Scheme 6, Table 1). The yields from these cyclocondensations are usually very high (sometimes, up to 100%). In some cases, addition of an equimolar amount of 30% oleum to H_2SO_4 was efficient. The structures of the resulting salts were unambiguously confirmed by ^1H NMR data: upon the aromatization, the signal for N—CH_2 of pyridone (2 H intensity) changes into a low-field singlet for the H(3) atom of oxazole (1 H intensity) (see Table 1). The structures of 12 perchlorates were proved by X-ray diffraction analysis.

Scheme 6

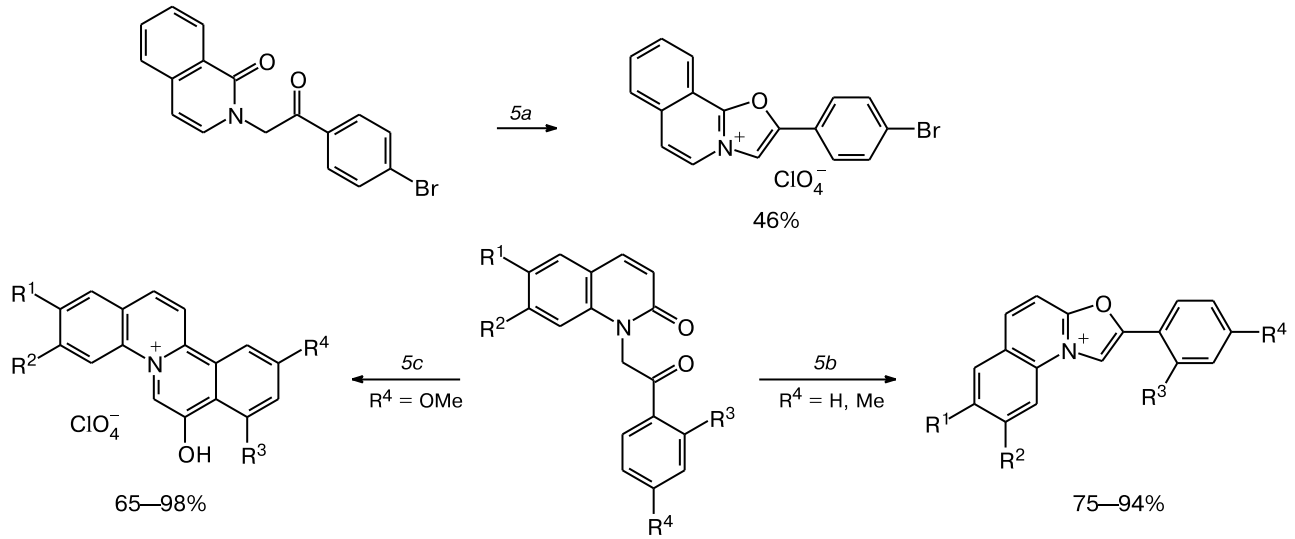


3 **2**

For pyridones with labile (under acid hydrolysis conditions) substituents, side processes could be expected. It turned out that the cyclization rates of *N*-phenacyl derivatives of 2-oxonicotinonitrile, 2-oxonicotinamide, and ethyl 2-oxonicotinate (Scheme 7) are higher than the hydrolysis rates of their functional groups.[23,32]

However, the cyclization rates of the cyclic homologs of such compounds were lower than their hydrolysis rates; as the result, the cyclization of nitriles yielded amides[33—35] (Scheme 8).

Scheme 5



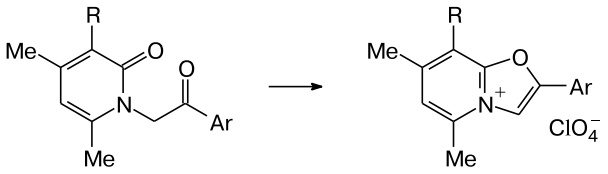
Reagents: H_2SO_4, $HClO_4$.

Table 1. Synthesis of oxazolopyridinium salts **2** and the starting pyridones **3**

Substituents					Salt **2**		Pyridone **3**		References
R^2	R^3	R^4	R^5	R^1	Yield (%)	H(3), δ[a]	Yield (%)	Reaction	
H	H	H	H	C_6H_5	83	8.63	85 (71)[b]	*9a*	19—21
H	H	H	H	*p*-BrC_6H_4	89	8.70	87 (62)[b]	*9a*	
H	H	H	H	*m*-$NO_2C_6H_4$	68	8.87	92 (51)[b]	*9a*	
H	H	H	H	*p*-$NO_2C_6H_4$	70	8.92	80 (54)[b]	*9a*	
Me	H	H	H	*p*-BrC_6H_4	79	8.50[c]	31	*9c*	21—23
Me	H	H	H	*p*-$NO_2C_6H_4$	69	8.86[c]	57—67	*9c*	
Me	H	H	H	C_6H_5	72	8.50[c]	14	*9c*	
Me	H	H	H	*p*-ClC_6H_4	46	9.49	48	*9c*	
Me	H	H	H	3,4-$Cl_2C_6H_3$	88	9.58	27	*9c*	
Me	H	Me	H	*p*-$NO_2C_6H_4$	83	9.68	39	*9c*	24, 25
Me	$(CH_2)_4$		H	*p*-BrC_6H_4	90	9.42	38	*9c*	
$(CH_2)_3$		Me	H	*p*-ClC_6H_4	98	9.33	42	*9c*	26, 27
$(CH_2)_4$		Me	H	*p*-ClC_6H_4	98	9,37	40	*9c*	28, 29
$(CH_2)_5$		Me	H	*p*-ClC_6H_4	97	9.58	58	*9c*	27, 30
$(CH_2)_6$		Me	H	*p*-ClC_6H_4	96	9.52	42	*9c*	31
$(CH_2)_4$		Me	H	*p*-$NO_2C_6H_4$	95	9.63	55	*9c*	28
Me	NO_2	Me	H	*p*-ClC_6H_4	92	9.72	6	*9c*	17
Me	H	Me	CN	*p*-BrC_6H_4	82	9.61	42	*9j*	23, 32
Me	H	Me	$CONH_2$	*p*-BrC_6H_4	74	9.43	34	*9j*	23
Me	H	Me	CO_2Et	*p*-BrC_6H_4	81	9.51	24	*9j*	23
$(CH_2)_3$		H	$CONH_2$	*p*-ClC_6H_4	97	9.50	45	*9j*	33
$(CH_2)_4$		H	$CONH_2$	*p*-ClC_6H_4	98	9.52	43	*9j*	34
$(CH_2)_5$		H	$CONH_2$	*p*-ClC_6H_4	96	9.76	21	*9j*	35
H	NO_2	H	H	*p*-MeC_6H_4	94	9.11	51	*9j*	36
H	NO_2	H	H	*p*-$NO_2C_6H_4$	66	9.18	38	*9j*	
H	NO_2	H	H	*p*-ClC_6H_4	95	9.13	79	*9j*	
H	H	H	H	*p*-$ClC_6H_4CH_2$	87	8.64	90	*13*	16, 37
H	H	H	H	*p*-$NO_2C_6H_4CH_2$	84	8.71	91	*13*	
H	H	H	H	Me	42	8.56	67	*13*	
H	H	H	H	Et	67	8.61	52	*13*	
H	H	H	H	4-Py	96	8.63	95	*13*	

[a] In DMSO-d_6. In CF_3COOH.
[b] The yield of chloropyridinium salt **4** is given in parentheses.
[c] In CF_3COOH.

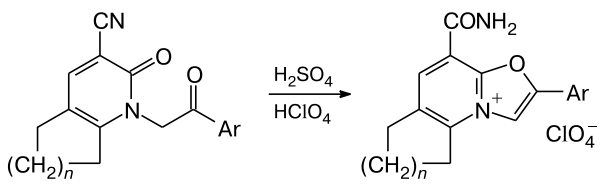
Scheme 7



R = CN, $CONH_2$, CO_2Et

Reagents and conditions: H_2SO_4, $HClO_4$, 30 min.

Scheme 8



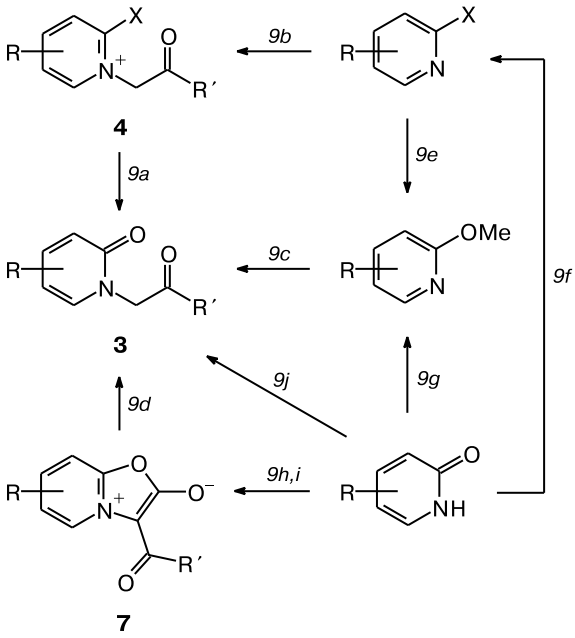
1.3. Distinctive features of the synthesis of intermediate *N*-(2-oxoethyl)pyridones 3

Since these are *N*-(2-oxoethyl)pyridones **3** that are key intermediates in the preparation of bicyclic oxazolopyridinium salts (see Scheme 6), let us briefly consider the methods of their synthesis (Scheme 9, see Table 1).

