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2-Halogen-Substituted Pyridinium-*N*-Phenacylides and Their Cycloiminium and Acyclic Analogs: Synthesis of the Parent Salts, Their Betaine-Ylides, and Oxazolium Analogs

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Abstract—This review deals with an important class of multifunctional reagents, namely, 2-halogen-*N*-phenacyl pyridinium salts **1** capable of forming betaine-ylides **2** (phenacylides) and thus undergoing 1,3-dipolar cycloadditions and various (cyclo)condensations involving the substitution of both α-halogen and keto-methylene groups. The chemistry of salts **1** and betaines **2** is closely related to the chemistry of oxazolo[3,2-a]pyridinium salts **3**. This relationship shows itself in the interconversions of ylides **2** to salts **1** or **3** and, vice versa, of salts **1** and **3** to ylides **2** and in the similarity of chemical transformations not involving such interconversions. This similarity (necessarily involving the α-halophenacylide–oxazolium parallel) is rather unusual and can persist after the replacement of the pyridinium fragment by other heterocycles (azolium and azinium rings) or on passing from halogen to other leaving groups (RS, RO, NR_2). This similarity is also manifested in nonheterocyclic open-chain salts where the potentially ylidic CH_2CO group is attached to the halogen-iminium group or its functional analog with another heteroatom. The review on the synthesis and transformations of salts **1** and **3** and phenacylides **2** is divided into two parts. The present part is devoted to the synthesis of salts **1** and ylides **3** and the interconversions of **1**, **2**, and **3**. It presents a detailed analysis of synthetic routes to salts **1** and their cycloiminium analogs containing α-halogen or a different (S, O, N) α-heteroatom that serves as a leaving group. The specific features of the synthesis of oxygen- and sulfur-containing salts and their ylides are revealed. Rare examples of the synthesis of aliphatic salts and their "phenacylides" containing the same structural motif and capable of undergoing ring closure to oxazoles are given. Methods for the generation of phenacylides **2** and their carbene and imine analogs, including the opening of oxazolium salts, are also considered.

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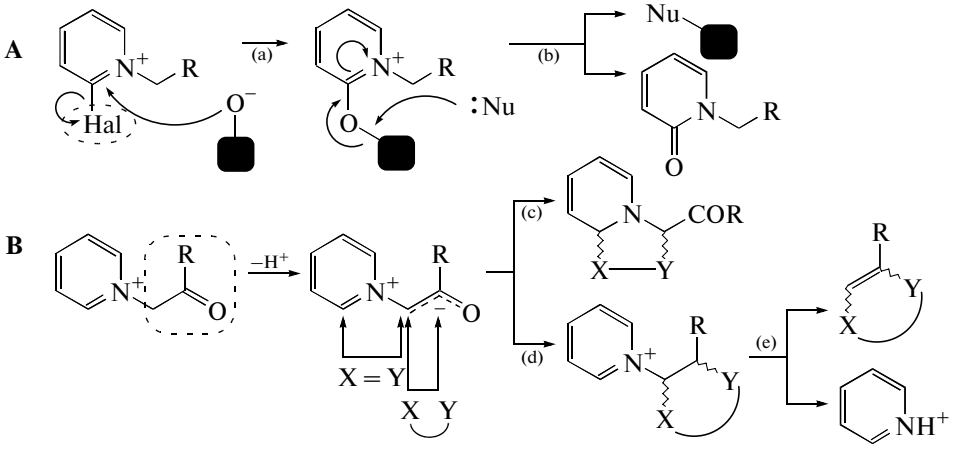
1. INTRODUCTION

N-Alkylpyridinium salts have found applications as reagents in the organic synthesis of other classes of substances. The most striking examples are 2-halopyridinium salts (**A**), known as Mukayama reagents, and *N*-phenacylpyridinium Kröhnke salts (**B**, R = Ar), readily forming ylides (traditionally called phenacylides) with bases (Scheme 1).

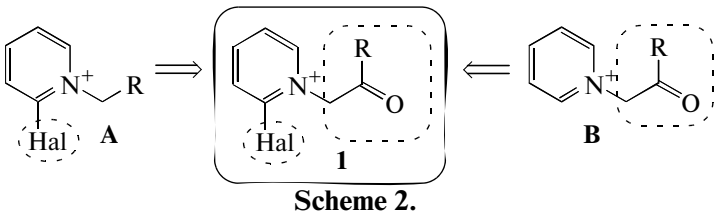


Scheme 1.

Mukayama salts **1** have a unique ability to undergo stepwise transformations into *N*-alkylpyridones by "withdrawing" the oxide ion from many oxygen-containing nucleophiles and donating their electrophilicity to the remaining species [1, 2]. This is achieved by facile replacement of α-halogen in salts **A** at stage (a) and fast elimination of the stable *N*-alkyl-2-pyridone residue at stage (b). The latter can occur as an S_N2 reaction under the action of another nucleophile (alcohols or carboxylic acids are activated in this way) or S_N1 reaction (e.g., in the synthesis of carbodiimides from ureas or of isonitriles from isocyanates). The salts of other α-halogen-substituted heterocycles have similar properties, with equally striking examples of dethionation found in addition to deoxygenations (for example, the "removal" of the sulfide ion from thioamides, thioureas, or xanthates).

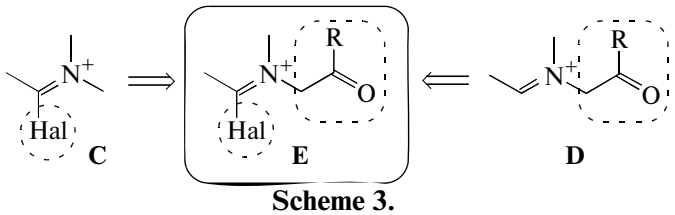
The use of Kröhnke salts **B** in the synthesis was dictated by other properties of pyridinium salts, namely, the ability of their phenacylides to undergo 1.3-dipolar cycloaddition [3, 4] by reaction (c) and the ability of the charged ring to initially involve the methyleneketone unit in various (cyclo)condensations (d), thereafter vanishing from the structure of the end product [5] and leaving an additional multiple bond in it, as shown by scheme (e).

This review deals with the chemistry of salts **1**, whose structure contains both strong functionalities: the α-halogen of Mukayama salts and the keto-methylene unit of Kröhnke salts (Scheme 2).



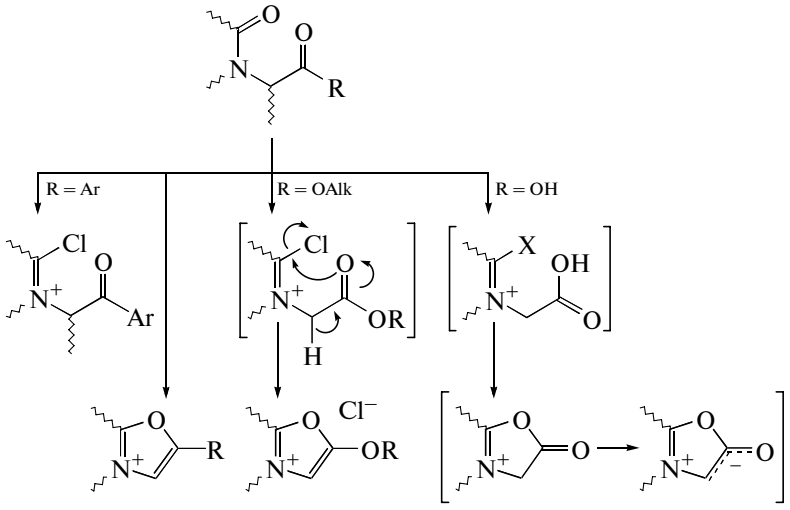
Scheme 2.

This combination of a potentially ylidic CH_2 group and an electrophilic haloiminium fragment in salts **1** generates a class of reagents that have no acyclic analogs. Indeed, if we mentally remove the cyclic bonds from **A** and **B** salts, leaving only the iminium group, Mukayama salts **A** will correspond to the well known Vielsmeyer reagent **C**, and Kröhnke salts **B** to the iminium salts of α-aminocarbonyl compounds (or amino acids) **D**, widely used as precursors in the synthesis of azomethine-ylides. The acyclic analogs of salts **1** will evidently correspond to a superposition of the **C** and **D** motifs, which is a rare type of synthon **E** (Scheme 3).



Scheme 3.

Reagents of class **E** have limited applications in synthesis. Attempts to obtain these salts (e.g., by reactions of element (oxo)chlorides with suitable amides) often led to closure of the oxazole ring (Scheme 4). Examples of these salts in the series of aminoketones are known [6], but their structure has been insufficiently studied because of an extremely easy hydrolysis. In the series of amino acid ethers [7], these salts are spontaneously electrocyclized (predominantly via the enol forms) into 5-alkoxyoxazole salts. In the series of amino acids themselves, there are no acyclic analogs of the **E** type at all, and their iminium lactones (intermediates of the Dakin–West reaction) are readily dimerized via unstable betaines (better known as munchnones).



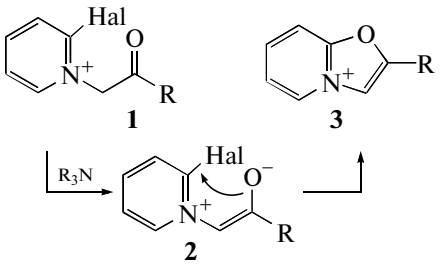
Scheme 4.

In contrast, pyridinium analogs **1** of acyclic reagents **E** are quite stable to hydrolysis and can be stored for years. Salts **1** can readily be obtained from accessible halopyridines and bromoketones (generally, phenacyl bromides) and are widely used in the synthesis of various classes of substances. The chemistry of salts **1** and their betaine-ylides (phenacylides), however, has not been reviewed.

2. THE CHEMISTRY OF SALTS **1** AND THEIR BETAINE-YLIDES **2** AND OXAZOLIUM ANALOGS **3**

The synthesis of salt **1** was described by Kröhnke in 1937 [9], but systematic studies of the chemistry of this family of compounds did not begin until the 1960s. The salts (and their azine and azole analogs) were found to react with a wide range of binucleophilic or bipolar reagents, generally forming families of bridged heterocycles that were difficult to access by other routes. (Many such reactions were found by the author's research group [10] at Moscow State University during the recent decade.) In contrast to the transformations of Mukayama and Kröhnke salts, the reactions of salts **1** have never led to the elimination of the pyridine (or pyridone) residue. Instead, another distinction of salts **1** (and their ylides **2**) was found, namely, their close relationship with oxazolopyridinium salts **3**.

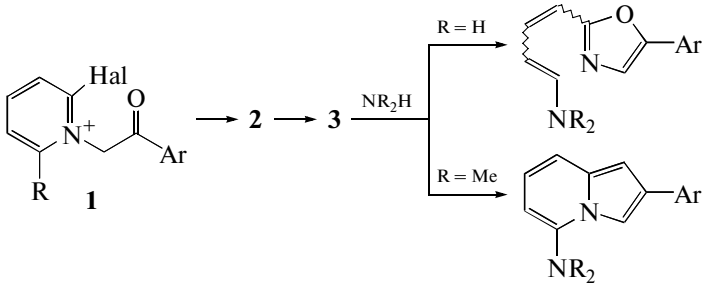
The first type of relationship can be called genetic (Scheme 5). In the 1970s Bradsher and Kröhnke showed that salts **1** could be converted into **3** by reactions with bases via the formation of betaine-ylides **2**.



Scheme 5.

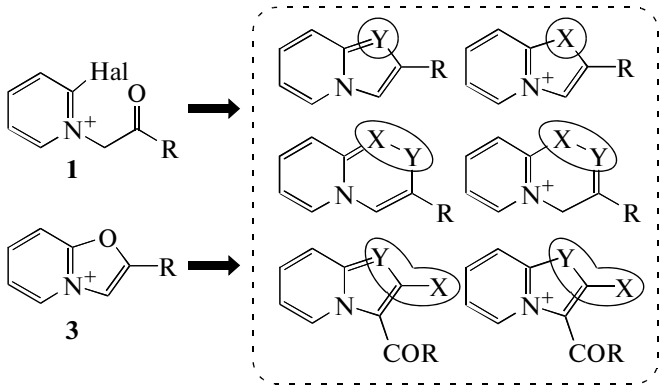
This relationship is an obvious analog of the closure of acyclic salts **E** into oxazolium cations (cf. Schemes 4 and 5). In some cases, the analogy was so complete that attempts to synthesize salts **1** gave only the corresponding oxazolium salts **3**. We revealed the main synthetic meaning of this relationship: the pos-

sibility of performing stepwise reactions of salts **1** with unusual transformations (Scheme 6), having preliminarily converted them into salts **3** via phenacylides **2**.



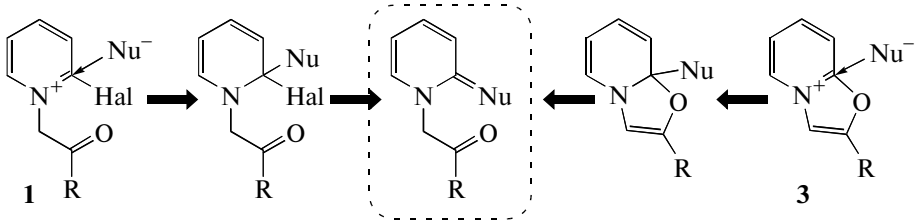
Scheme 6.

The second type of relationship. In many reactions, monocycles **1** and bicycles **3** form exactly the same products without being converted into one another; i.e., they behave as synthetic equivalents (Scheme 7).



Scheme 7.

This relationship is due to the similarity of the mechanisms of the first stage of these reactions (Scheme 8). In both cases, the nucleophile attacks the electrophilic carbon site lying between two heteroatoms (nitrogen and halogen in **1** or nitrogen and oxygen in **3**); this attack leads via different adducts to a single intermediate.

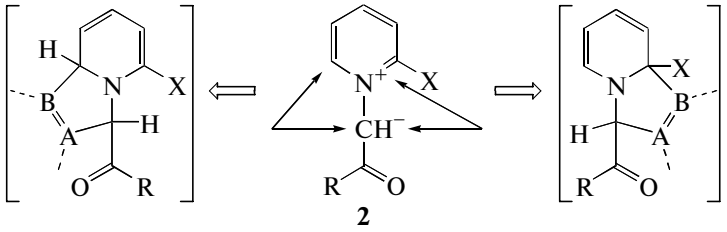


Scheme 8.