The simplest route to pyridones **3** involves the hydrolysis of 2-halopyridinium salts **4** (Scheme 9, reaction *9a*).[19,20] Salts **4** can be easily prepared by quaternization of 2-halopyridines (reaction *9b*); however, this method is unsuitable for sterically hindered pyridines.[22]

An efficient route to pyridones **3** containing a second α-substituent involves *N*-alkylation of 2-methoxypyridines (reaction *9c*). In this case, the OMe group serves as a protective function and the reaction is accompanied by demethylation. 2-Methoxypyridines are easily prepared from 2-halopyridines and sodium meth-

Scheme 9

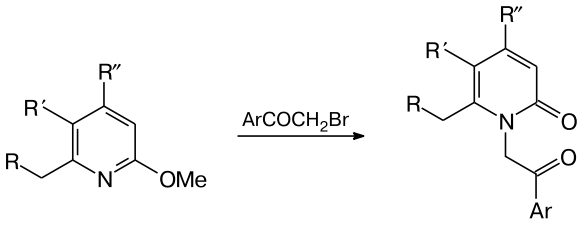


X = Cl, Br

Reagents: (*9a*) NaOH, H_2O/EtOH; (*9b*, *9c*) R´$COCH_2Br$; (*9d*) H_3O^+; (*9e*) MeONa/MeOH; (*9f*) $POCl_3$; (*9g*) Ag_2CO_3, MeI; (*9h*) NaOH/$ClCH_2COOH$; (*9i*) $Ac_2O/HClO_4$, R_3N/R´COCl; (*9j*) 1) NaOH, H_2O/EtOH, 2) R´$COCH_2Br$.

oxide (reaction *9e*) or by methylation of silver pyridinolates (reaction *9g*). We employed this strategy to obtain a large number of α-alkylpyridones **3** (and their cyclic homologs)[22,23,25,27] and the corresponding salts **2** (Scheme 10). Sterically hindered 2-alkyl-6-methoxypyridines are alkylated in moderate to high yields (see Table 1).

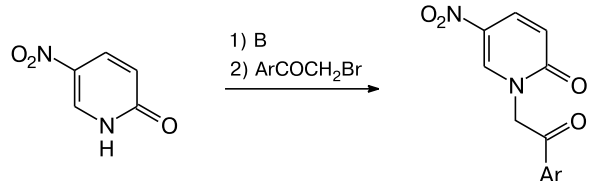
Scheme 10



Direct phenacylation of sodium salts of pyridones (reaction *9j*) was efficient to obtain pyridones **3** containing an electron-withdrawing β-substituent in the ring. For instance, alkali metal salts of 5-nitro-2-pyridone are alkylated regioselectively at the N atom (Scheme 11).[36]

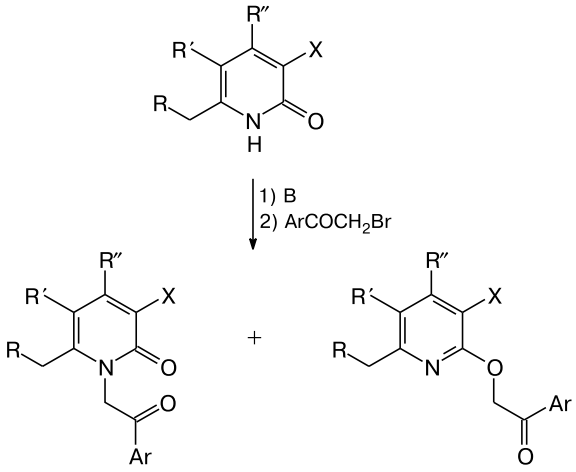
Alkylation of pyridones combining an electron-withdrawing group in the β-position and a second α-substituent (methyl group or an alicyclic fragment), gives mixtures of *O*- and *N*-phenacyl derivatives (Scheme 12).[23,35,38] Preparatively, such mixtures are not difficult to separate: the *O*-isomers are more soluble and chromatographically mobile, which allows easy isolation of the *N*-isomers **3** in the individual state.

Scheme 11



B is a base

Scheme 12



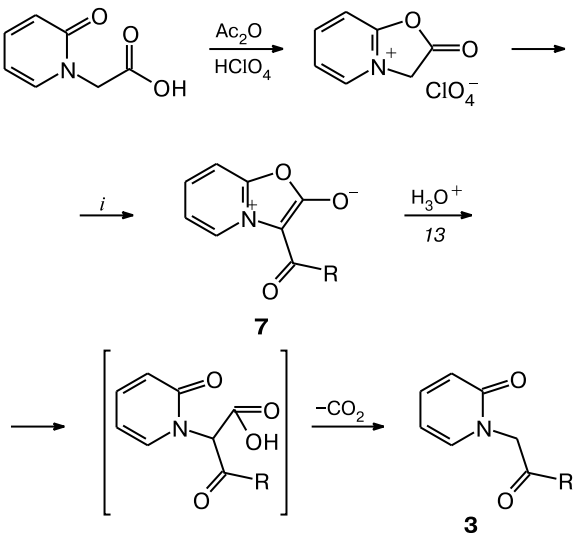
X = CN, $CONH_2$, CO_2Et
B is a base

The last strategy in the synthesis of pyridones **3** involves hydrolytic opening of the oxazolone ring in mesoionic oxazolopyridinium-2-olates **7** (see Scheme 9, reaction *9d*).[37,39,40] Bicyclic münchnones **7** are prepared from (2-oxopyridyl)acetic acid and acid anhydrides (chlorides) (Scheme 13).

Structurally, the overall sequence of transformations in Scheme 13 resembles the Dakin—West conversion of an amino acid into an amino ketone, provided that (2-oxopyridyl)acetic acid is regarded as a peculiar amino acid. This step sequence has a number of distinct advantages over the methods discussed above (see Scheme 9, reactions *9a*, *9c*, *9j* and Schemes 10—12). First, no lachrymatory bromo ketones are employed; second, the resulting pyridones can contain at the N atom such a methyl ketone residue (*e.g.*, that of benzyl methyl ketone or 4-acetylpyridine) that is otherwise difficult (or impossible) to introduce into structure **3**.

Thus, Scheme 6 provides a reliable route to oxazolopyridinium salts **2** starting from N-substituted pyridones **3**, which in turn can be prepared in various ways. This meth-

Scheme 13



i. Et_3N, $(RCO_2)O$ or Et_3N, RCOCl

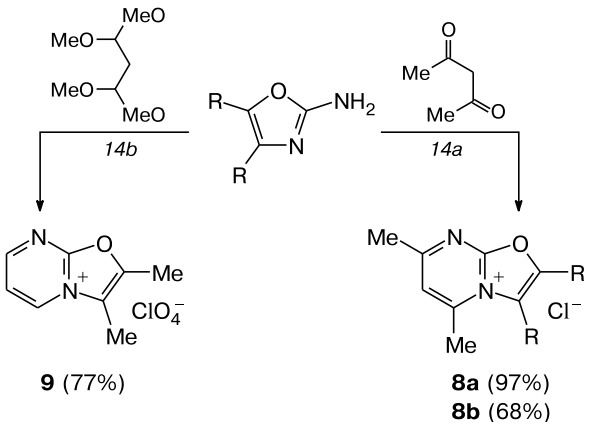
odology allows broad variation of the nature of the substituents in the pyridine and oxazole fragments of salts **2**.

2. Methods for the synthesis of oxazolo[3,2-*a*]pyrimidinium salts

2.1. Synthesis from oxazoles

Oxazolo[3,2-a]pyrimidinium salts, which are aza analogs of salts **2**, can be obtained by constructing the second ring on both oxazoles and pyrimidines. Condensation of accessible 2-aminooxazoles with acetylacetone gave salts **8a,b** (Scheme 14, reaction *14a*).[41] Condensation of aminoazoles and aminoazines with 1,3-dicarbonyl compounds leading to cationoid bicycles is well known, being a general method for their synthesis.[42,43]

Scheme 14



Reagents and conditions: (*14a*) HCl, R = Ph (**8a**), Me (**8b**); (*14b*) HCl, Δ, $HClO_4$, R = Me.

We used this strategy[17] in the synthesis of novel oxazolopyrimidinium salt **9** containing no substituent in the pyrimidine fragment: the target salt was obtained by condensation of 2-amino-4,5-dimethyloxazole with malondialdehyde acetal (reaction *14b*).

2.2. Synthesis from pyrimidines

An alternative route to the salts in question (construction of an oxazole ring on the pyrimidine one) has been described by Liebscher group.[44,45] The key intermediate was *N*-phenacylpyrimidine-2-thione prepared in a rather unusual fashion (Scheme 15); such pyrimidinethiones were converted in two different ways (*15a* and *15b*) into oxazolo[3,2-*a*]pyrimidinium salts **10**. It should be emphasized that the chemical properties of salts **8** and **10** have not been studied in the cited papers.[41,44,45]

During the multistep transformation (see Scheme 15), the pyrimidine fragment of the target oxazolopyrimidines **10** is originally assembled in a very complicated way, presenting a striking contrast to the simple reaction sequence in the synthesis of their pyridine analogs **2**: pyridines→*N*-alkylpyridones→oxazolopyridinium salts. We wondered whether oxazolopyrimidinium salts could be directly obtained from easily accessible pyrimidone (by analogy with the aforesaid tandem of reactions shown in Schemes 6 and 9 (reaction *9j*)).