Varying the nucleophile in Schemes 7 and 8 (e.g., incorporating an electrophilic fragment in its structure), we can add pyrroles, thiazoles, oxazoles, imidazoles, phospholes, triazines, pyridines, isoquinolines, and other rings with a wide range of donor and acceptor, hydrophobic and hydrophilic, acidic and basic functions to the pyridine ring.

The third type of relationship between salts **1** and **3** was found recently. Pyridinium ylides **2** formed from **1** can undergo 1,3-dipolar cycloadditions; the chemistry of these compounds changes due to the presence of α-halogen (or another X leaving group) in phenacylides **2**. Because the nitrogen atom in **1** has no symmetric environment (compared with B salts), the regioselectivity of the attack of the dipolarophile can vary. Upon the attack of the dipolarophile at the *ipso*-position relative to the X α leaving group (the adduct in the right-hand part of Scheme 9), the forming five-membered fragment of the cycloaddition is more significantly oxidized (compared with the isomer in the left-hand part) and can be aromatized more readily, eliminating an HX species. While the influence of the β and γ substituents in Kröhnke phena-

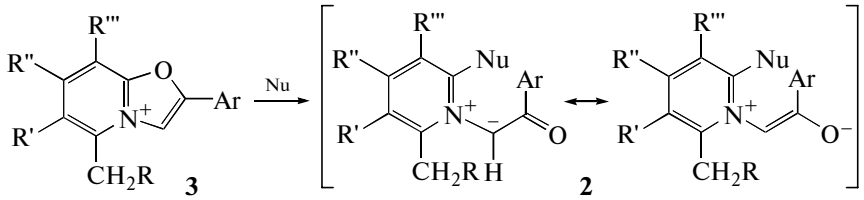
cylides on the regioselectivity of the cycloaddition is clear in general [11], the effect of the α groups in ylides **2** has been studied insufficiently and is hindered by the accessibility of the analogs of salts **1**.



2

Scheme 9.

The ability of pyridinium "ylidogens" **1** to undergo cycloaddition would seemingly differentiate them from electrophilic bicycles **3**. We proved, however, that **1** and **3** are also related in this respect because the oxazolium ring is opened in several cations **3**, also generating ylides **2** (Scheme 10) and the products of their transformations. Curiously, the corresponding pyridinium precursors **1** were inaccessible in many such cases. The ability to generate ylides is a relationship of the third type between **1** and **3**.

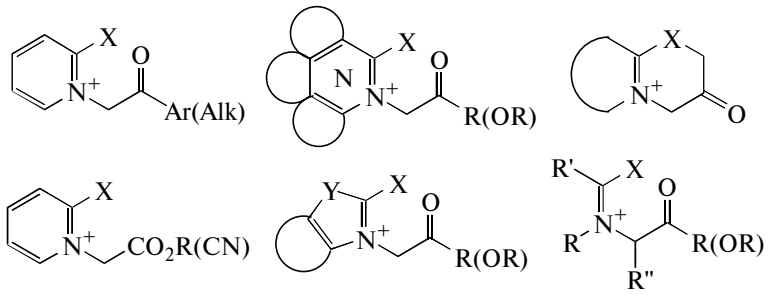


3 **2**

Scheme 10.

The three types of relationship between **1** and **3** ultimately allow flexible planning of syntheses by using the readily accessible equivalents instead of the less accessible (or inaccessible) substances. This relationship (and the property of being interchangeable) is not absolute and occasionally depends on the reagent and substrate. The goal of this review was to examine the scope of synthetic equivalence, systematizing the enormous material from this viewpoint.

This review deals with salts **1** and their analogs presented in Scheme 11. In addition to 2-halopyridinium salts with a methylketone residue, it considers their analogs with N^+-CH_2COOR and N^+-CH_2CN fragments. We tried to review all data on the salts of other α-halogen-substituted heterocycles (azines, azoles, and their benzo derivatives) and acyclic analogs **E**. The data on the analogs of salts **1** with heteroatoms other than halogen (X = S, O, N) in the α-position were also included in the review.



Scheme 11.

The similarity between salts with the **E** fragment and the corresponding oxazolium salts will be traced wherever possible; for bicycles **3** with a pyri(mi)dine fragment, we used our recent review [12] on the synthesis and properties of these compounds, which facilitated this work. The present review is divided into two parts because of the enormous amount of data. This part is devoted to methods for the synthesis of salts **1**, which can be converted into betaine-ylides **2** or salts **3**. Other methods for generating betaine-ylides **2** are also considered (the use of carbenes and the opening reactions of oxazolium salts). In view of the scanty amount of relevant literature data and wishing to emphasize the variety of potential types of salts **1**, we included our own results in the review (occasionally giving references to the theses and diplomas defended in 1995–2010 at Moscow State University).

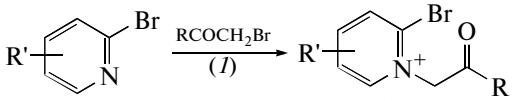
Table 1. Yields in the syntheses of **1a–c** from 2-bromopyridine and its homologs

No.	Substituents in **1a–c**	Additional substituents, yields
1a	R=Ph, R'=H	65% [116], 72% [117], 60–75% [16], 83% [118]
	R=Ph, R'=Me	R'=3-Me: 74% [117], 35% [16]; R'=4-Me: 78% [117]; R'=5-Me: 77% [117], 81% [16]
	R=Ar, R'=H (substituents in the aryl group)	p-Br 54% [16] (36% [117]); p-NO_2 50% [16]; m-NO_2 82% [16]; p-Ph 69% [16]; m-NHAc 44% [16]; m-(*i*-PrO) 32% [16]; p-SMe 53% [16]; p-SO_2Me 72% [16]; p-$OCHF_2$ 28% [119]; Ar = 2-thienyl 10% [16]
1b	R=Alk, R'=H	Alk = Me 56% [117], *t*-Bu 57% [117], *i*-Pr 48% [120]
1c	R=OEt	71% [121], 76% [17]

3. SYNTHESIS OF 2-HALOPYRIDINIUM SALTS

3.1. 2-Bromopyridinium Salts

Quaternization of 2-bromopyridine and its homologs with α-bromoketones, forming salts **1a–c**, was studied most comprehensively (reaction (*1*), Scheme 12, Table 1). The synthesis of a wide range of such salts in the 1950s [13–15] was performed in an effort to find anticancer drugs among them. In the late 1970s, another series of salts **1a** (containing substituents that were thoroughly selected based on the maximum variety principle) was obtained and used as reagents for the synthesis of thiazolopyridinium salts [16] with an antiglycemic acitivity. Variants of quaternization (*1*) generally include the heating of a mixture of reagents without a solvent for many days (sometimes in benzene or toluene) or in sulfolane (for 1 day at 100°C with reprecipitation of salts with ether).



1a–c

1a: R = Ar;
1b: R = Alk;
1c: R = OEt

Scheme 12.

The structure of salts **1a–c** was generally identified by element analysis except for **1c**, for which XRD data were obtained [17]. The yields were sufficiently high and almost independent of the reaction conditions (Table 1).

In 1969 Bradsher performed a reaction between bromopyridinium salt **1a** and triethylamine and obtained unstable phenacylide: orange-red enol-betaine **2a** [18] (Scheme 5, R = Ph, Hal = Br); after 3 h boiling in acetonitrile and the addition of chloric acid, **3a** was converted into 2-phenyloxazolopyridinium perchlorate **3a** with a 68% yield. Under the action of less basic *N*,*N*-dimethylaniline, the yield of **3a** decreased to 51% (or even twofold after prolonged boiling). Salt **3a** also formed in the reaction of 1,1-dimethylhydrazine with bromide **1a** (boiling for 14 h, 41%) and in the reaction of **1a** with the butylamine byproduct (11%).

In 1980 Kost reported the first example of cycloaddition of DMAD to ylide **2a** from salt **1a** [19]. Salt **1c** with an ester residue at a methylene unit is also formed from ylide, which tends toward self-condensation according to our observations. This often gives rise to extremely unusual products in the reactions of **1c** with simple nucleophiles and dipolarophiles [17, 20].

3.2. 2-Chloropyridinium Salts

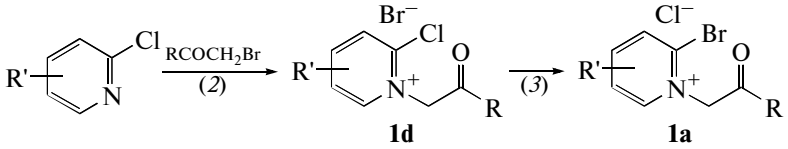
2-Chloropyridinium derivatives react with bromoketones equally easily, forming salts **1d** (Table 2). The mixtures of reagents are most often boiled in acetonitrile [21]. The residue can be separated several times while boiling the mixture for 5–7 days [10]. The components can be heated without a solvent (2 h, 80°C) and then diluted with acetone and kept for 1 day at 0°C [22]. In the procedure described in [23], the prod-

Table 2. Yields in the syntheses of **1d** from 2-chloropyridines

No.	Substituents in **1d**		Substituents in aryl group, yields
1d	R=Ar	R'=H	H 78% [21]; p-Me 68% [21]; p-NO_2 54% [122], 65% [10]; m-NO_2 51% [122]; p-Br 62% [10]; 3,4-$(OH)_2$ 10% [15]
		R'=4-Me	H 63% [16]; p-Br 78% [21]
	R=Me	R'=H	65% [21]
		R'=4-Me	68% [21]

ucts were purified by placing the mixture on silica gel and washing out the unchanged reagents with ethyl acetate, and the desired salts with ethanol.

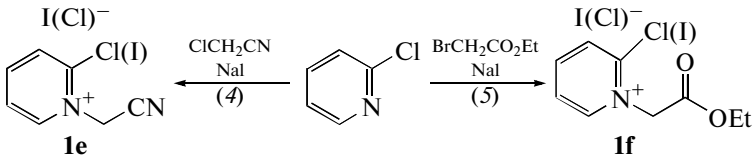
The data for 2-chloropyridinium salts **1d** are less representative than for 2-bromopyridinium. Table 2 is incomplete for several reasons. For many examples of **1d** cited in the literature (we found about twenty in [13, 14, 22, 24, 25]), there were no data about their yields, purity, and properties. The authors possibly omitted these data because of the seemingly apparent simple structures. The structures of 2-chloropyridinium bromides, however, are ambiguous and have not been sufficiently studied. Reaction (2) can be followed by an exchange of ionic halogen for a covalent one according to scheme (3), especially during prolonged heating of the reaction mixtures (Scheme 13).



Scheme 13.

This problem was first revealed in the alkylations of 2-halopyridines with methyl iodide in the 1950s [26]. It appeared that 2-chloro- and 2-bromopyridine in this reaction were completely converted into 2-iodopyridinium iodomethylates. A similar exchange in 2-chloropyridines under the action of alkyl bromides has not been studied. The alkylation of 2-chloropyridine with *p*-nitrophenacyl bromide formed a salt whose ^{1}H NMR spectrum had close-lying signals of two CH_2 groups with different intensities. This enigma was resolved only after the recording of the mass spectrum of this salt. The mass spectrum contained a peak of 2-bromopyridinium **1a** along with a peak corresponding to 2-chloropyridinium cation **1d**. It was thus confirmed that bromide in pyridinium salts **1d** (if bromoketone was taken for the synthesis) could also replace the covalent chlorine atom. An admixture of an "ionic–covalent" isomer may not influence further transformations if the halogen (no matter which) is replaced by the nucleophile at the next stage. If, however, the halogen atom is preserved in the structure of the end product (for example, in cycloaddition to ylides from **1d** [27, 28]), this inevitably leads to mixtures of chlorine- and bromine-containing covalent products.

In this respect, it is reasonable to adopt a more critical attitude when reviewing publications in which the nature of the ionic and covalent halogen in salts **1** is ambiguous. Salts **1e** and **1f** were obtained [23] by the activation of the alkylating agent (chloroacetonitrile or ethyl bromoacetate) with sodium iodide (Scheme 14). Although the resulting salts were identified as chloropyridinium iodides, it is reasonable to ask what the fraction of iodopyridinium was in them.



Scheme 14.

Many examples of the alkylation of 2-chloropyridines were cited in [23], and the efficiency of using microwave radiation in order to accelerate quaternizations (*4*) and (*5*) was demonstrated. Under normal conditions (boiling without a solvent), quaternization with chloroacetonitrile (*4*) takes 50 h and gives a

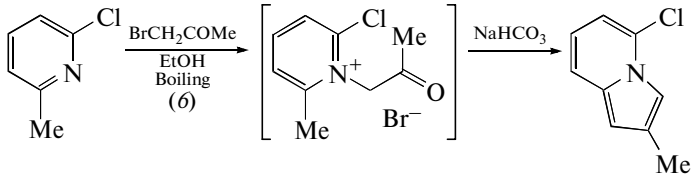
10% yield, whereas in a microwave furnace a 56% yield is attained within 40 min. For reaction (*5*), the yield of **1f** increased from 46 to 80% and the reaction time decreased from 23 h to 40 min.

For quaternization of 2-chloro(bromo)pyridines, only bromo(chloro)ketones were used. The combinations of iodo- and fluoro derivatives (of pyridines or ketones) were not studied, except the NaI addition to reaction mixtures. Examples of using haloacetates (**1c**, **f**) and chloroacetonitrile (**1c**) were given above. Propargyl bromide is an interesting alkylation agent [29]; it quaternizes 2-chloropyridine with a 37% yield, and the resulting salt acts as a synthetic equivalent of 2-chloro-*N*-acetonylpyridinium in reactions with nucleophiles (as in Scheme 7). The reactions of benzyl halides with 2-chloropyridine form salts (capable of giving ylides) that easily undergo photochemical cyclization into isoindolo-pyridinium cations [30]. The alkylation of 2-chloropyridine with compounds of the series $RS-CH_2-Cl$ (R = Me, Ar) also incorporates a potentially ylidic fragment in the resulting salts; these reactions occurred with good yields (48–75%), whereas the use of $PhSO_2CH_2Cl$ did not give any signs of reaction [23].