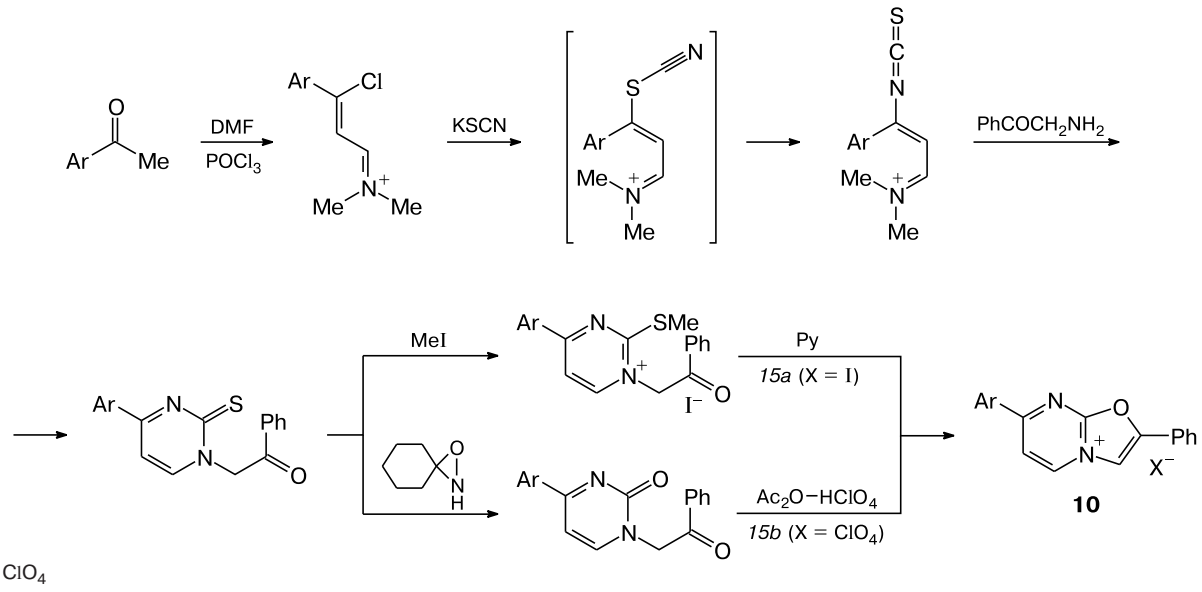
It turned out (Table 2)[46] that alkali metal salts of 2-pyrimidone undergo high-yielding regioselective *N*-phenacylation (Scheme 16, reaction *16a*). The IR spectra of the resulting compounds **11** contain two groups of CO vibrations ($CH_2C{=}O$ and $N{-}C{=}O$). The structure of one N-isomer was confirmed by X-ray diffraction analysis.[47]

Table 2. Synthesis of oxazolopyrimidinium salts from 2-pyrimidone[46]

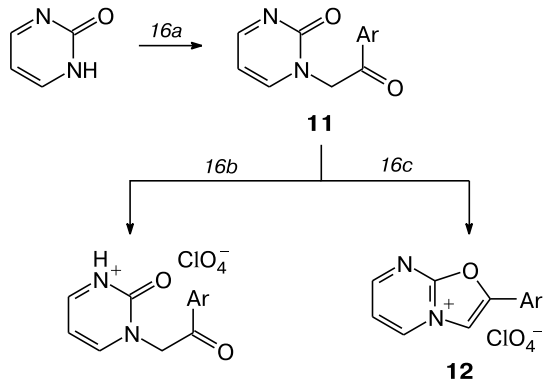
Ar	Pyrimidone **11**		Salt **12**	
	Yield (%)	δ_{NCH_2}[a]	Yield (%)[b]	$\delta_{H(3)}$[a]
p-ClC_6H_4	90	5.48	90	9.31
p-BrC_6H_4	95	5.43	85	9.31
p-$NO_2C_6H_4$	65	5.55	80	9.50
C_6H_5	79	5.50	55 (79)[c]	9.81[d]
p-$CH_3C_6H_4$	81	5.45	75[c]	9.20
p-$CH_3OC_6H_4$	70	5.40		

[a] DMSO-d_6.
[b] $H_2SO_4 + SO_3$.
[c] CF_3SO_3H/P_2O_5.
[d] CF_3COOD.

Scheme 15



Scheme 16



Reagents and conditions: (*16a*) $ArCOCH_2Br$, K_2CO_3—Me_2CO, 20 °C, 48 h; (*16b*) Ar = *p*-ClC_6H_4, $HClO_4/Ac_2O$ or $H_2SO_4/HClO_4$, or polyphosphoric acid/$HClO_4$; (*16c*) $H_2SO_4 \cdot SO_3/HClO_4$, CF_3SO_3H—P_2O_5, $HClO_4$—H_2O, Ar = Ph, *p*-MeC_6H_4.

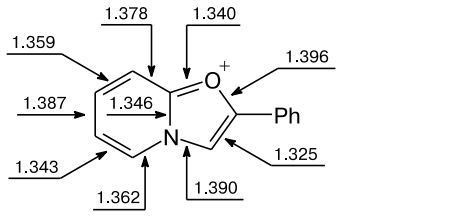
Cyclocondensation of compounds **11** into salts **12** has been carried out[46] under the action of oleum. With H_2SO_4 or polyphosphoric acid, reaction *16b* stops at the protonation step. To avoid sulfonation for Ar = Ph and *p*-MeC_6H_4, we used CF_3SO_3H—P_2O_5 as an efficient dehydrating agent. The ^1H NMR spectra of salts **12** show a characteristic low-field signal for the oxazole proton at δ 9.2—9.8; the structure of one salt was proved by X-ray diffraction analysis.[48]

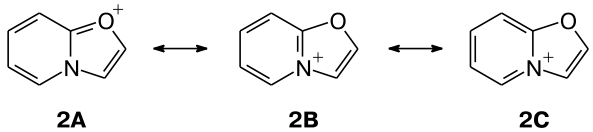
Thus, the above strategies allow oxazolopyrimidinium salts to be obtained from both oxazoles and pyrimidines. The substituents in positions 2, 3, 5, and 7 of the bicycle can be varied by using different synthetic strategies.

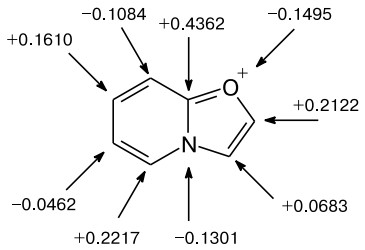
3. Structure and reactivity of oxazolopyridinium salts

3.1. Structure of salts 2

It follows[49] unambiguously from X-ray diffraction data for salts **2** that the pyridine fragment of the bicyclic compound exhibits a slight quasidiene character. Therefore,







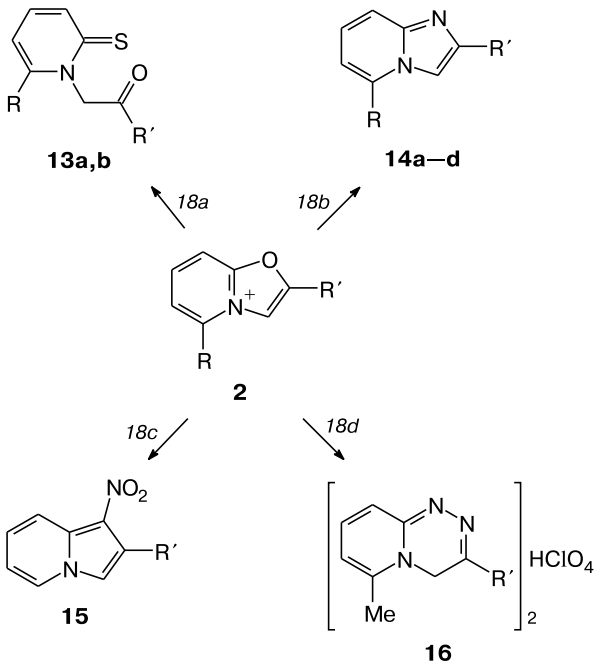
the structure of this aromatic system is accurately described by superposition of resonance structures **2A** and **2B** (not **2C**) with the positive charge delocalized over the chain of the atoms N—C(9)—O. According to quantum chemical calculations,[20,21,50,51] the greatest positive charge is localized on the bridgehead C(9) atom. That is why nucleophiles should be expected to attack this position with subsequent opening of the oxazole ring.

3.2. Reactions of oxazolopyridinium salts 2 with nucleophiles

Before our investigations, reactions of salts **2** with nucleophiles included only a few documented examples (Scheme 17). It has been mentioned[11] that the oxazole ring in salt **2** undergoes opening in the presence of alkali (reaction *17a*) to give *N*-phenacyl-2-pyridone in a nearly quantitative yield. In some cases, the opening of the oxazole ring was accompanied by closure of a new ring. For instance, prolonged reflux of salt **2** in *n*-butylamine transformed the oxazole ring into an imidazole one (reaction *17b*) to give a 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium salt;[10] no analogous recyclization with aniline occurs. On short-time reflux in *n*-butylamine (10 min), the intermediate of this transformation can be isolated: this is a cyclic hydrate that undergoes dehydration and aromatization under the action of polyphosphoric acid. The formation of imidazo[1,2-*a*]pyridinium salts can be promoted by other primary amines.[52] Reactions with phosphorus- and arsenic-containing nucleophiles (reactions *17c*,*d*) afford very uncommon azolopyridines with the ring P or As atoms.[53]

Insofar as the range of the nucleophilic agents used was not representative enough, we studied reactions of salts **2** with simple O-, N-, S-, and C-nucleophiles. In all the cases, a nucleophilic attack follows an analogous pattern, with opening (and/or recyclization) of the oxazole ring (Scheme 18). Salts **2** reacted with sodium hydrosulfide[23,51] (reaction *18a*) to give the corresponding pyridinethiones **13**, which are inaccessible (*e.g.*, **13b**) *via* direct *N*-alkylation of pyridine-2-thione. Reactions of salts