The transformations of 2-chloropyridinium bromides **1d** into oxazolopyridinium salts **3** (Scheme 5) were first studied by Kröhnke in 1976 [21]. In 1937 he tried to obtain an ylide from salt **1d** (R = Ph) [9] using aqueous sodium bicarbonate, but this led to hydrolysis of the chloropyridinium salt into *N*-phenacylpyridone-2. After Bradsher's publications in the 1970s, Kröhnke suggested an excellent modification of the procedure for the conversion of **1** into **3** (R = Ph 91%, *p*-MeC_6H_4 72%), namely, boiling the dioxane solution of **1** with an excess of ethyldiisopropylamine for 1 h. He also observed this cyclization with 2-picoline, 2,4-lutidine, quinoline, and lepidine; with pyridine and 4-picoline, however, the reaction followed another route (see below). The structure of the products of DMAD cycloaddition to ylide from **1d** (R = *p*-$NO_2C_6H_4$) was studied in detail by XRD [27, 28].

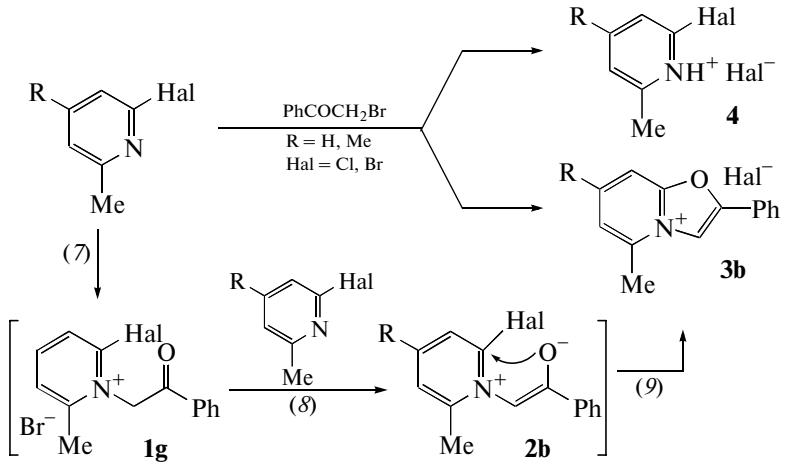
*3.3. Formation of Ylides and Oxazoles as a Hindrance to the Synthesis of **1***

One problem common to the syntheses of halogen-substituted salts **1** was revealed in the alkylation of sterically hindered 6-methyl-2-chloro(bromo)pyridines with bromoketones [31, 32]. The methylation of halopicolines was reported in [33]; a study of the reaction kinetics unexpectedly showed that the alkylation rate of the chloro derivative was higher than that of the bromo derivative [34], although both are basic substances. In 1928 A.E. Chichibabin showed in his German patent [35] that the reaction of 6-chloro-2-methylpyridine with bromoacetone led to 5-chloroindolizine (Scheme 15). This cyclocondensation should inevitably include the formation of a chloropyridinium salt as an intermediate (reaction (*6*)), although the author himself did not isolate it and regretfully did not give the yield of the end product.



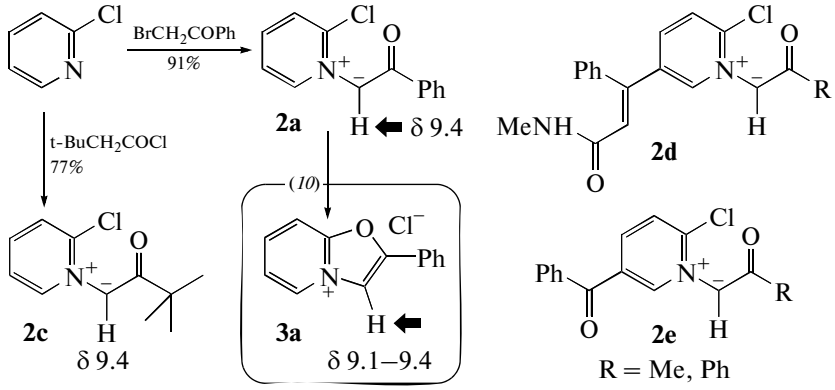
Scheme 15.

These data suggested that the synthesis of salts **1** from 6-halo-2-picolines would be successful. However, our attempts to isolate these salts using bromoacetone failed because of significant tar formation. The replacement of aliphatic bromoketone by thermally more stable phenacyl bromides led to an unexpected result (Scheme 16). The reactions with 6-chloro- and 6-bromo-2-picoline [31, 32] and 6-chloro-2,4-lutidine [36] gave mixtures of hydrohalides of starting halopyridines **4** and oxazolo[3,2-a]-pyridinium salts **3b** (which were separated) instead of the expected *N*-phenacylpyridinium salts **1g**. This result can only be explained if we assume that 2-halopyridinium salts **1g**, which slowly formed by reaction (7), were deprotonated into ylides **2b** in reaction (*8*) of the starting halopyridines. Enol-betaines **2b** easily underwent ring closure to oxazoles by reaction (*9*). The structure of **3b** was identified by alternative synthesis (completing the corresponding pyridone-2 with an oxazole ring).



Scheme 16.

This result makes us more cautious when considering the cited reference [23] and its continuation [37], which reported that the reactions of several 2-chloropyridines with haloketones gave stable substances called heterobetaines **2a** and **2c–2e** instead of **1a** (Scheme 17).



Scheme 17.

This conclusion was probably drawn from ^{1}H NMR spectra (which showed a low-field methine signal at 9.4 ppm instead of the singlet of the methylene group) and element analysis data (formally corresponding to ylides but not salts). The suggested formulas, however, are dubious.

As mentioned above, halopyridinium betaine–ylides **2** are orange-red, and when heated to 100°C they are converted into colorless (sometimes yellowish) oxazolopyridinium salts **3**. Compounds **2** were reported to be colored from pale white to pale brown; they were synthesized in a microwave furnace at 170°C. We can assume that here we have a closure of the oxazole ring (as in Schemes 5 and 16) by reaction (*10*), forming chloride **3a**. The typical chemical shift of the methine proton in pyridinium phenacylides is generally up to 6.8 ppm [38]. The low-field singlet at 9.4 nm observed by the authors may correspond to the oxazolium proton in salts **3**, which generally resonates at $\delta = 9.1–9.4$ ppm (slightly changing depending on the solvent, counterion, and substituents). The example in Scheme 17 shows another problem of the chemistry of salts **1d**, which is again associated with some kind of isomerism. In this case, a covalent substance (neutral chlorobetaine **2a**) and its ionic valent isomer (chloride **3a**) are identical in composition, due to which the salt can easily be mistaken for betaine if we judge only from element analysis data.

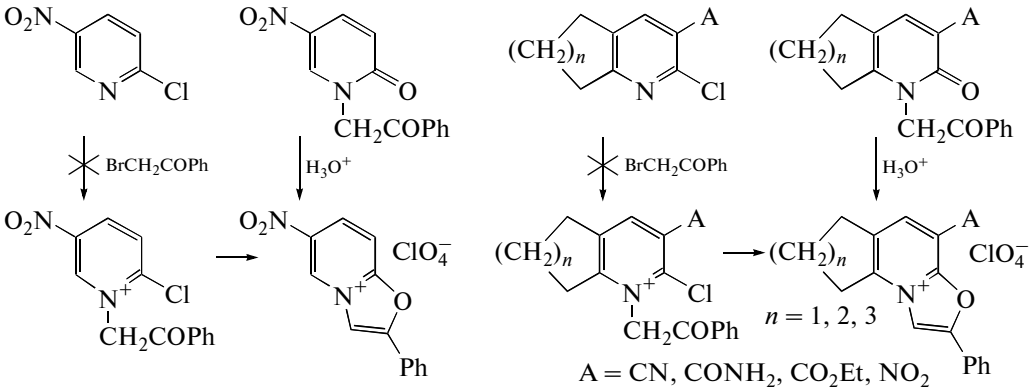
According to the above examples, the structural factor (the steric hindrances to *N*-phenacylation) and/or the rigid conditions of the reaction can make the isolation of salts **1** impossible because of their conversion to **3**.

*3.4. Selective Replacement of Inaccessible Salts **1** by Their Oxazolium Equivalents*

Several 2-halopyridines do not undergo reactions with bromoketones at all. For 2-chloro-5-nitropyridine (whose alkylation with trialkyloxonium salts is known), phenacylation with bromoketones did not occur even under the most rigid conditions [10]. The large family of 6-alkyl-2-chloropyridines with acceptor groups (CN, $CONH_2$, COOR) in the 3 position and their 5,6-cyclohomologs can readily be

obtained from inexpensive and easily accessible pyridones by the reaction with $POCl_3$; these chloropyridines, however, cannot be phenacylated either.

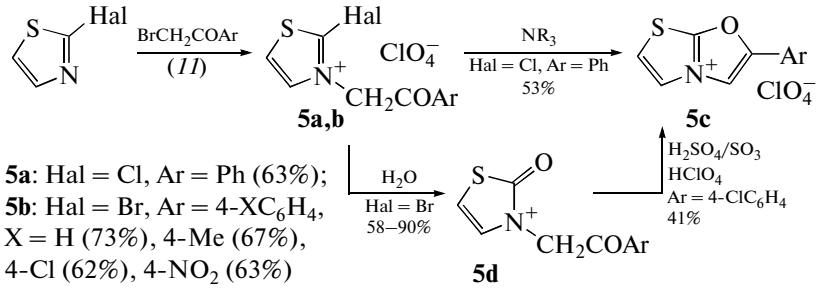
Nevertheless, oxazolo-pyridinium salts **3**, which are the equivalents of inaccessible pyridinium salts **1**, can be synthesized by another procedure involving two stages (see review [12]). At the first stage, the alkaline salts of pyridones-2 are phenacylated. This reaction is almost insensitive to the steric and electronic hindrances of substituents. At the second stage, *N*-phenacyl-2-pyridones are cyclodehydrated into condensed oxazoles **3** with quantitative yields. This is a facile route to salts **3** with acceptor groups in the pyridine ring and/or a (cyclo)alkyl residue at the nitrogen atom (Scheme 18). If phenacylides were accessible, they would be converted into these bicycles **3** from salts **1**. Since salts **1** and **3** are generally obtained and used as reagents, it is important that they be interchangeable. Many new transformations of readily synthesized bicycles **3** were cited in review [12]. These transformations afford new subclasses of substances (e.g., 5-substituted indolizines), which were unknown for a long time because of the inaccessibility of their halopyridinium precursors.



Scheme 18.

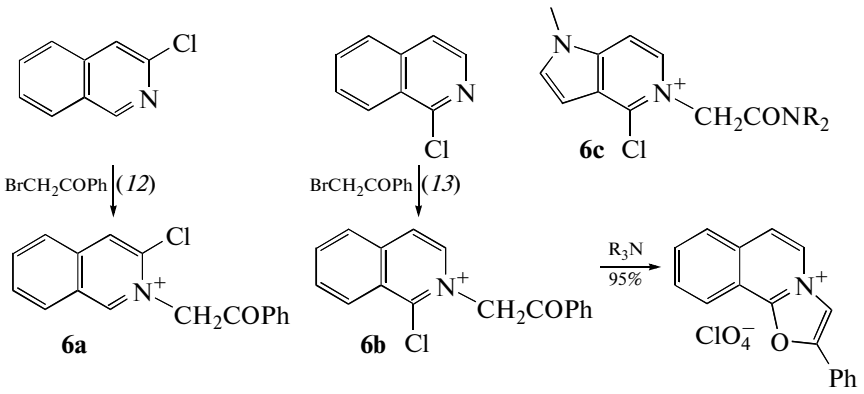
4. SYNTHESIS OF OTHER α-HALOGEN-CYCLOIMINIUM SALTS

Reaction (11) with 2-chlorothiazole had long been the sole example of phenacylation of α-haloazoles [39]. We showed that 2-bromothiazole was equally easily quaternized into salts **5b** (Hal = Br) in acetonitrile [40] (Scheme 19). For the 2-chlorothiazolum salt, the formation of phenacylide and its cyclization into oxazolothiazolium salt **5c** were described [39]. For 2-bromo derivatives, this cyclization could not be performed preparatively, but we succeeded in synthesizing salts **5a** by a two-stage reaction via thiazolones **5d**.

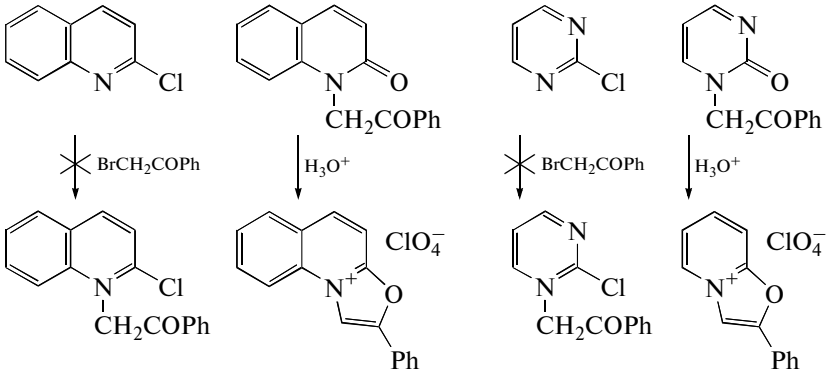


Scheme 19.

In the series of azines with an α-carbon relative to the heteroatom, phenacylation was reported only for α-chloroisoquinolines (Scheme 20). The yields in reactions (*12*) and (*13*) were nearly identical: 65% for 3-chloro derivative **6a** [41] and 68–70% for 1-chloroisoquinolinium 26b [39] [42]; in the latter case, phenacylide was successfully converted into tricyclic oxazole [39]. Salt **6c** was obtained in a 78% yield from chloro-azaindole and an exotic chloroacetamide (where NR_2 is a phenothiazine residue) [43]. We failed to perform phenacylation of 2-chloroquinoline; the reaction is probably hindered by the adjacent benzene ring. 2-Chloropyrimidine was also extremely inactive; its phenacylation at 20°C did not terminate even after half a year, while heating in different media quickly led to tar formation [10]. The chloroazinium salts were not obtained in either case, but the corresponding oxazolo-azinium salts (Scheme 21) readily formed from accessible *N*-phenacylquinolones [44] and -pyrimidones [45].