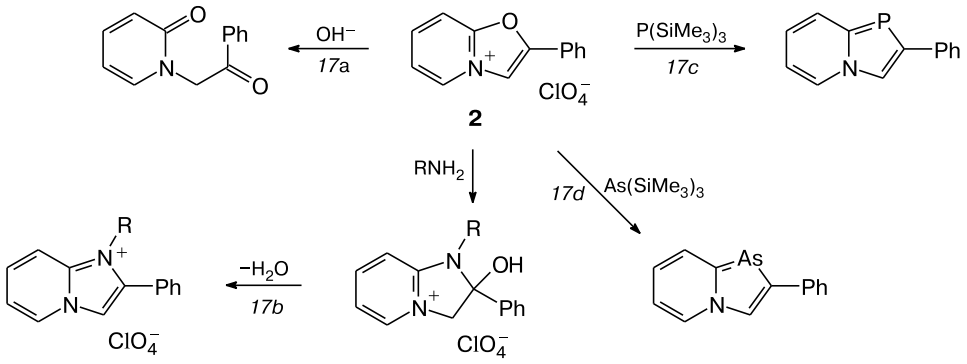
Scheme 18



Compound	R	R′	Yield (%)
13a	H	Ph	90
13b	Me	3,4-$Cl_2C_6H_3$	52
14a	H	Ph	60—80
14b	Me	*p*-$NO_2C_6H_4$	98
14c	H	γ-Py	10
14d	H	*p*-$ClC_6H_4CH_2$	40
15	H	Ph	74
16	Me	*p*-$NO_2C_6H_4$	78

Reagents: (*18a*) NaSH; (*18b*) NH_3/DMF; (*18c*) $MeNO_2$, K_2CO_3; (*18d*) N_2H_4.

Scheme 17



R = Bu^n, $PhCH_2$

2 with ammonia (reaction *18b*) give, through the ring opening and recyclization steps, a new imidazole ring.[23,37,51,54] 5-Methylimidazopyridine **14b** is obtained in a virtually quantitative yield. (An alternative synthesis by cyclocondensation of 2-amino-6-methylpyridine with phenacyl bromide affords this compound in very low yield.) Also note that imidazopyridines with the γ-pyridyl (**14c**) or benzyl residues (**14d**) are difficult to obtain in an alternative way (*e.g.*, according to the Chichibabin scheme). Reactions of salts **2** with nitromethane[55] (reaction *18c*) result in the recyclization of the oxazole ring into a pyrrole one; this reaction is a new route to indolizines (nitroindolizine **15** is difficult to obtain by direct nitration of 2-phenylindolizine). Reaction *18d* of salt **2** with hydrazine gives 1,4-dihydropyrido[2,1-*c*]-1,2,4-triazinium perchlorate **16**, which constitute an unusual heterocyclic system.[54] The base—perchloric acid ratio in the product was 2 : 1. Interestingly, according to X-ray diffraction data, the arrangement of the bicyclic structures in the crystal packing of compound **16** makes it impossible for pairs of its molecules to be linked by linear N—H—N hydrogen bonds.

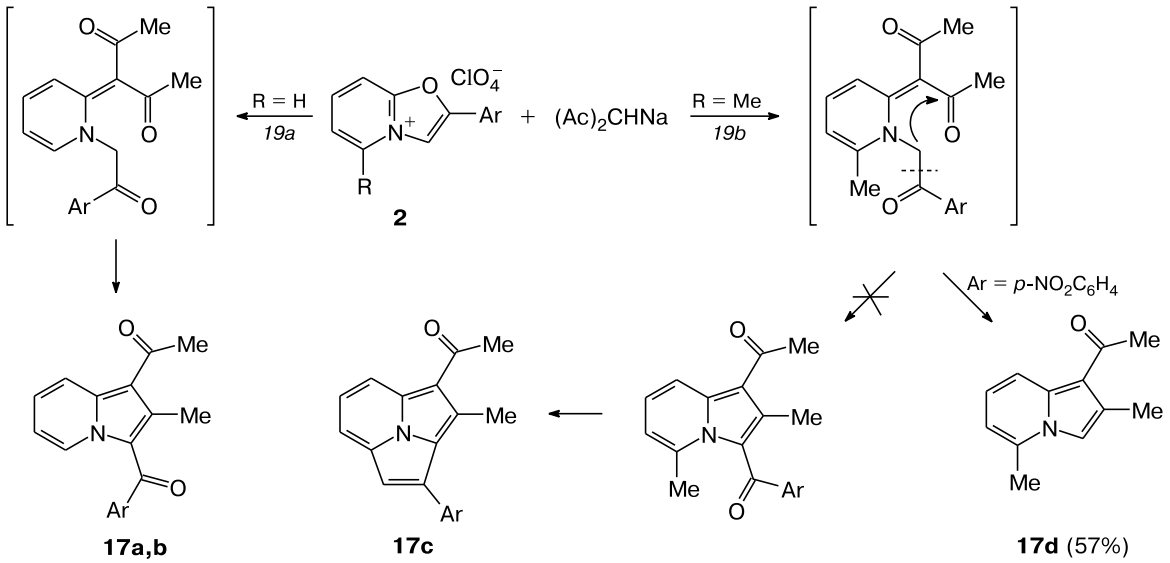
In reactions with the acetylacetonate anion, salts **2** undergo transformations into indolizines **17a,b** (Scheme 19, pathway *19a*).[56] The reaction scheme involves a nucleophilic attack of a carbanion resulting in opening of the oxazole ring. In the reaction intermediate, an acetyl group acts as a carbonyl component in condensation with the methylene fragment of the *N*-phenacyl residue. The proposed new scheme of construction of the indolizine framework can be formally regarded as the formation of two bonds, C(2)—C(3) and C(9)—C(1), in the pyrrole fragment. With a homologous salt (pathway *19b*), further cyclization of an analogous indolizine into cyclazine **17c** could not be excluded. However, according to X-ray diffraction data,[57] the reaction product was 1-acetyl-2,5-dimethylindolizine **17d** (*i.e.*, the formation of indolizine *via* closure of the pyrrole ring is accompanied by elimination of the *p*-nitrobenzoyl residue, probably because of the steric hindrance created by the methyl group).

For rational classification of the types of possible transformations of salts **2**, we should introduce the following definitions.[40] By convention, let nucleophiles be classified under the "XH type" if their anions contain at least one extra H atom (XH^- = OH^-, SH^-, RNH^-, $NO_2CH_2^-$, and Ac_2CH^-) or under the "X type" if the anion contains no extra proton (X^- = RO^- or R_2N^-). In all the reactions studied above, we used XH-type nucleophiles. As the result, upon the ring opening in adduct **18a** (Scheme 20), unstable ylide **18b** can be stabilized by an extra proton of the XH group through tautomerization into covalent structure **18c**.

The atom at which subsequent cyclizations occur is determined by the nature of the residue X. Obviously, for X-type nucleophiles, an analogous transformation of ylide **19** into any covalent structure is impossible. We found it interesting to study reactions of salts **2** with X-type nucleophiles.

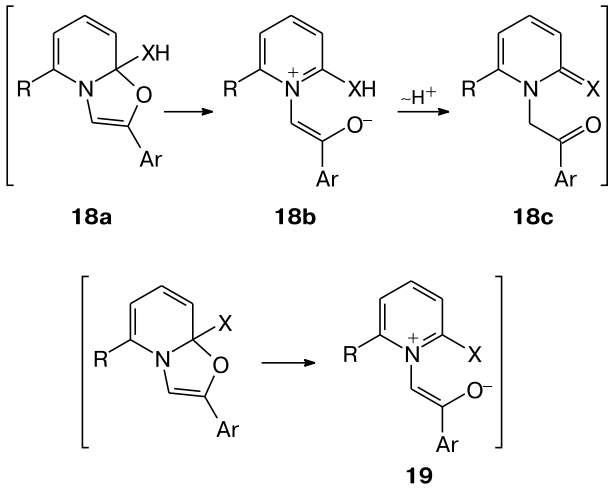
It turned out that salts **2** react with such nucleophiles (alkoxide or secondary amines) in an uncommon way (Scheme 21). A reaction of salt **2** with sodium methoxide (reaction *21a*) gives ketal **20**,[58] while reactions of salts **2** with secondary amines (reaction *21b*) yields amino dienes **21** (Table 3).[19—21]

Scheme 19

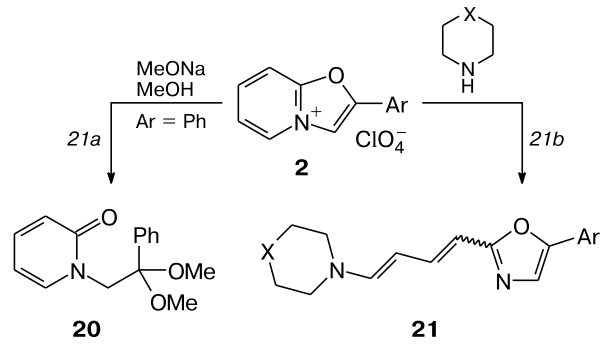


Ar = Ph (**17a**), 55%; *p*-$NO_2C_6H_4$ (**17b**), 15%

Scheme 20



Scheme 21



Dienes with the *p*-nitrophenyl residue (in contrast to compounds containing other aryl substituents) are colored deep dark cherry, probably because of intramolecular charge transfer. In the mass spectra of amino dienes, the peak $[M - NR_2]$ is most intense (apparently, because of cyclization into aromatic cation **2**). The stereochemistry of dienes, determined from NOESY spectra in C_6D_6 and X-ray diffraction data,[59] depends on the conditions for their synthesis and isolation. Short-time stirring of the neat reagents at room temperature gives butadienes with the 1*E*,3*Z*-configuration, while reflux of the reagents in MeCN yields 1*E*,3*E*-dienes. On keeping the solutions of the dienes, the 1*E*,3*Z*-isomer undergoes a slow transformation into the 1*E*,3*E*-isomer. The higher thermodynamic stability of the *trans-trans* isomer is confirmed by quantum chemical calculations of the enthalpies of formation of the isomeric molecules.

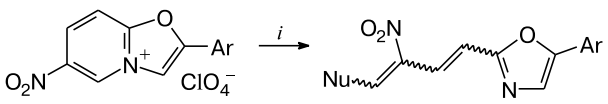
Table 3. Characteristics of 1-amino-4-(oxazol-2-yl)buta-1,3-dienes (**21**)

Ar	X	Yield (%)	λ_{max} (log ε), EtOH	*m/z* (I_{rel} (%))	
				M^+	$M - NR_2$
Ph	CH_2	67	382 (4.38)	280 (34)	—
p-BrC_6H_4	CH_2	70	391 (4.47)	360/358 (46/40)	276/274 (94/100)
m-$NO_2C_6H_4$	CH_2	68	400 (4.37)	325 (47)	241 (100)
p-$NO_2C_6H_4$	CH_2	81	464 (4.88)	325 (63)	241 (100)
	$(CH_2)_2$	96	475 (4.33)	339 (63)	241 (100)
	O	62	439 (4.34)	327 (40)	241 (100)

Unusual opening of salts **2** in Scheme 21 should be associated with the fact that the formation of intermediate ylide **19** (in the case of a nucleophilic attack on the C(9) atom) is thermodynamically unfavorable. As the result, the nucleophilic attack occurs either at the C(2) atom (for MeONa) followed by addition of a methanol molecule to the intermediate or at the C(5) atom (for amines) followed by opening of the adduct into diene **21**. Our quantum chemical calculations[20,51,58] confirmed that the energies of the adducts and the open species depend on the nature of the nucleophile.

Interestingly, when oxazolopyridinium salts contain an additional nitro group in position 6, their reactivities change dramatically. An attack of not only secondary amines but also primary amines or ammonia (Scheme 22), as well as an attack of CH acids (Scheme 23), occurs always at the C(5) atom, giving oxazole derivatives.[17,36]

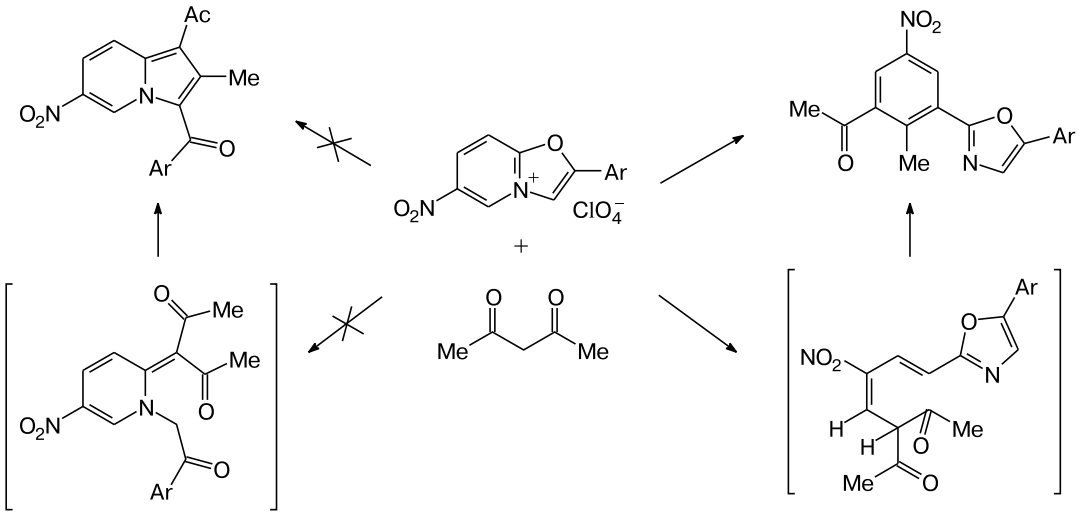
Scheme 22



i. NuH (Nu = NH_2, NHBu, piperidino, morpholino)

Thus, oxazolopyridinium salts **2** are promising reagents for the synthesis of unknown or difficult-to-obtain classes of organic compounds (Schemes 18, 19, and 21—23). Such salts are ambident systems capable of opening the oxazole or pyridine rings of the bicyclic molecule, depending on the nucleophile (XH- or X-type) and the substituent in the pyridine fragment. It remains unclear how X-type nucleophiles will react with homologous oxazolopyridinium salts **2** containing a methyl group at the C(5) atom that could present steric hindrances to an attack on the position 5.

Scheme 23

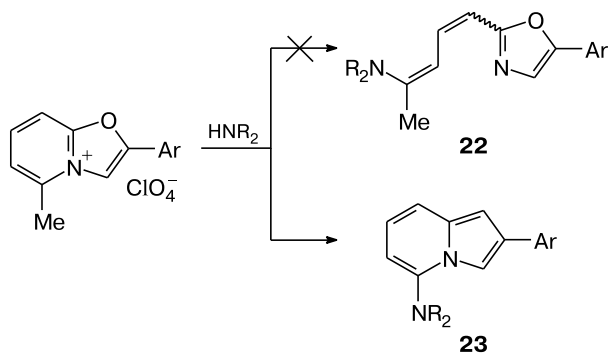


Ar = *p*-tolyl

3.3. Recyclization of 5-methyloxazolo[3,2-*a*]pyridinium salts into indolizines

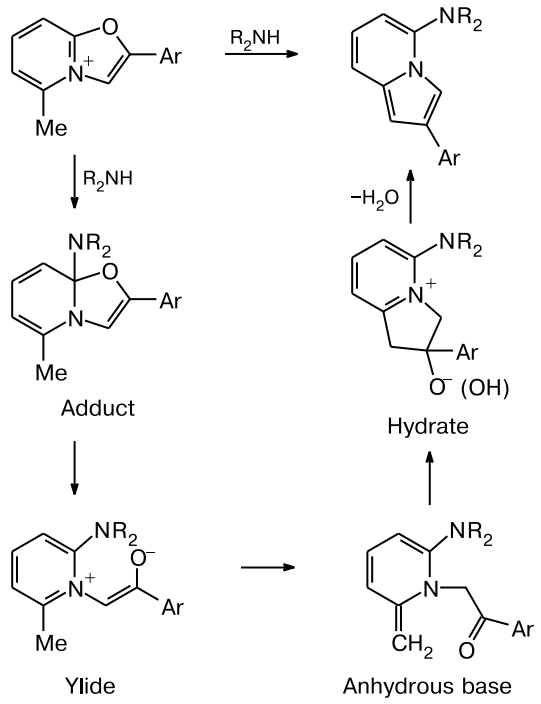
We found[60] that salts **2** containing the methyl group in position 5 react with secondary amines in a very uncommon way (Scheme 24). Instead of the expected amino dienes **22**, we obtained representatives of the novel family of 5-aminoindolizines **23**.

Scheme 24



The possible mechanism of this recyclization seems to involve an initial nucleophilic attack on the C(9) atom to give intermediate ylide (Scheme 25).[21,23] The α-methyl group (acidic CH group) of the pyridinium ylide acts as a nucleophilic site in closure of a new five-membered ring followed by aromatization of the pyrrole fragment. Using the ^{1}H NMR technique, we detected an intermediate hydrate, which forms rapidly and undergoes slow dehydration.[23]

Scheme 25



Apparently, in the reactions of salts **2** containing the 5-CH_3 group with secondary amines, the regioselectivity changes because the methyl group creates steric hindrance to a nucleophilic attack on the C(5) atom. According to calculated data,[21] the energy difference between the adducts at positions 5 and 9, which is small for 5-unsubstituted salts, increases substantially for 5-methyl derivatives so that the formation of the adduct at the C(9) atom is more favorable.

Variation of the secondary amine and the aryl residue in 5-methyloxazolopyridinium salts showed (Table 4) that reaction *26a* is of general character and provides good yields.[40] The stability of the resulting 5-aminoindolizines largely depends on the electron-withdrawing nature of the aryl residue in position 2: for Ar = *p*-$NO_2C_6H_4$ or 3,4-$Cl_2C_6H_3$, the indolizines are stable in storage; otherwise, they rapidly oxidize in air.[23,25] Another stabilizing factor is introduction of an electron-withdrawing substituent into position 6 or 8 of indolizine.

It turned out that when secondary amines are replaced by alkoxides, recyclization proceeds analogously (reaction *26b*, see Table 4) to give novel 5-alkoxyindolizines.[24] The reaction did not occur with sterically hindered high-basicity nucleophiles (*tert*-butoxide and diisopropylamine), as well as with phenoxides and secondary aromatic amines (probably because of their low nucleophilicities).