Scheme 20.

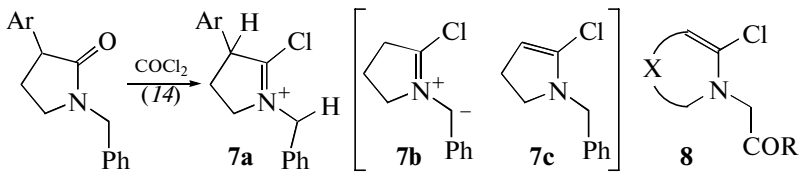


Scheme 21.

The failure of attempts (with a few exceptions) to quaternize the α-halogen derivatives of heterocycles with phenacyl bromide may be attributed to the peculiarities of the chemistry of α-haloketones. The acyl residue of bromoketone increases the CH-acidity of the CH_2Br group, imparting undesirable carbenoid properties to this carbon center. One of the most striking examples of these competing processes is smooth transformation (by some kind of "carbene trimerization") of phenacyl bromides into 1,2,3-tribenzoyl cyclopropanes under the action of even weak bases [46, 47].

Numerous syntheses of the *N*-alkyl salts of α-halogen-substituted heterocycles (from pyridinium, benzoxazolium, benzothiazolium, and other series) were successful due to the use of highly electrophilic alkylating agents (triflates, tosylates, and trialkyloxonium salts) and reported because of interest in Mukayama reagents. A potentially ylidic *N*-benzyl residue was introduced in this way in several compounds. It is not yet clear, however, whether this method is applicable to the synthesis of analogs of **1** or not (by replacing halogen in haloketones by a more nucleofuge group).

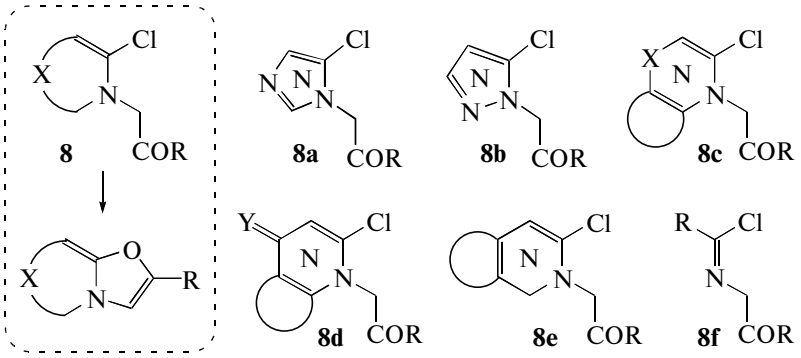
In the series of nonaromatic α-halogen-cycloiminium structures, it is noteworthy to consider 2-chloro-*N*-benzylpyrrolinium structure **7a** [48] (Scheme 22). It was obtained by simple reaction (*14*), which has not yet been summarized for the synthesis of the analogs of **1**. Although structure **7a** resembles the ordinary Vielsmeyer reagent, it is interesting in view of its ability to be deprotonated by two routes. The first route is the possible formation of ylide **7b**, which makes this structure related to reagents of class **E**.



Scheme 22.

The second route is proton elimination; it forms covalent chloroenamine **7c** —the prototype of the large family of compounds **8**, which are the "neutral analogs" of salts **1**. Structures **8** are widespread

among imidazoles (**8a**), pyrazoles (**8b**), and their aza analogs (denoted by *N* in the cycle in Scheme 23) and are also encountered among azines and their benzo/aza analogs, and purines. In these structures, the positive charge of salts **1** is "neutralized" due to the endocyclic heteroatom X (**8c**), the exocyclic oxo(thio) group C=Y (**8b**), and even hydride (when the methylene unit appeared in the ring) (**8e**). Among acyclic reagents are similar neutral structures, e.g., imidoyl chlorides **8f**, which are the tautomers of the enamines being discussed.



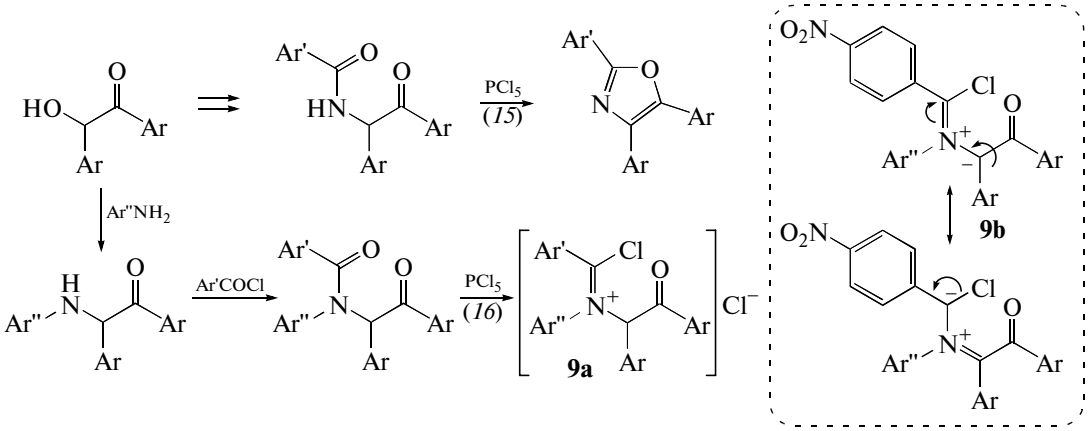
Scheme 23.

Importantly, compounds **8** slightly resemble salts **1** in their reactivity in the transformations similar to those given in Scheme 7 with a closure of the neutral oxazole ring. The alkylation of **8** (at the Y exo group or a pyridine type endo atom) would open up one more strategy for the synthesis of the analogs of **1**. Surprisingly, such transformations have not yet been studied.

5. SYNTHESIS OF ACYCLIC ANALOGS OF 2-HALOPYRIDINIUM SALTS

Examples of chloroiminium salts with an **E** structural motif like the one in salts **1** are scanty. The well-known Gabriel cyclodehydration (*15*) of acylaminoketones into oxazoles readily occurs under the action of various dehydrating reagents including PCl_5. At the turn of the 1960s, however, Heinze and Baumgartel showed that the reaction (*16*) of similar tertiary amines (from the series of *N*-aroyl-desylamines) with PCl_5 formed extremely hygroscopic chlorides **9a**, whose IR spectra contained the vibrations of the chloroiminium group instead of those of amide carbonyl.

A wide range of salts **9a** was obtained (15 examples of combinations of aryl groups), but the yields and element analysis data were given only for ionic chloride **9a** (all Ar = Ph) and covalent mesomeric betaine **9b** (Ar = Ar" = Ph, Ar' = p-nitrophenyl), which contained one HCl molecule less than **9a**. The role of the acceptor residue in the stabilization of the negative charge of **9b** is evident and shown in Scheme 24. The transformations of betaine were not studied, but we note that it is structurally related to 2-chloropyridinium phenacylides **2**.

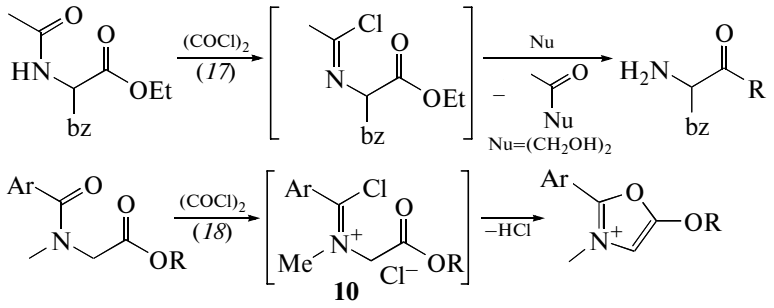


Scheme 24.

In [6] and later in [49–52], Heinze and Baumgartel studied the transformations of salts **9a** under the action of various binucleophiles, which surprisingly resembled the reactions of **1** in Scheme 7. In the

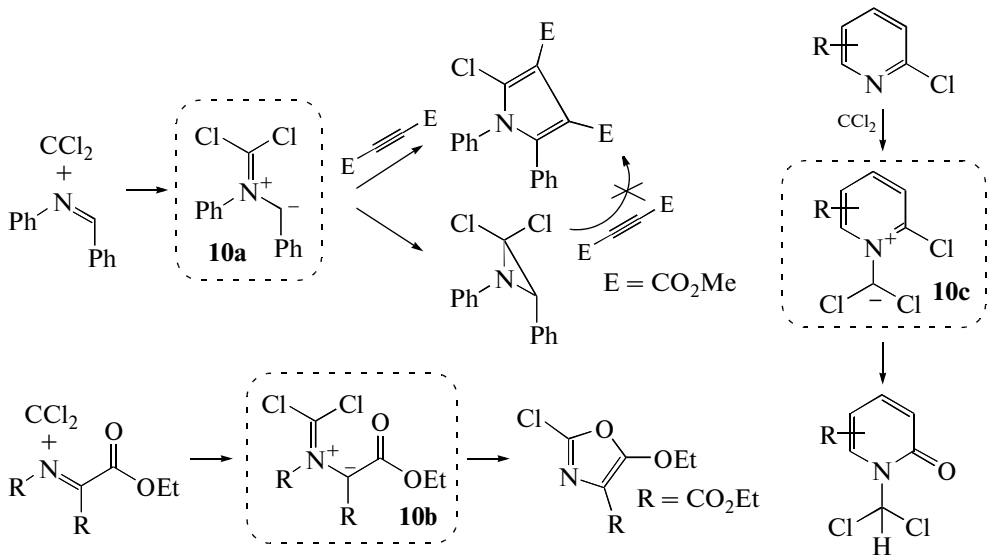
1980s, other authors studied these transformations with other nucleophiles [53] and substrates [54] (with the *N*-aryl instead of *N*-alkyl residue in the latter case). Note that the structures of **9** are too overcrowded with aryl residues (because they were obtained from benzoins, anilines, and benzoic acids); this probably explains why this class of substances has not attracted due attention.

Interest in these transformations and classes of substances has recently arisen in the chemistry of acylamino acids (Scheme 25). It appeared that the use of oxalyl chloride in reaction (*17*) led to a smooth transformation of amides into imidoyl chlorides, whose splitting with glycols proved an excellent strategy for deprotection of the starting acylamides [55] without epimerization of the amino acid residue (Scheme 25). The introduction of *N*-aroyl-*N*-methylamino acid ethers in a similar reaction (*18*) led to salts **10** with the **E** structural motif [7]. Despite the high reactivity of salts **10** (and their ylides) leading to a closure of the oxazolium ring, a number of their reactions (including cycloaddition) were successfully studied.



Scheme 25.

Interesting examples of structures with a similar motif are encountered in halocarbene chemistry (see review [56]; Scheme 26). In reactions with azomethines, dichlorocarbene forms chlorobetaine adduct **10a** [57], which is capable of not only closing the three-membered azirine ring, but also of undergoing 1,3-dipolar cycloaddition with dipolarophiles. The closest analog of structure **E**, betaine **10b**, (with a higher degree of oxidation due to an extra chlorine atom) is formed [58] as an adduct of dichlorocarbene and somewhat peculiar azomethine with three CO_2Et groups. Betaine **10b** experiences the expected closure of the oxazole ring (cf. Scheme 25), losing the substituent at the nitrogen atom. The reaction of 2-chloropyridine with dichlorocarbene is the last example of the unexpected interrelation of their chemistries, forming 2-chloropyridinium ylides **10c** and explaining the formation of the pyridone end product.



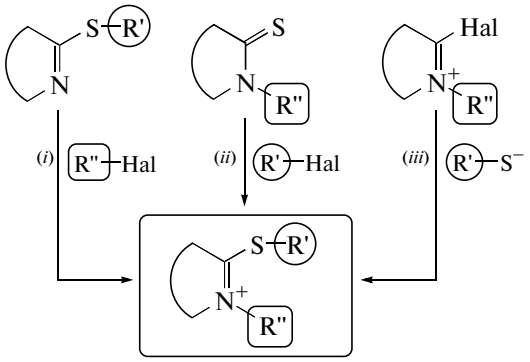
Scheme 26.

6. SYNTHESIS OF THE ANALOGS OF SALTS **1** WITH OTHER α-HETEROATOMS INSTEAD OF HALOGEN

In some interesting subclasses of pyridinium salts (and other heterocycles), the α-halogen atom of **1** is formally replaced with a bivalent heteroatom (S, O, NR). We are concerned only with those cases in which the new heteroatom does not hinder the formation of betaine-ylides and, like α-halogen, is capable of serving as a leaving group (at least, theoretically).

6.1. Analogs with a Sulfur-Containing Group in the α-Position

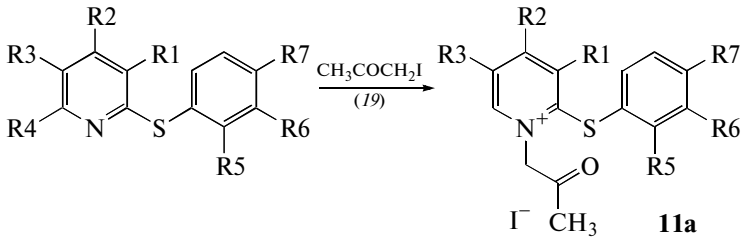
The α-alkylthio group often serves as a leaving group in neutral heterocycles and their quaternary salts. These salts are readily obtained by (i) *N*-alkylation of heterocycles already having a 2-SR' group, (ii) S-alkylation of thiones already having an NR" group, and (iii) replacement of halogen in Mukayama reagents by their reaction with mercaptane anions. These salts are well defined for cases when the radical R" at the nitrogen atom is an alkyl or benzyl group. If, however, R" is a methylketone residue (or a CH_2COOR fragment), the general picture is more complicated.



Scheme 27.

Strategy (III) should be rejected. Our attempts to use it for 2-halo-*N*-phenacylpyridinium salts **1** (by performing their reaction with the alkaline salts of mercaptane) failed; in one experiment with $PhCH_2SH$, only dibenzyl disulfide was identified in the reaction mixture.

For the synthesis of the sulfur-containing analogs of **1**, the literature gave a detailed strategy (I) for the *N*-phenacylation of 2-arylthiopyridines as an example. The starting substances are accessible (obtained by reactions of 2-halopyridines and thioophenols), and their quaternization with iodoacetone (*19*) occurs quite readily (Scheme 28).