The scope of the recyclization we had discovered earlier were investigated in a study published in 2006.[62] In that study, several interesting observations were cited. It turned out that the molar amount of secondary amine required for the reaction can be lowered by adding a tertiary amine. In addition, reaction *26a* can be efficiently accelerated by microwave radiation. Finally, with an ambident reagent

Scheme 26

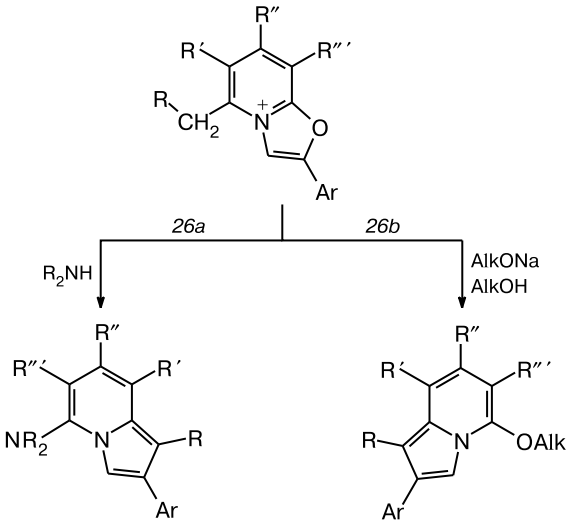


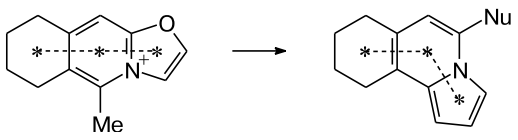
Table 4. Synthesis of 5-substituted indolizines and their (cyclo)homologs

R	R′	R″	R‴	Ar	HNR_2 or OAlk	Yield (%)	References
H	H	H	H	*p*-$NO_2C_6H_4$	Piperidine	66	21
H	H	H	H	*p*-$NO_2C_6H_4$	Hexamethylenimine	65	61
H	H	H	H	*p*-$NO_2C_6H_4$	Diethylamine	37	23
H	H	H	H	*p*-$NO_2C_6H_4$	Morpholine	79	60
H	H	H	H	*p*-$NO_2C_6H_4$	Pyrrolidine	60	23
H	H	H	H	*p*-$NO_2C_6H_4$	*N*-Methylpiperazine	74	23
H	H	H	H	*p*-BrC_6H_4	Piperidine	71	23
H	H	H	H	*p*-BrC_6H_4	Morpholine	38	23
H	H	H	H	3,4-$Cl_2C_6H_3$	Piperidine	88	23
H	H	H	H	*p*-ClC_6H_4	Piperidine	89	23
H	H	Me	H	*p*-$NO_2C_6H_4$	Pyrrolidine	45	25
H	H	Me	H	*p*-$NO_2C_6H_4$	Piperidine	83	25
H	H	Me	H	*p*-$NO_2C_6H_4$	Hexamethylenimine	63	25
H	$(CH_2)_4$		H	*p*-BrC_6H_4	Piperidine	60	25
H	$(CH_2)_4$		H	*p*-BrC_6H_4	Morpholine	25	25
$(CH_2)_3$		Me	H	*p*-ClC_6H_4	Piperidine	98	28
$(CH_2)_3$		Me	H	*p*-$NO_2C_6H_4$	Morpholine	40	28
$(CH_2)_5$		Me	H	*p*-ClC_6H_4	Piperidine	97	27
$(CH_2)_4$		Me	H	*p*-ClC_6H_4	Piperidine	72	27
H	H	Me	CN	*p*-BrC_6H_4	Morpholine	56	23
H	H	Me	$CONH_2$	*p*-BrC_6H_4	Morpholine	41	23
H	H	Me	CO_2Et	*p*-BrC_6H_4	Morpholine	35	23
$(CH_2)_3$		H	$CONH_2$	*p*-ClC_6H_4	Piperidine	87	34
$(CH_2)_4$		H	$CONH_2$	*p*-ClC_6H_4	Piperidine	67	35
H	NO_2	Me	H	*p*-ClC_6H_4	Morpholine	65	17
H	H	H	H	*p*-$NO_2C_6H_4$	MeO	66	24
H	H	H	H	*p*-$NO_2C_6H_4$	EtO	43	24
H	H	H	H	*p*-$NO_2C_6H_4$	Pr^iO	63	24
H	H	Me	H	*p*-$NO_2C_6H_4$	MeO	39	24
H	$(CH_2)_4$		H	*p*-BrC_6H_4	MeO	79	24
$(CH_2)_3$		Me	H	*p*-$NO_2C_6H_4$	MeO	62	28

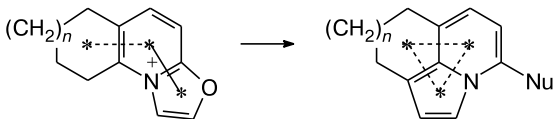
(4-aminopiperidine), it was found that the reaction involves a more nucleophilic site (secondary N atom of the diamine).

Note that we studied in detail the behavior in this recyclization of fused tricyclic salts **2** containing annulated alicyclic rings of different sizes.[27,35] Such transformations are very uncommon since they are associated with a dramatic topological reconstruction of the tricycle: during the rearrangement, a linear structure is transformed into an angular one (Scheme 27) and an angular system is transformed into a *peri*-fused tricycle (Scheme 28).

Scheme 27



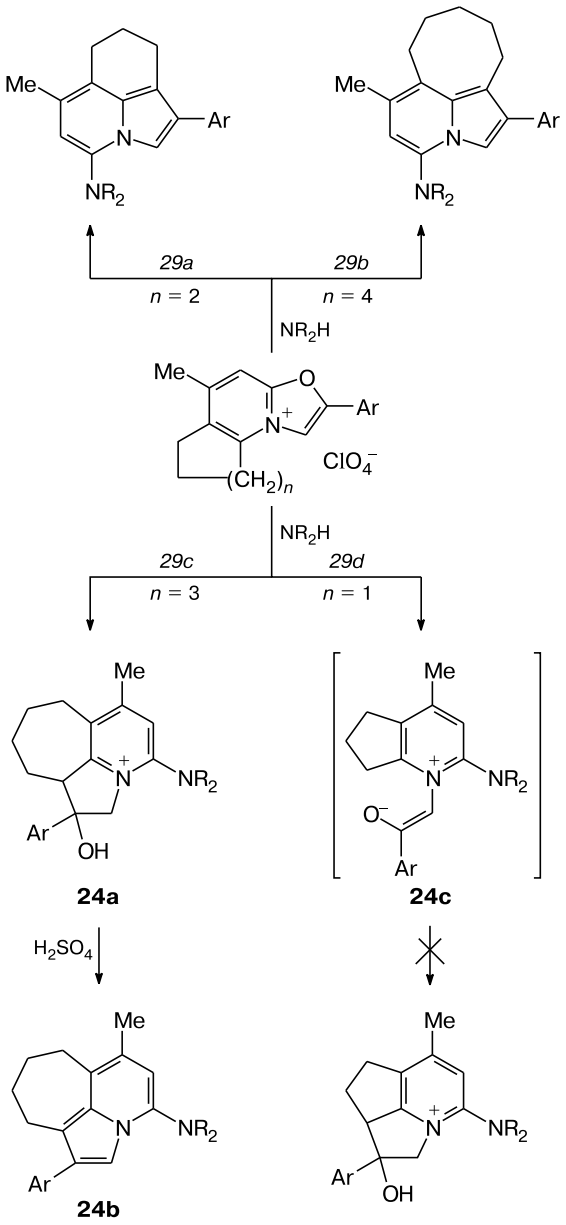
Scheme 28



Moreover, by varying the size of the alicyclic ring (Scheme 28), we determined the scope of the recyclization depending on nonevident steric factors, *viz.*, the strain of the alicyclic ring annulated with the aromatic bicycle.[25,27,28] For a six- or eight-membered cycloalkane fragment, the recyclization proves to occur easily (Scheme 29, reactions *29a*, *29b*). For a seven-membered alicyclic ring (reaction *29c*), the reaction stops to yield stable intermediate **24a**, which is less strained than aromatic system **24b**.

Finally, for a five-membered alicyclic ring (reaction *29d*), the oxazole ring seems to undergo opening; however, subsequent cyclization is impossible because the methylene unit and the electrophilic site in intermediate **24c** are distant from each other. An analogous effect was observed[35] in tricyclic salts **2** containing an additional acceptor (an amide group in position 8).

Scheme 29



4. Reactivity of oxazolopyrimidinium salts

4.1. Recyclization of the salts containing the 5-Me group

As mentioned above, oxazolo[3,2-*a*]pyrimidinium salts **8a,b** containing the 5-Me group are easiest to obtain (reaction *14a*, Scheme 14). (The starting 2-aminooxazoles can be, in turn, easily prepared by condensation of cyanamide with accessible α-hydroxy ketones: acetoin or benzoin.) Such salts are isostructural with the 5-Me homologs of oxazolopyridines and hence can be involved in the recyclization of the oxazole ring into a pyrrole one under the action of *X*-type nucleophiles.

We studied reactions of salts **8a,b** with secondary amines and alkoxides. It turned out that tetramethyl salt **8a** smoothly undergoes an earlier unknown recyclization to give the corresponding 1-amino- or 1-alkoxypyrrolo[2,1-*c*]pyrimidines **25** (Scheme 30, Table 5).[17,63] In analogous reactions of salts **8b**, the yields were substantially lower.