Scheme 28.

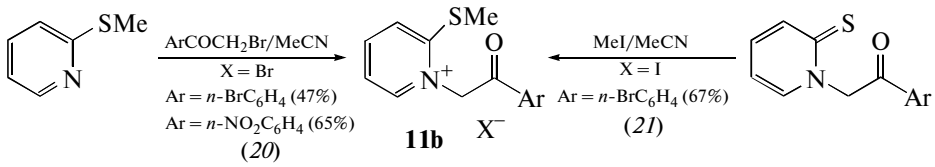
Salts **11a** are formed with nearly quantitative yields (Table 3), and even at negative temperatures the reaction occurs for 1–5 days [60–62]. DMF was used as a medium. The salts were reprecipitated from this highly polar medium after diluting the mixture with ethyl acetate. An exception was a sterically hindered homolog (R4 = Me), for which no traces of reaction were observed even after keeping the mixture at 0°C for half a year or boiling in alcohol with chloroacetone. The ylides of these salts have not yet been studied.

Table 3. Yields of **11a** in reaction (19)

Degrees of radical substitution in **11a**	Additional substituents*, yields (the reaction time is given in parentheses in days)
2-Phenylthiopyridine (R=H)	91% (1) [60]
Unsubstituted pyrydyl (R1=R2=R3=R4=H)	R5=Me 86% (2) [60]; R6=Me–** (2) [60]; R7=Me 90% (2) [60]; R7=Cl 69% (2) [60]; R7=t-Bu 80% (10) [61]
Unsubstituted phenyl (R5=R6=R7=H)	R1=Me 96% (5) [61]; R2=Me 93% (1) [61]; R3=Me 96% (5) [61]; R4=Me 0% (180) [61]
Other R*** and their combinations	R2=R5=Me 98% (1) [61]; R2=R6=Me 91% (1) [61]; R5R6=benzo 85% (7) [62] 75% (40) [123]; R5R6=benzo, R3=Me 73% (7) [62]; R6R7=benzo 88% (7) [62]; R6R7=benzo, R3=Me 66% (7) [62]

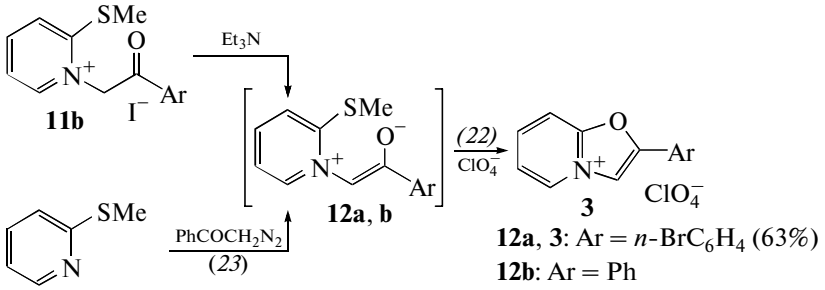
Notes: * @.
** @.
*** @.

2-Methylthiopyridinium analogs **11b** had remained unknown for a long time until we obtained them by two procedures corresponding to strategies (I) and (II) [63] (Scheme 29). Route (I) (reaction (*20*)) was *N*-phenacylation of accessible 2-methylthiopyridine with bromoketones similar to syntheses of **1** and **11a**. For route (II) (reaction (21)), we used S-methylation of *N*-phenacylpyridine-2-thiones (which can be readily obtained by reactions of **1** or **3** c Na_2S with Na_2S). These thiones can also be effectively alkylated with Merryfield resin [64]. Salts **11b** were thus deposited (via the sulfur atom) on a polymer substrate.



Scheme 29.

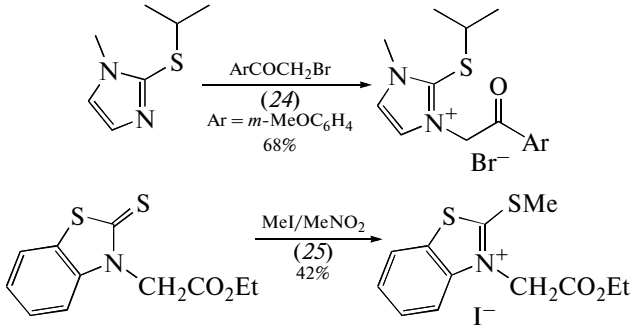
The reaction of salt **11b** (Ar = *p*-BrC_6H_4) with Et_3N forms phenacylide **12a**, which undergoes a closure of the oxazole ring and is transformed into salt **3** with a 63% yield [63] (reaction (*22*), Scheme 30). This transformation vividly illustrates the relationship between class **11** and classes **1** and **3**. It is interesting that phenacylide analog **12b** (Ar = Ph) can be generated by *N*-alkylation of 2-methylthiopyridine with diazoketone in the presence of rhodium salts [65] (reaction (*23*)); the ylide obtained in situ was introduced in a reaction with a dipolarophile.



Scheme 20.

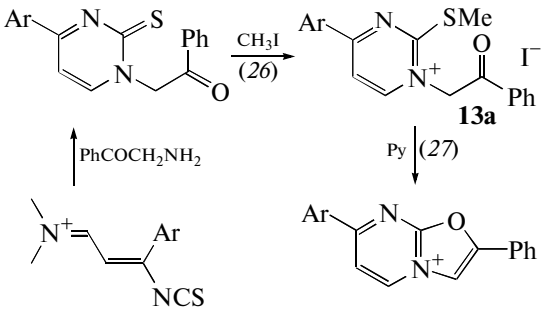
The salts of other heterocycles structurally related to salts **11** were represented in the literature by single examples. Strategy (I) was used only once for 2-(alktlthio)imidazoles [66], for which *N*-phenacylation

(*24*) was performed under mild conditions (20°C, MeCN, 12 h). Strategy (II) was used for S-methylation (*25*) of *N*-substituted benzothiazolyl-2-thione (Scheme 31).



Scheme 31.

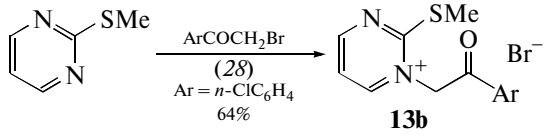
As described in [68], the complex pathway to the assembly of the pyrimidine ring (Scheme 32) led to the *N*-phenacyl derivatives of pyrimidine-2-thione, which readily underwent S-methylation (*26*) to form salts **13a**. The resulting salts easily experienced a closure of the oxazole ring by reaction (*27*). Transformation (*27*) was similar to the conversions of **1** into **3**, while the type of heterocycle and the type of leaving group differed.



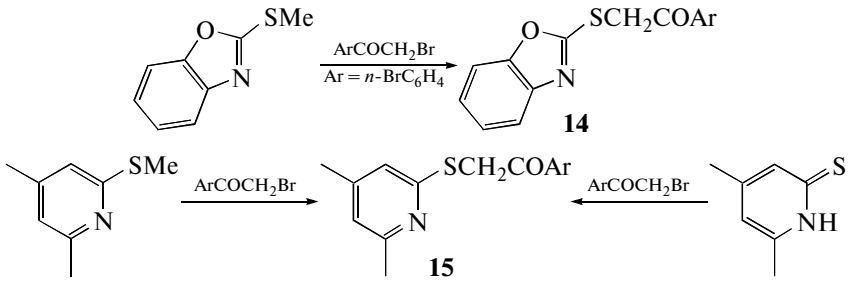
13a: Ar = C_6H_5 (65%), p-MeC_6H_4 (86%), p-$MeOC_6H_4$ (66%), p-ClC_6H_4 (67%),

Scheme 32.

We have not found any other literature data on the synthesis of salts with a combination of *N*-phenacyl and 2-RS groups in their structure. The scantiness of data on these salts seemed strange, because heterocyclic α-thiones are readily available and liable to smooth S-alkylation, generating convenient substrates for *N*-phenacylation. We attempted to study these transformations; for this we prepared a series of α-MeS-substituted azoles and azines [69] and applied strategy (II) to them. It appeared that 2-methylthiopyrimidine reacted with phenacyl bromide (reaction (*28*)) to form desirable salt **13b**. The route to this product was much shorter (Scheme 33) than the one to its analog **13a** (Scheme 32). After a long period of selecting conditions for these transformations, we found an optimum procedure: keeping the reagents in warm sulfolane for many days. Meanwhile, 2-(methylthio)benzothiazole was phenacylated, forming a complex mixture of products, and its benzoxazole analog, as well as 4,6-dimethyl-2-methylthiopyridine, transformed into the slightly discouraging structures of S-phenacyl derivatives **14** and **15** (Scheme 34). The structure of benzoxazole **14** was confirmed by XRD data, and the structure of pyridine **15**, by its alternative synthesis from thione.

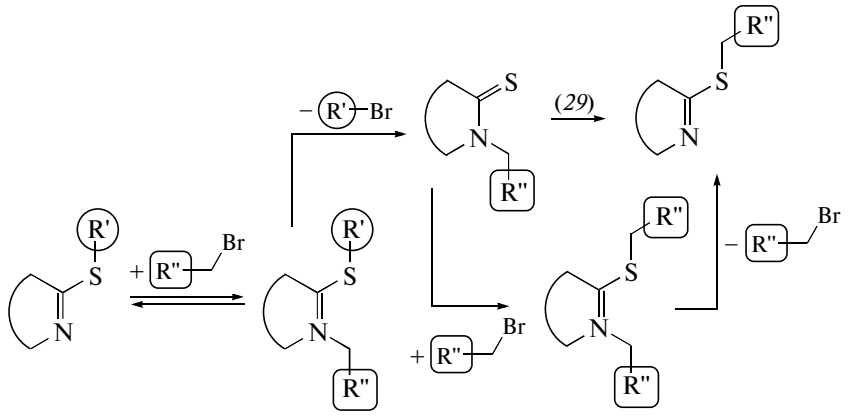


Scheme 33.



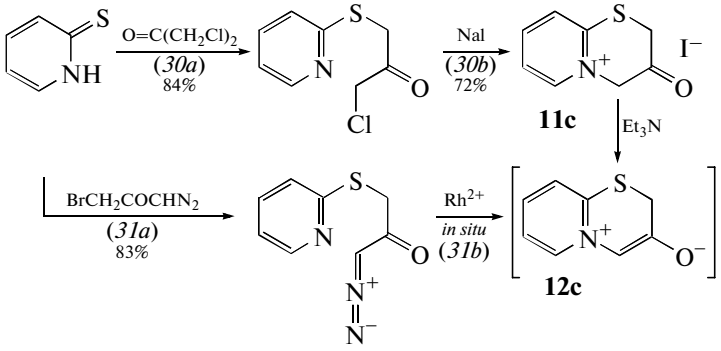
Scheme 34.

It seems unlikely that these products were obtained by direct phenacylation of the α-methylthio group, because this group is conjugated to the hetero ring and hence inactive. A possible explanation for this was encountered in publications on the alkylation of sulfur-containing pyridines [70] and thiazoles [71] already having at least one alkyl group at the heteroatom (the 2-RS or 1-NR group in thione). It appeared that the salts formed from compounds of all these classes and, having alkyl groups at two heteroatoms, are capable of losing any of these groups on heating (Scheme 35); *N*-alkyl-2-thiones can additionally undergo the Chapman rearrangement into S-alkyl isomers by reaction (*29*). Probably for these reasons, the phenacyl residue is attacked at the sulfur atom in **14** and **15**.



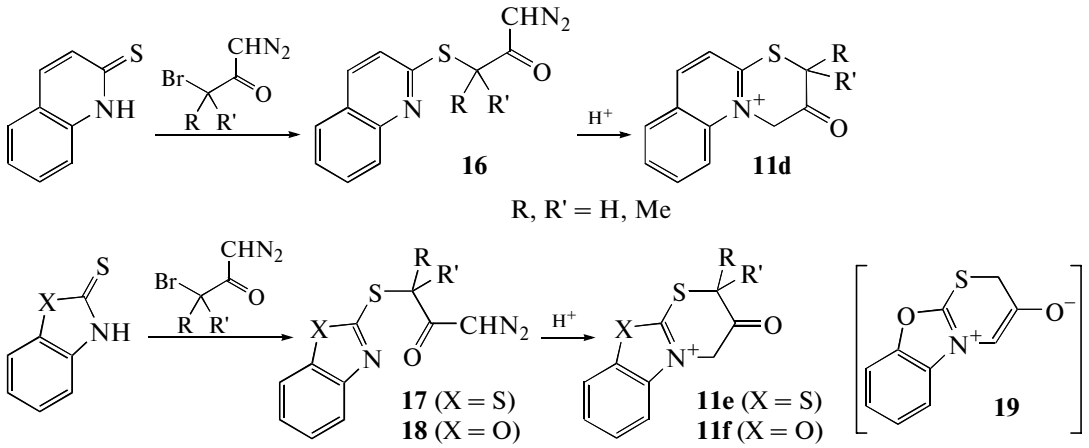
Scheme 35.

The possibility of alternating *S*- and *N*-alkylations of heterocyclic thiones was effectively demonstrated for the α,α'-dichloroacetone bis-alkylating agent. In a reaction of this agent with pyridine-2-thione [72] (Scheme 36), intermolecular alkylation (*30a*) at the sulfur atom was followed by intramolecular alkylation (*30b*) at the nitrogen atom and formed an interesting bicyclic salt **11c**. This salt readily transformed into betaine-ylide **12c**, which easily reacted with dipolarophiles. According to [65], however, ylide **12c** was generated by double alkylation of pyridine-2-thione with α-halodiazoacetone (*31a,b*).



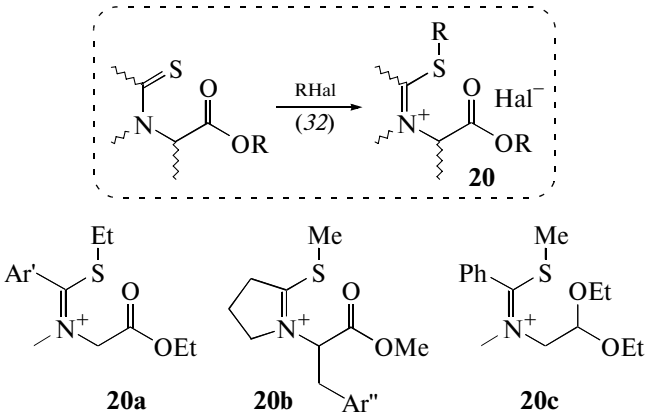
Scheme 36.

Similar *S*,*N*-double alkylation of heterocyclic thiones with α-halodiazoketones was studied in the series of quinoline and benz-1,3-azoles (Scheme 37) [73–75]. In acetonitrile, closure of the thiazine ring in **16**–**18** under the action of chloric acid occurred almost quantitatively, while in water (and sulfuric or acetic acid) solvolysis of the diazo group proceeded without cyclization. The formation of ylides from salts **11d**–**f** was not reported in that series of publications. Meanwhile, other authors [65] found independently that under the action of rhodium salts, diazoketone **18** (R = R' = H) cyclized into ylide **19**. The ability of ylides obtained from **11c**–**f** to undergo closure to the oxazolium ring remains dubious (this would demand a rearrangement), but they are structurally related to halophenacylides **2** and their thia analogs **12a** and **12b**.



Scheme 37.

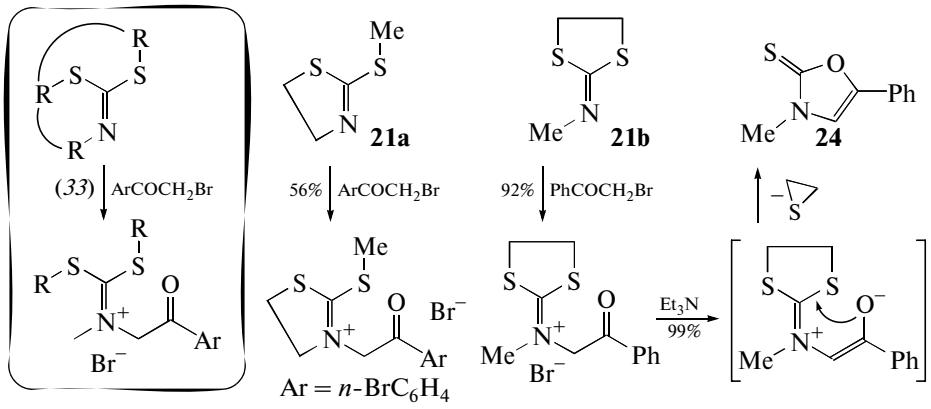
The acyclic analogs of the class in question deserve special attention; these are cations **20** with the **E** structural motif (Scheme 38), in which halogen was replaced by an RS group. The few examples of these salts are obtained by *S*-alkylation (*32*) of the corresponding thioamides. The derivatives of amino acid **20a** [76], **20b** [77], and even aminoacetal **20c** [78] were obtained in this way. Note, however, that these salts were obtained quite accidentally; the aryl residue in **20a** and **20b** is exotic, and the chemistry of their betaine-ylides has not yet been studied.



Scheme 38.

Reaction (*32*) in Scheme 38 is quite consistent with strategy (ii) of *S*-alkylation used for the transformation of heterocyclic thiones into salts **11**. The analog of strategy (i) for alicycles is also known; this is *N*-phenacylation (*33*) of compounds **21a** and **21b** in Scheme 39. The resulting salts **22** contain two (ring) heteroatoms at the iminium carbon atom; i.e., they have a greater degree of oxidation than salts **20**.

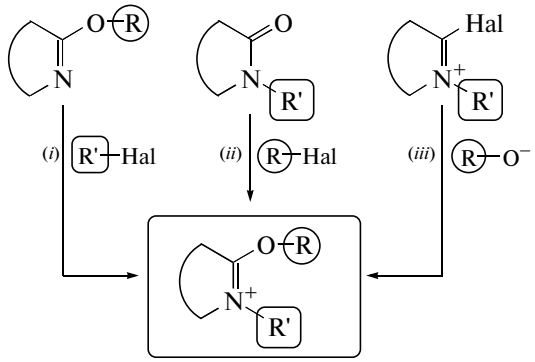
Using thiazoline **21a** as an example, we proved that salt **22a** could be formed in this way [69]. For dithiolane **21b**, Japanese researchers [79, 80] showed that salt **22b**, obtained by similar alkylation, quantitatively formed phenacylide **23** under the action of a base and that **23** was liable to undergo dipolar cycloadditions. As in many other examples discussed above, the enolate iminium motif of this phenacylide was unstable, and betaine **23** readily underwent ring closure to oxazole **24** (with elimination of thiirane, according to the authors). The examples in Schemes 38 and 39 prove the similarity (in synthetic routes and channels of transformations) of structures **20** and **22**, which are, to a certain extent, analogs of **1**, **11**, and open-chain reagents **E**.



Scheme 39.

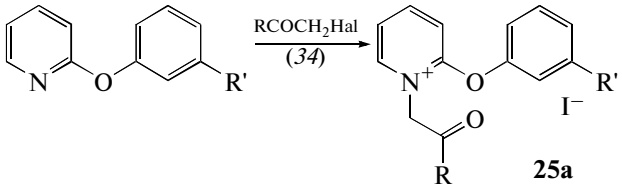
6.2. Analogs with an Oxygen-Containing Group in the α-Position

The family of stable analogs of salts **1** with an OR oxygen-containing group instead of halogen is small. To summarize the synthetic routes of these substances, we use Scheme 27 discussed above, in which the sulfur atom in the substance is replaced by the oxygen atom (Scheme 40).



Scheme 40.

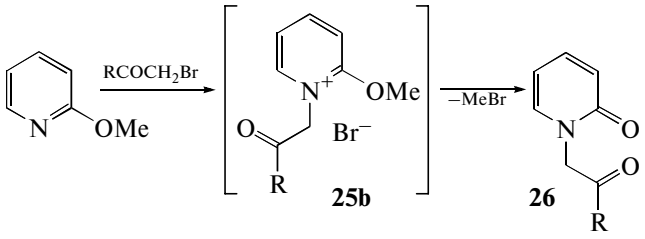
For 2-RO pyridinium salts, as well as their 2-RS analogs, the three strategies were effectively used only for those cases when the R' residue at the nitrogen atom was alkyl or benzyl. If, however, R' was a fragment of methylketone, the three methods were much less effective. Strategy (I)—*N*-phenacylation of 2-RO-substituted pyridines—was successfully used only when the RO group was a phenol residue (Scheme 41). 2-Phenoxypyridines (readily obtained by the reactions of halopyridines with phenoxides) smoothly reacted with iodoacetoneor phenacyl bromide, forming pyridinium salts **25a** [81]; the only exception was sterically hindered α-methyl-α'-(phenoxy)pyridine, which was not alkylated with iodoacetone. Curiously, with a *meta*-alkoxy group introduced in the phenol fragment, the yield of salts **25a** in reaction (*34*) increased appreciably (Table 4). We showed [10, 82, 84] that salts **25a** resembled halopyridinium salts **1** in some of their properties, forming colored ylides under the action of bases and the analogs of the products obtained from **1** in reactions with certain nucleophiles.



Scheme 41.

In similar reactions with phenacyl bromides, 2-methoxypyridine formed a different type of product (Scheme 42). *N*-Phenacylpyridones **26** formed instead of the expected *N*-phenacyl-2-methoxypyridinium salts **25b** [44, 12]. Bromoacetone reacted similarly. Intermediate salts **25b** were quantitatively *O*-demethylated in this case due to the attack of the bromide ion, which is a relatively weak nucleophile, at the

methyl group. This result is explained by the easy elimination of the *N*-alkylpyridone residue in the *N*-alkyl-2-alkoxypyridinium salts, which was mentioned (in the Introduction) as a major distinction of the reactions of Mukayama salts with alcohols.

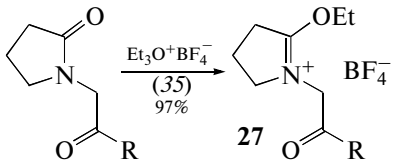


R	Yield
4-BrC_6H_4	78%
4-$C_6H_5C_6H_4$	55%
4-$CH_3OC_6H_4$	52%
C_6H_5	74%
CH_3	Not indicated

Scheme 42.

While the strategy depicted in Scheme 42 did not afford salts **25b** (direct analogs of **1, 11**, and **25a**), the formation of pyridones **26** in this reaction proved extremely useful in the synthesis of various oxazolopyridinium salts **3**, because (Schemes 18 and 21) pyridones **26** can be quantitatively transformed into salts **3** by the reaction with sulfuric acid. *N*-Phenacylpyridones **26** can also be prepared by other procedures [12], for example, direct phenacylation of pyridone-2 anions, but these syntheses are complicated by the formation of a mixture of *N*- and *O*-alkylation products. The strategy presented in Scheme 42 can therefore serve as a regioselective procedure for the synthesis of *N*-phenacylated pyridones **26**; i.e., the methyl part of the methoxy substituent in pyridine acts as a protective group that hinders *O*-alkylation.

Strategy (I) of *N*-alkylation is thus effective only for the synthesis of 2-phenoxy-substituted salts **25a**, but not their alkoxy analogs **25b**. An alternative for the synthesis of **25b** can be strategy (II), i.e., the *O*-alkylation of *N*-substituted pyridones **26**, probably demanding powerful alkylating agents with a nucleofuge residue (triflate, tetraborate, and other types). No such attempts have yet been reported for pyridones **26**, although a close analog of this transformation (reaction (*35*)) was described [84]. Salt **27** with an α-alkoxy group and the desirable **E** structural motif was obtained in this way (Scheme 43); the ethoxy group in these salts was shown to be leaving and easily replaced, e.g., under the action of CH-acids.

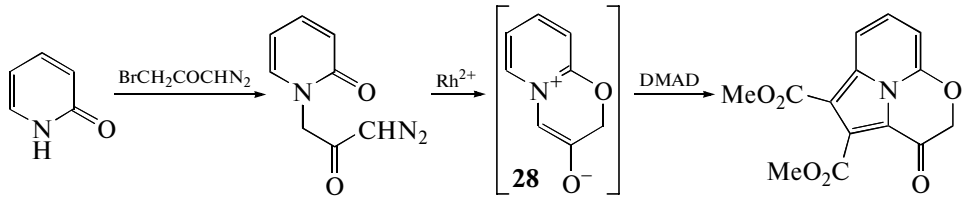


Scheme 43.

As shown above (Schemes 36 and 37), double alkylation of both heteroatoms proved effective for the synthesis of salts and their ylides in the series of pyridine-2-thione and its analogs. This method also proved applicable to pyridone through its alkylation with α-halodiazoacetone [65] (Scheme 44). In contrast to reaction (*30a*), the first stage of this alkylation was *N*-alkylation; at the next stage, betaine-ylide **28**, which reacts with dipolarophile as the expected 1,3-dipole, formed in situ.

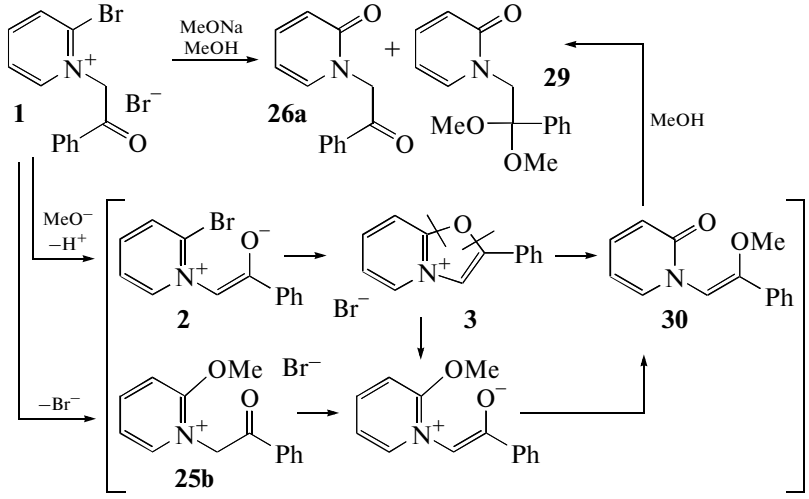
Table 4. Yields of **25a** in reaction (34)

Substituents		Yields of salts **25a**
R in bromoketone	R' in phenoxypyridine	
CH_3	H	73%
Ph	H	39%
CH_3	OCH_3	84%
Ph	OCH_3	100%
CH_3	OC_2H_5	91%



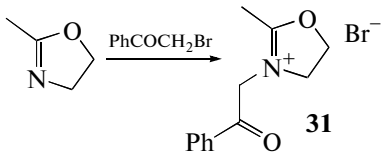
Scheme 44.

Strategy (III) shown in Scheme 40, i.e., the nucleophilic substitution of halogen in salts **1** under the action of an equivalent of alkoxide, is the last promising method for the production of the "elusive" 2-alkoxy-substituted salts **25b**. For salt **1a** with sodium methoxide [85, 36], however, this experiment led to an unexpected result, namely, quantitative formation of a mixture of phenacylpyridone **26a** and ketal **29** (in a ratio of 3 : 2, Scheme 45). The formation of the ketal function of compound **29** in a nucleophilic medium was the least trivial result in this transformation. The formation of ketal **29** can only be explained if we assume that vinyl ether **30** formed as an intermediate and added a methanol molecule. Compound **30** could form by different routes presented in Scheme 45. In the control experiment, oxazolium salt **3** reacted with sodium methoxide to form the same ketal **29** possibly through cleavage of one of the CO bonds. The transformation chain 1–2–3 could thus explain the observed result. The formation of intermediate **25b**, however, cannot be excluded; this powerful methylating agent could be the reason for the *O*-methylation of the *N*-phenacylide residue, leading to the same intermediate **30** via a different pathway.



Scheme 45.

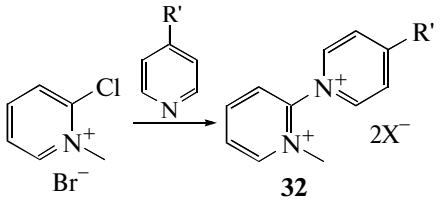
The acyclic analogs of the structures (with the **E** motif and the RO group instead of halogen) are unknown except one example in the series of unsaturated cycles [86], namely, oxazoline salt **31** obtained by *N*-phenacylation strategy (I) and liable to form betaine-ylide (Scheme 46).