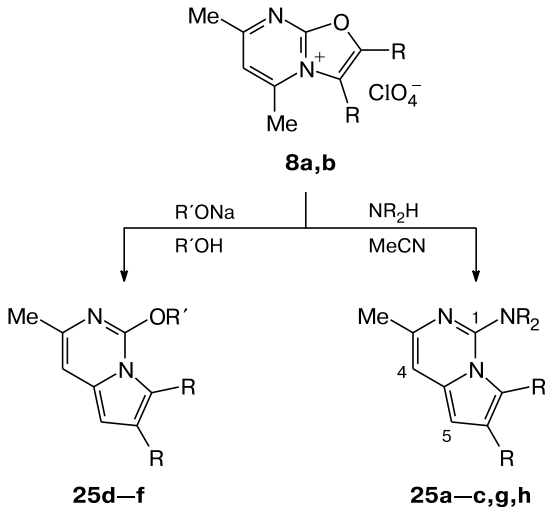
The formation of pyrrolopyrimidines **25** is confirmed by mass spectra of the compounds obtained: in all cases,

Table 5. Characteristics of pyrrolo[2,1-*c*]pyrimidines **25**

Compound	Substituents		Yield (%)	M.p. /°C	δ[a]		*m/z* $[M]^+$
	R	1-X			H(4) (s, 1 H)	H(5) (s, 1 H)	
25a	Me	$N(CH_2)_4$	40	[b]	6.50	5.91	229
25b	Me	$N(CH_2)_6$	65	[b]	6.52	5.92	257
25c	Me	$N(CH_2)_7$	48	[b]	6.52	5.92	271
25d	Me	OMe	73	30(2)	6.45	5.87	190
25e	Me	OEt	80	38(2)	6.42	5.85	204
25f	Ph	OMe	7	128(1)	6.74	6.49	360
25g	Ph	$N(CH_2)_7$	13	146(1)	6.72	6.33	381
25h	Ph	$N(CH_2)_4$	2	137(2)	6.72	6.38	—

[a] The ^{1}H NMR spectrum (DMSO-d_6).
[b] Liquid.

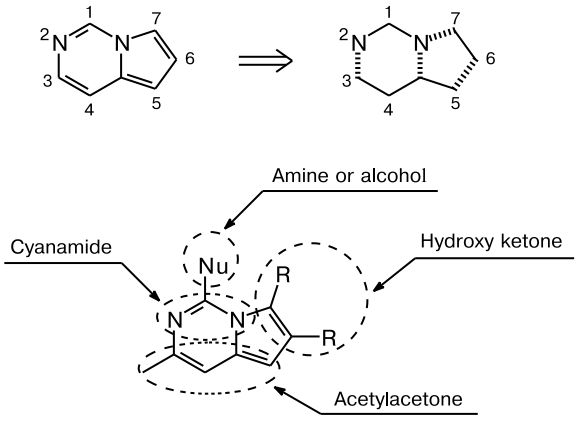
Scheme 30



the mass spectra contain a molecular ion peak and the molecular mass of the product equals the sum of the masses of the starting cation and anion of the nucleophile (alkoxide or amide ion) minus the mass of a water molecule. In the ^{1}H NMR spectra, a signal for the methyl group disappears (this signal was present in the spectrum of the starting cation) but a new aromatic singlet appears at δ 5.9 corresponding to the H(5) proton of the newly formed pyrrole ring. The resulting pyrrolopyrimidines, as well as indolizines, show a positive Ehrlich color probe; note that these pyrrolopyrimidines are more stable than analogous amino- and alkoxyindolizines.

The discovered reaction provides a novel strategy for the synthesis of the aromatic pyrrolo[2,1-*c*]pyrimidine system. In fact, we managed to effect a stepwise conversion of 2-aminooxazoles into pyrrolo[1,2-*c*]pyrimidines through 5,7-dimethyloxazolopyrimidinium salts as intermediates. Consideration of the overall strategy of assembly of this bicycle with regard to the reagents used and the newly formed framework bonds (Scheme 31) shows that this strategy is very unusual.

Scheme 31



Scheme 31 displays the reagents from which we "assembled" the pyrrolo[1,2-*c*]pyrimidine system; particular emphasis should be given to the fact that these reagents are accessible and inexpensive.

Seeking to understand the causes of the low yields in the recyclization of salts **8b**, we varied the secondary amines and the reaction conditions. It turned out[17] that reactions of the salt in boiling pure amine occur in an uncommon way (Scheme 32).

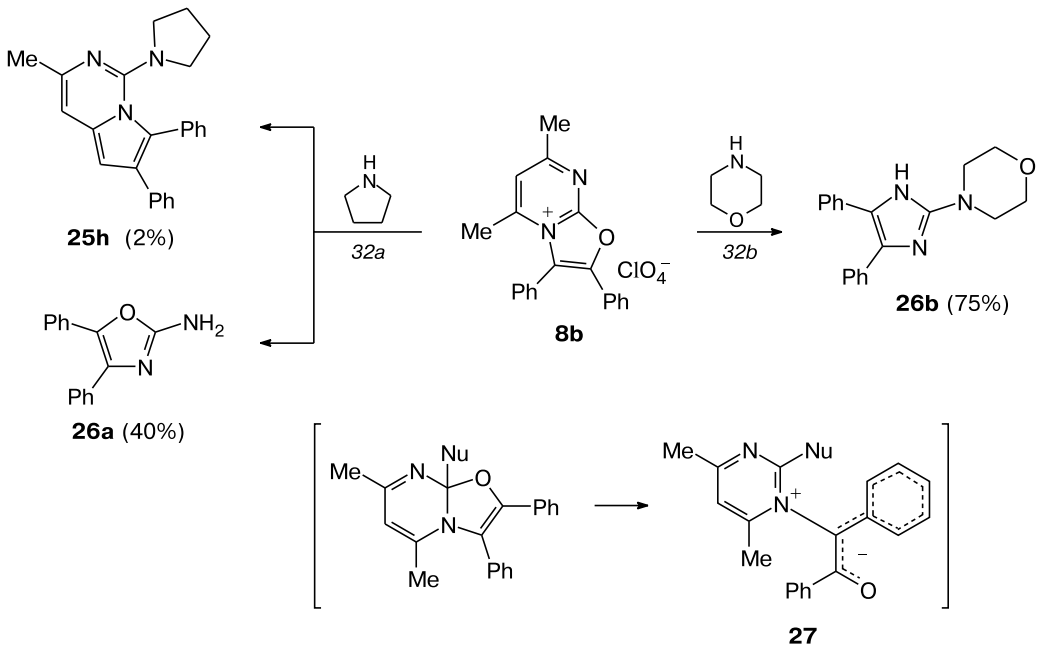
A reaction of salt **8b** with pyrrolidine (reaction *32a*) gave only trace amounts of pyrrolopyrimidine **25h**, while the major product was 2-amino-4,5-diphenyloxazole (**26a**). When salt **8b** was refluxed in morpholine (reaction *32b*), we unexpectedly isolated 2-morpholino-4,5-diphenylimidazole (**26b**) as the sole product.

To explain the observed facts, one should consider the structure of the plausible intermediate ylide **27** formed from salt **8b** (see Scheme 32). Obviously, such an ylide is stabilized by additional delocalization of the negative charge over the phenyl ring; this stabilization is impossible in the ylides formed from salts **8a** and **2**. The stability of the ylide hinders cyclization of the pyrrole ring, which can be responsible for the noticeably lower yields of pyrrolopyrimidines from salt **8b** (see Table 5).

The formation of 2-aminooxazole **26a** in reaction *32a* with pyrrolidine can be explained only by opening (and complete decomposition) of the pyrimidine ring during this reaction. Therefore, two processes proceed in parallel: opening of the oxazole ring gives pyrrolopyrimidine **25h** and opening of the pyrimidine ring gives aminooxazole. Therefore, the bicyclic system of oxazolopyrimidinium exhibits ambident properties in this reaction, which were not observed in other cases.

The unexpected formation of aminoimidazole **26b** (reaction *32b*) can be explained under the assumption that

Scheme 32



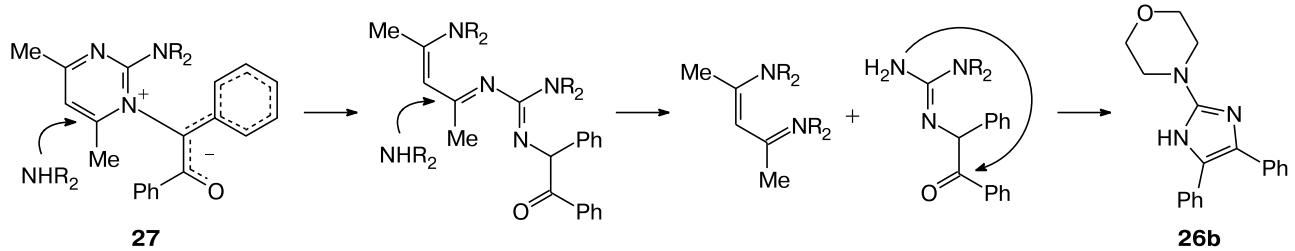
the opening of the pyrimidine ring of salt **8b** (as in reaction *32a* of salt **8b** with pyrrolidine) initially gives 2-aminooxazole, which under drastic conditions (reflux in amine) can further undergo recyclization into imidazole **26b**. Similar examples of the oxazole→imidazole conversion have been documented (*e.g.*, upon reflux of oxazoles with formamide).[64] However, it turned out that oxazole is not a precursor of imidazole **26b** (in a control experiment, oxazole remains intact upon reflux in morpholine). The formation of the imidazole ring cannot be explained without plausible participation of intermediate ylide **27** (Scheme 33).

Apparently, it is ylide **27** that reacts with the amine *via* stepwise decomposition of the pyrimidine ring and the formation of the guanidine fragment that undergoes cyclization into imidazole. In other words, the formation of aminoimidazole **26b** can be explained under the assumption that both rings in the bicyclic system undergo opening and that a new cyclization involves a fragment of the resulting chain.