Scheme 46.

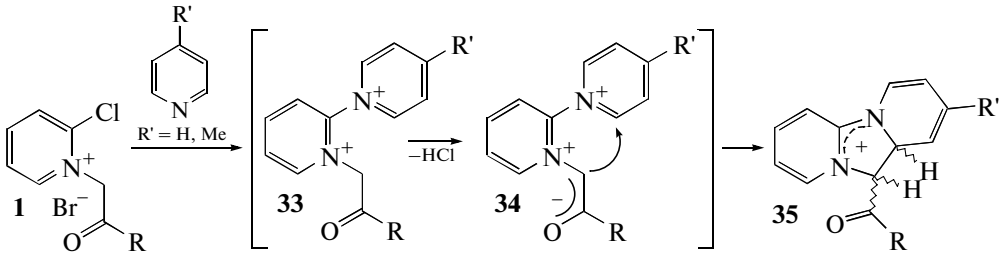
6.3. Analogs with a Nitrogen-Containing Group in the α-Position

At first sight, it is somewhat difficult to imagine analogs of **1** with a nitrogen heteroatom instead of halogen as a leaving group. The best nitrogen-containing leaving groups are generally charged fragments, namely, the trialkylammonium group of the pyridinium cation (and their analogs) attached to the center of substitution by the quaternary nitrogen atom. Hence the most complete analogs of **1** should be dications. Several unusual examples of pyridinium dications **32** (obtained from Mukayama salts and pyridines [87]) were described in which the nucleophilic substitution of the nitrogen-containing residue could occur (Scheme 47).



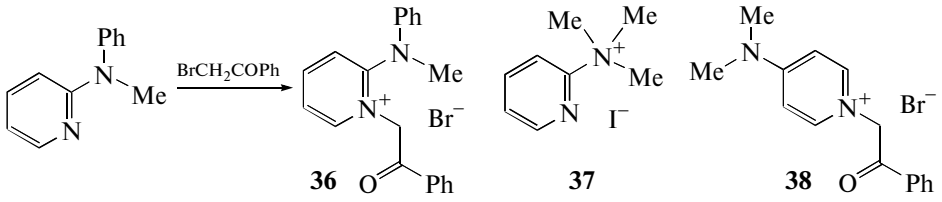
Scheme 47.

The corresponding analogs of **1** with a pyridinium residue instead of halogen could be obtained from salts **1** by a similar procedure. As shown by Kröhnke [21], such dications **33** are actually formed from salts **1** treated with unsubstituted pyridine (or γ-picoline, Scheme 48). In basic media, however, dications **33** were deprotonated into phenacylides **34**, which readily underwent closure of the imidazoline ring to form tricycles **35** capable of further aromatization [21] and interesting transformations of both pyridine rings [10, 88]. An attempt to replace pyridine by another tertiary amine (triethylamine, α-picoline, or quinoline) in this reaction led only to the enolization of salts **1** into phenacylides **2** and the formation of oxazolopyridinium salts **3**, as mentioned in Section 3.2. In the case of the 2-chloro [21] and 2-bromo [40] derivatives of *N*-phenacylthiazolium, similar cyclizations with dications were observed.



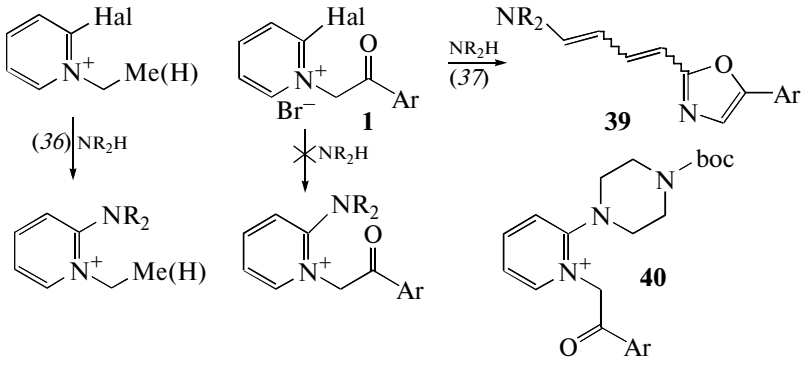
Scheme 48.

The salts related to **1** could be *N*-phenacylpyridinium salts with an α-NR_2 group. Only one example of this salt was described in the literature, namely, salt **36**. It was readily obtained by phenacylation of 2-(*N*-methylanilino)pyridine at the endocyclic nitrogen atom [89] (Scheme 49), but the properties of this compound were not studied. The possibility of obtaining other analogs of **36** by alkylation of 2-NR_2-pyridines remains questionable because the reaction can be complicated by an attack of the quaternizing agent at the exocyclic amino group. Thus the alkylation of 2-dimethylaminopyridine with methyl iodide gave quaternary salt **37** [90]. For the 4-dimethylaminopyridine isomer (DMAP, widely used as a base), phenacylation proceeded regioselectively at the pyridine nitrogen atom and formed salt **38** [91].



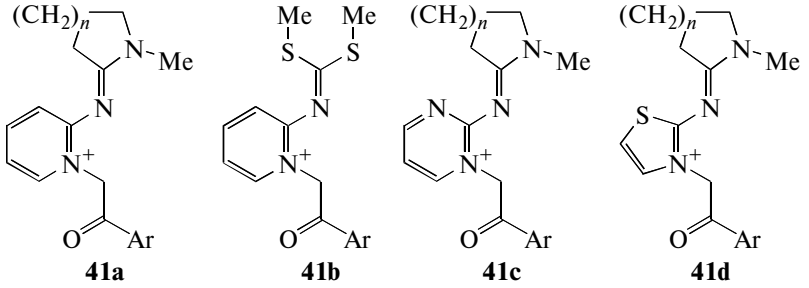
Scheme 39.

The analogs of **36** should probably be obtained by an alternative strategy, for example, by replacing α-halogen in **1** by a dialkylamino group. Examples are encountered in the chemistry of Mukayama salts [2], easily reacting with secondary amines by reaction (*36*). Our attempts to obtain salts **36** by reactions of phenacyl salts **1** with secondary amines, however, led to extremely unusual recyclizations (*37*) of pyridinium salts into oxazoles **39** [92] (Scheme 50). These reactions occurred smoothly for a wide series of secondary amines in MeCN [92] and even in water when aqueous dimethylamine was used [93]. Other analogs of **1** containing the 2-RS [63, 64] and 2-PhO [82, 83] groups experienced a similar rearrangement into oxazoles. This reaction is related to the sequence of transformations **1**–**2**–**3** and discussed in another part of this review. It is not excluded, however, that in the complex chain of transformations [37], one of the stages involves direct withdrawal of halogen by reaction (*36*). The reaction of salts **1** with *N*-boc-piperazine [94] thus gave a substance whose NMR spectra corresponded to 2-(dialkylamino)pyridinium salt **40**.



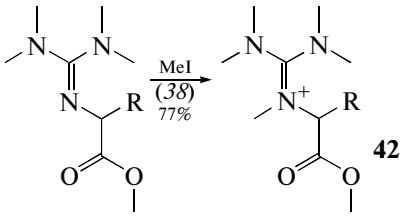
Scheme 50.

Compounds **41a** [95] and **41b** [96] and their analogs **41c** and **41d** [95] with a different type of ring (Scheme 51) are an interesting subclass of *N*-phenacylpyridinium salts with a modified α-amino group. They are synthesized by phenacylation of the corresponding heterocycles at the endocyclic atom of the aromatic ring. Under the action of bases, salts **41** undergo interesting heterocyclizations, whose key stage is the generation of ylide and its intramolecular attack at the electrophilic center of the α-substituent.



Scheme 51.

This is only one example of the acyclic analogs of salts **36** and **40** (with an **E** structural motif and an NR_2 group instead of halogen), namely, guanidinium salts **42**, which are the derivatives of amino acid ethers (Scheme 52). These salts were recently obtained by quaternization (*38*) in an effort to find a new type of chiral ionic liquids.



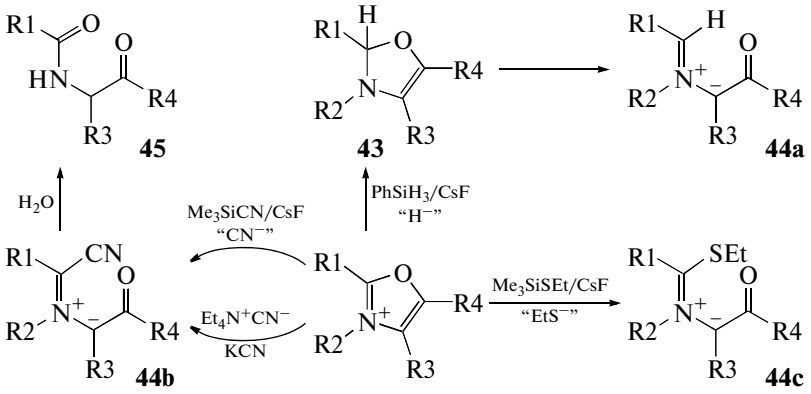
Scheme 52.

7. GENERATION OF BETAINE-YLIDES FROM OXAZOLIUM SALTS

As we can see, a typical distinction of halopyridinum salts **1** is the transformation of their phenacylides **2** into salts **3** with a closure of the new oxazolium ring. Heteroanalogs of salts **1** (with a different heteroring and/or heteroatom instead of halogen) equally readily form ylides capable of a similar closure into oxazolium salts. The motive force of such cyclizations of ylides is quite evident and associated with the aromaticity of the oxazole products. The reverse transformation—the opening of oxazolium salts into ylides under the action of a number of nucleophiles—is less trivial.

Ring cleavage in the oxazolium salts under the action of hydrides was reported long ago, but the intermediate formation of azomethine-ylides in these reactions had not been proven until the 1980s.

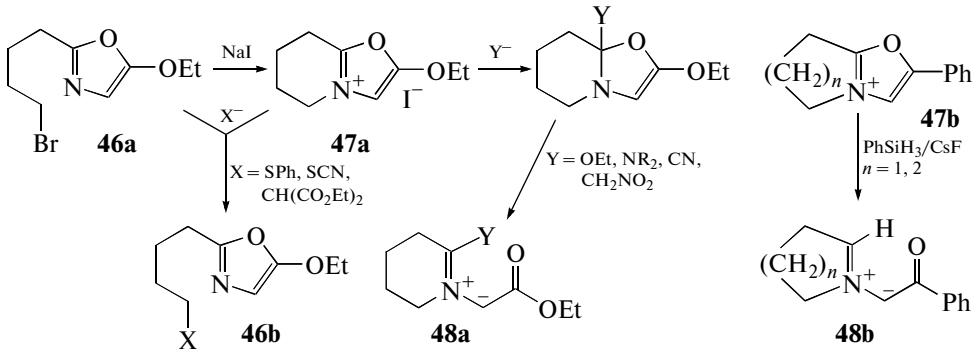
The $PhSiH_3$–CsF combination was suggested as the best source of the hydride ion that causes ring opening but does not react with ylide or external dipolarophiles [98, 99]. The oxazolium salts in this case smoothly transformed, via the formation of unstable oxazolines **43**, into azomethine-ylides **44a** due to the formation of cycloadducts with dipolarophiles. Using other nucleophiles (as silicon-containing reagents or usual anions) led to ylides **44b** and **44c** with the (CN or EtS) leaving groups [100, 101]. The structures of the resulting ylides exactly correspond to the **E** structural motif; the cycloadditions involving these compounds led to more significantly oxidized products than in the case of ylide **44a**. When the R4 group in oxazolium salts was replaced by an extended chain with an acetylene residue, cycloaddition to the generated ylides occurred intramolecularly, due to which a number of effective syntheses of natural polycyclic substances were carried out [102, 103, 104].



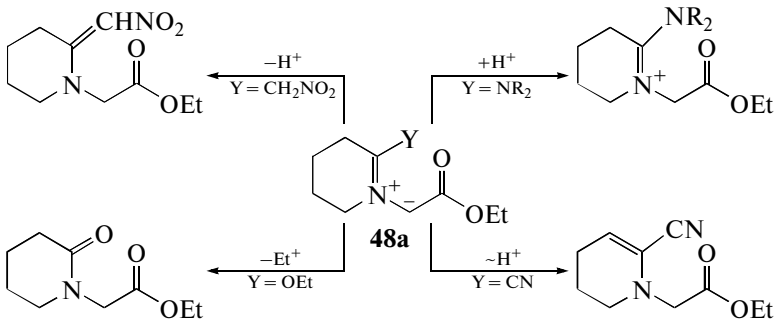
Scheme 53.

An attempt of another research group to trace the fate of cyano-substituted ylide **44b** (R1 = Ph, R2 = Et, R3 = H, R4 = ORt) by chromatography of the reaction mixture led to the isolation of product **45** [101]. As can be seen, the cyano group of ylide was replaced during the hydrolysis, as expected, but this was accompanied by an extremely unusual dealkylation of the R2 substituent (ethyl group). According to the authors, the ethyl residue could migrate at the intermediate stage to the oxygen heteroatom of ylide and then vanish during subsequent hydrolysis.

The generation of analogous ylides and a series of their transformations were studied [101, 105] by investigating the structure of bicyclic oxazole **47a**, slowly formed (with a half-period of 20 min) from monocycle **46a** under the action of NaI (Scheme 54). It appeared that the possibility of ylide formation was determined by the nature of the X and Y nucleophiles (probably, their hard or soft nature); in some cases, covalent products **46b** (of another type) formed instead of ylides **48a**. Similar bicycles **47b** successfully formed phenacylides **48b** [103]. The generation of ylides **48a** (Y = CN, NR_2) and **48b** was proved by the formation of cycloadducts with DMAD. Curiously, the further chemical fate of ylides **48a** depended on the nature of the Y group (Scheme 55). It can be seen that the possible channels of the transformations of betaine-ylides involve protonation into a quaternary salt (Y = NR_2) or transformations into covalent enamines due to protonation (Y = CH_2NO_2), tautomerization (Y = CN), or dealkylation into piperidone (Y = OEt).