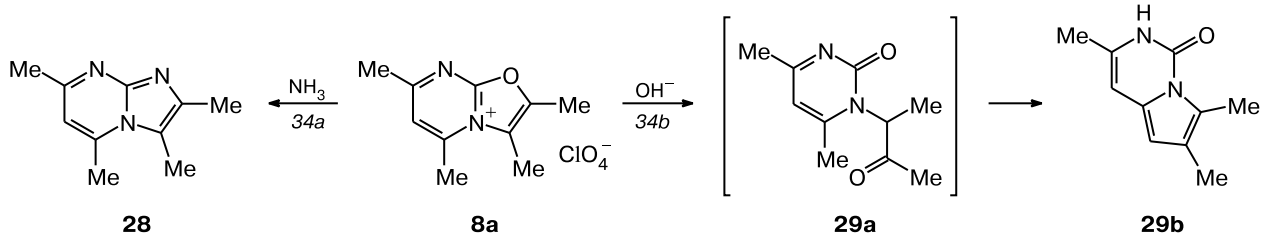
Thus, two competitive processes proceed *in parallel* during reaction *32a*: opening of both the oxazole and pyrimidine rings. The same processes are *sequential* in reaction *32b*: the opening of the oxazole ring is followed by the opening of the pyrimidine one. In other words, the ambident nature of the oxazolopyrimidinium system is manifested in two different ways, which is very uncommon in heterocyclic systems.

When passing from X-type to XH-type nucleophiles, the oxazole ring in system **8a** undergoes regioselective opening (Scheme 34).[63] Reaction *34a* with ammonia gives imidazopyrimidine **28**; its properties are identical with the literature data. Reaction *34b* with an alkali could be expected (as with salts **2** by analogy with reaction *17a*) to yield pyrimidone **29a**. However, the final product is pyrrolopyrimidone **29b**, probably

Scheme 33



Scheme 34



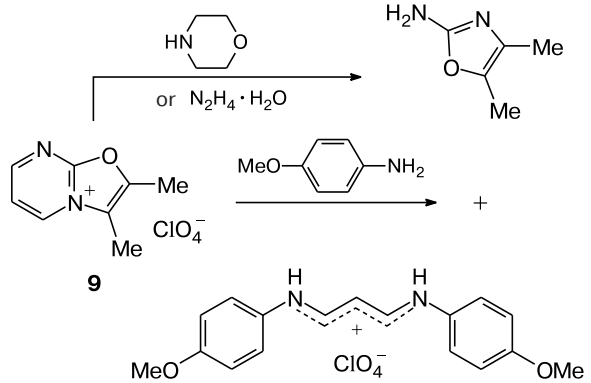
28 **8a** **29a** **29b**

because of the high acidity of the α-methyl group in intermediate **29a**.

4.2. Reactions of nucleophiles with 5-unsubstituted oxazolopyrimidinium salts

Salt **9** (see Scheme 14, reaction *14b*) reacts with various XH- and X-type nucleophiles through opening of the pyrimidine ring.[17] In reactions with morpholine, a primary aromatic amine, or hydrazine, salt **9** is transformed into 2-amino-4,5-dimethyloxazole (Scheme 35). (Remember that oxazolopyridine analogs **2** do not react with anilines at all, while their reactions with hydrazine involve opening of the oxazole ring followed by recyclization (see Schemes 17 and 18).) In a reaction of salt **9** with *p*-anisidine (reaction *35b*), we isolated salt **30**, which is a peculiar "fragment" of the opened pyrimidine ring. The structure of salt **30** was convincingly proved by ^{1}H NMR spectroscopy (because of the molecular symmetry, the corresponding peaks of the protons show double intensities). Note that even in a reaction with an alkali, no opening of the oxazole ring of salt **9** was detected, which was typical of oxazolopyridinium salts **2** and their 5-Me homologs. The ^{1}H NMR spectrum of the unstable compound obtained in the reaction of salt **9** with an alkali contained no signals characteristic of *N*-substituted pyrimidone and the product seemed to result from an attack of the hydroxide ion on the pyrimidine ring of the salt: an adduct or an open-chain tautomer.

Scheme 35

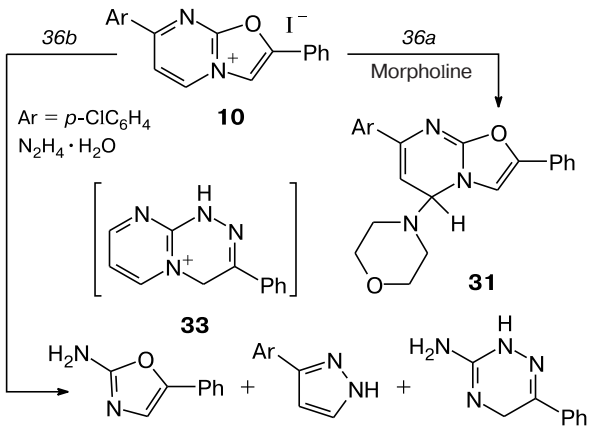


9 **30**

Preparatively, a combination of Schemes 14 and 35 (transformation of oxazole into oxazolopyrimidine and the reverse conversion into the same oxazole) seems to hold no promise. Nevertheless, the transformations of oxazolopyrimidines into oxazoles make sense and are of practical value if one tries to synthesize an oxazolopyrimidinium salt from pyrimidine derivatives rather than from oxazoles. This would allow one to effect the interesting tandem sequence pyrimidines—oxazolopyrimidines—oxazoles as a novel promising strategy in heterocyclic chemistry.

We reproduced one of few routes from pyrimidine to oxazolopyrimidinium salts according to Scheme 15 and obtained the desired representative **10** of this series (Ar = *p*-ClC_6H_4). It turned out (Scheme 36)[17,25] that this salt reacts with a secondary amine (reaction *36a*) to give stable adduct **31** at the C(5) atom, which undergoes no further opening of the pyrimidine fragment.

Scheme 36



10 **31** **33** **32a** **32b** **32c**

Compound	**32a**	**32b**	**32c**
Yield (%)	12	88	80

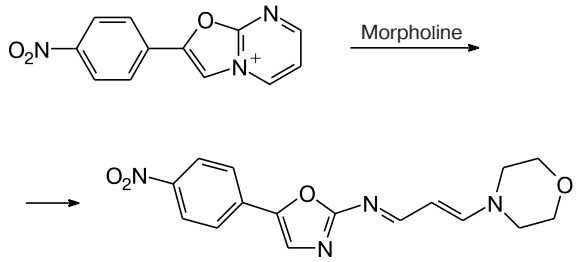
(with respect to salt **10**)

Hydrazinolysis of salt **10** (Scheme 36, reaction *36b*) proceeded in a more complicated way to give a mixture of three compounds **32a—c**. Along with the expected products (oxazole **32a** and pyrazole **32b**) resulting from the decomposition of the pyrimidine ring of salt **10**, the reaction yielded triazine derivative **32c**, probably *via* recyclization of the oxazole ring of salt **10** into triazine **33** followed by decomposition of its pyrimidine ring. Obviously, in this case too, the oxazolopyrimidine system exhibit ambident properties: decomposition of the pyrimidine ring competes with opening (and recyclization) of the oxazole ring followed by the decomposition of the pyrimidine one.

Thus, the synthesis of 2-aminooxazole (*e.g.*, **32a**) from pyrimidine through oxazolopyrimidinium salt **10** is fundamentally feasible; however, the overall reaction sequence consists of many steps, is labor-consuming, and is complicated by a side process.

We developed a novel, much simpler and more efficient strategy of the synthesis of oxazole derivatives from pyrimidines through oxazolopyrimidinium salts. Above, we discussed the simple and convenient route from 2-pyrimidone to 2-aryloxazolopyrimidinium salts **12** (see Scheme 16, reactions *16a*, *16c*). It turned out[17] that salts **12** react with secondary amines to give stable, brightly colored azadienes (Scheme 37) (*e.g.*, compound **34** characterized by X-ray diffraction data).

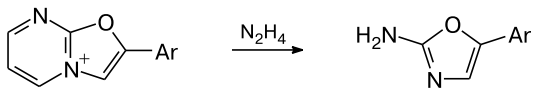
Scheme 37



34

Hydrazinolysis of salts **12** (Scheme 38) gives 2-amino-5-aryloxazoles **35** in high yields (Table 6).[46] The constants of the oxazoles (melting points, ^{1}H NMR spectra) are identical with the literature data. We also recorded their ^{13}C NMR and mass spectra missing in the literature; the structure of one of the compounds was confirmed by X-ray diffraction analysis.[65]

Scheme 38



12 **35**

Table 6. Synthesis of oxazoles **35**

Ar	Yield (%)	M.p./°C
p-ClC_6H_4	95	220
p-BrC_6H_4	96	221
p-$NO_2C_6H_4$	93	236
Ph	90	215
p-$CH_3C_6H_4$	82	218

Note that usually the current routes to 2-aminooxazoles either are complicated by side processes or consist of many steps involving complex reagents. The "textbook" reactions of cyanamide with α-hydroxy carbonyl compounds are not suitable for the synthesis of 2-amino-5-aryloxazoles because α-hydroxyphenylacetaldehydes are not easily accessible. Thus, not only does the method proposed supplement successfully the current ones but it can also serve as their convenient alternative since it involves a straightforward sequence of high-yielding reactions of accessible and inexpensive starting materials.

Recently,[66] we have shown that the strategy under discussion (synthesis of 2-amino-1,3-azoles from pyrimidines through azolopyrimidinium salts) can be extended, *e.g.*, to the synthesis of not easily accessible 2-aminoimidazoles from 2-aminopyrimidine derivatives.

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