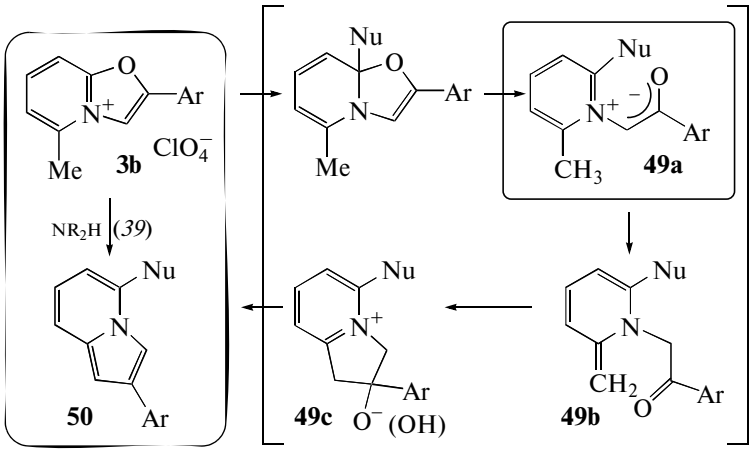


Scheme 54.



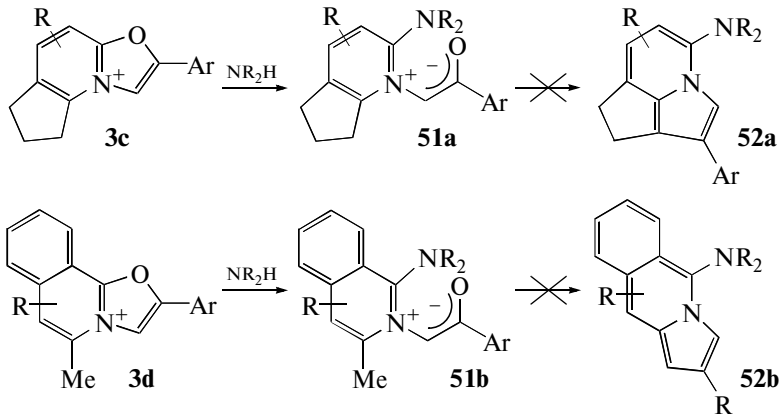
Scheme 55.

The possibility of a similar route to pyridinium phenacylides by the opening of oxazolium salts **3** was first discovered by the research group of the author in the late 1990s [12, 106, 107]. In the reactions of nucleophiles with salts **3b** (Scheme 56; Nu are secondary amines or alkaline alkoxides), the pale color of the substrates changed to bright crimson, probably due to the formation of pyridinium phenacylides **49a**. The forming betaine-ylides have no channels of transformation other than tautomerization into enamines **49b** (due to the high CH-acidity of the α-methyl groups in pyridinium salts).



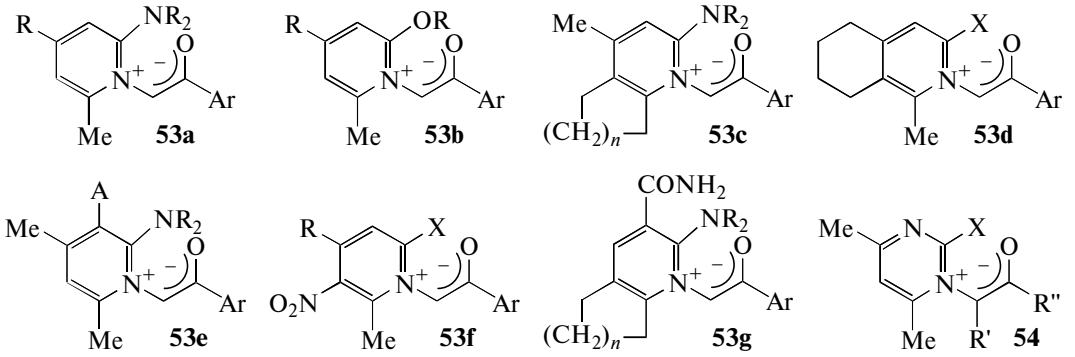
Scheme 56.

Enamines **49b**, in turn, are classic intermediates of the Chichibabin synthesis of indolisines and are quickly cyclized into pyrroline hydrates **49c** aromatized into 5-substituted indolisines **50**. When experiments were performed in an NMR ampoule [32], the formation of phenacylides **49a** was not recorded; only fast formation (and slow disappearance) of hydrates **49c** was detected experimentally. External dipolarophiles could not be used as traps for phenacylides because of the high activity of the nucleophiles. In two instances, however, the formation of phenacylides was indirectly confirmed by creating maximum hindrances for the closure of the pyrrole ring (Scheme 57). In the first example [108, 109], substrate **3c** had a structure that created maximum steric hindrances in indolisine product **52a**. In the second example of isoquinolinium salt **3d** [110], the thermodynamically unfavorable quinoid character of the forming tricycle **52b** served as a hindrance to cyclization. In both cases, the ylides were brightly colored, as expected, but only the products of the hydrolytic splitting of ylides **51** containing a fragment of *N*-phenacylpyridone were isolated (by chromatography), instead of indolisines **52**.



Scheme 57.

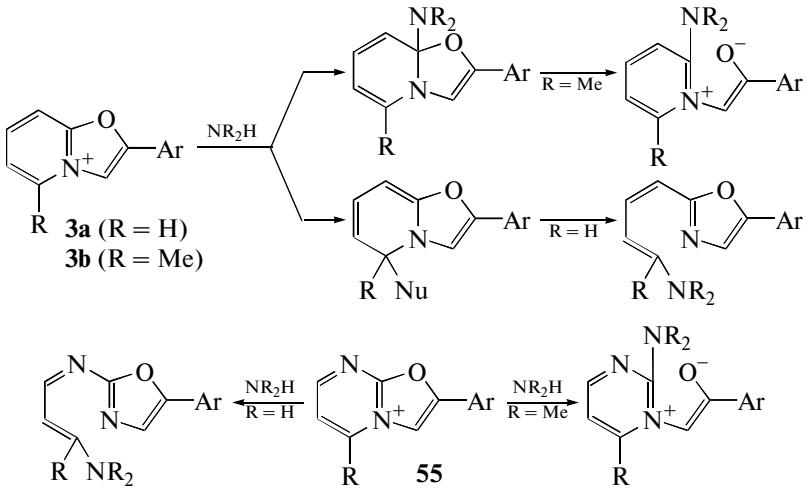
The preparative aspects of this new strategy for the synthesis of indolisines (and other condensed pyrroles from oxazolium salts) were considered in detail in the review [12]. Since the subject of this publication is phenacylides, we restrict ourselves to a short list of the structural types of ylides that can (or cannot) be prepared from salts **3** and their analogs by reaction (39). The possibility of generating ylide structures was confirmed for the series of pyridinium (**53**), isoquinolinium (**52b**), and pyrimidinium (**54**) (Scheme 58).



Scheme 58.

An essential condition for the generation of all these ylides is the presence of a methyl group in the azine ring of the starting condensed oxazolo-azine (as in the structural prototype **3b**, Scheme 56). All ylides in Scheme 58 ultimately have the same type of α-methyl radical (or the α-methylene unit as in **53c** and **53g**) in the azine ring. Clearly, these ylides cannot be obtained from the *N*-phenacyl-α-methylpyri(mi)dinium salts, because these salts do not exist at all (Schemes 16 and 18).

If the starting condensed oxazolium salt has no methyl (methylene) groups (Scheme 59), an ylide is not generated and the six-membered ring is opened instead of the oxazolium ring [122, 107]. (The oxazolopyrimidinium salts **55** behave similarly [45, 111].) As shown by quantum-chemical calculations [107, 112], oxazolopyridinium system **3a** is ambidental, and the nucleophilic attack leading to the opening of the pyridine or oxazole ring is almost equiprobable. The introduction of a CH_3 group in the dicycle drastically decreases the probability of the pyridine ring opening (presumably because of the steric effect), and the opening of the oxazolium ring into phenacylide in **3b** becomes preferable.



Scheme 59.

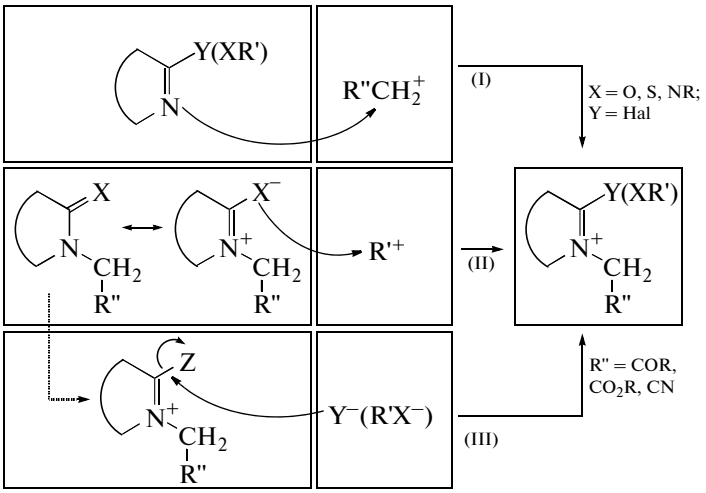
The variability of functions in the pyridine fragment of ylides **53** in Scheme 58 (the presence of acceptor substituents A = CN, $CONH_2$, CO_2Et, R alkyl groups, and/or alicycles with the number of additional methylene units *n* from 1 to 4) depends only on the availability of substituted pyridones, from which condensed oxazoles are obtained [12]. The residue at the nitrogen atom in ylides **53**, **54** is the phenacyl group; for **54**, the combination R' = R" = Me was also studied.

Recyclization (*39*) successfully occurred only when secondary amines or alkoxides were used [12, 113–115]. The typical ylides in Scheme 58, like structures **53a** and **53b**, therefore have a residue X = OR, NR_2. Sections 6.2 and 6.3 showed that *N*-phenacylpyridinium salts with these radicals (OR or NR_2) in the α-position remain the least-known analogs of **1**; hence, phenacylides on the basis of these salts are unavailable. The ring opening strategy for condensed oxazoles offers a partial solution to this problem. The generation of ylides by reaction (*39*), however, has a number of limitations; with phenoxides and thiophenoxides there is no reaction [10], while the corresponding phenacyl salts (and then ylides) can readily be synthesized from 2-(thio)phenoxypyridines (Tables 3 and 4). In other words, conventional syntheses of pyridinium phenacylides from salts **1** and their hetero analogs and oxazolium salts **3** are often complementary.

8. CONCLUSIONS

Synthesis of salts 1 and their analogs. As shown by our analysis of the literature, 2-halogen-substituted *N*-phenacylpyridinium salts **1** are an available class of reagents readily obtained by quaternization of appropriate 2-bromo(chloro)pyridines. For their analogs with a different heterocyclic residue and/or different type of heteroatom in the α-position, however, there are many problems. In some instances (α-MeO and several α-MeS derivatives), this is associated with the fact that direct phenacylation of α-substituted heterocycles is impossible, hindered, or complicated by the dominant side-processes. There were few attempts to synthesize these analogs. The same holds for **E**-type acyclic reagents, which are the structural analogs of salts **1**.

Although the picture is incomplete, we can present three general strategies for the synthesis of heteroanalogs of **1** (Scheme 60). The above-discussed particular strategies for the synthesis of the oxygen- and sulfur-containing analogs of **1** (Schemes 27 and 40) are naturally included in this scheme; it is also convenient for classification of the synthetic routes of **E**-type alicyclic salts and even systematization of the known methods for the synthesis of Mukayama salts and their heteroanalogs.



Scheme 60.

Strategy (I) is phenacylation at the endocyclic nitrogen atom; it is most widespread and involves Schemes 12–14, 17, 19, 20, 28, 33, 37, 39, 41, 46, 49, and 51 and reactions (*20*), (*23*), (*24*), (*28*), and (*30b*). The next (in importance) strategy, (II), is alkylation at the exocyclic X group (for clarity, the resonance form is shown in which the X group is negatively charged). This strategy is represented by few examples (reactions (21), (25), (26), (32), and (35)). Curiously, of the whole set of analogs of **1**, only one subclass (XR' is a mercapto group) can be prepared by either of the strategies (I) or (II), i.e., by *N*- or *S*-alkylation (or even their combination) of inexpensive and accessible substrates including acyclic structures. Consequently, it is most promising to study the synthetic routes of this subclass.

The last strategy (III), the nucleophilic modification of the Z α-substituent, was not adequately studied in the series of heterocyclic analogs of salts **1** (cf. Schemes 13, 14, 45, 48, and 50). Nevertheless, this is just the mechanism by which amides are converted into chloroiminium salts in Schemes 22, 24, and 25. The activation of amide evidently requires an electrophile, as denoted by a dashed arrow in Scheme 60. Scheme 60 could be complemented with a promising (but unknown) strategy of alkylation of enamines **8** (Scheme 23); transformation (*38*) should obviously be attributed to this type.

Synthesis of phenacylides 2 and their analogs. Phenacylpyridinium salts **1** with a leaving group in the α-position (as well as Kröhnke salts **B**) readily form ylides **2** under the action of strong bases, which are weak nucleophiles. The major distinction of ylides **2** is their ability to undergo the intramolecular closure of the oxazole ring **3**. This review revealed the general character of this reaction; it is observed for pyridinium, thiazolium, isoquinolinium, and pyrimidinium phenacylides having different types of leaving group in the α-position (halogen or a mercaptane or phenol residue). This cyclization is also experienced by their acyclic analogs. The cyclization of iminium phenacylides with an **E** structural motif into oxazoles should thus be regarded as a general strategy for the synthesis of compounds of the oxazole series.

It should be noted that the cyclization of phenacylides **2** into salts **3** can severely complicate the possibility of obtaining salts **1** or their analogs (Section 3.3). Due to the synthetic equivalence of **1** and **3** (Schemes 5–10), we have a rare situation when "by-products" **3** are not only equivalent to desired compounds **1** but often preparatively far more accessible by other methods. In other words, if **1** cannot be prepared, its equivalent **3** can be synthesized by more facile procedures.

An analysis of the literature revealed two more general methods for the generation of phenacylides **2**. The first is a reaction of azomethines with (di)halocarbenes (Scheme 26) or direct precursors of carbenes: diazoketones (Schemes 30, 36, 37, and 44). The second is an unusual formation of phenacylides **2** by cleavage of oxazolium cations, both monocyclic and condensed (in particular, salts **3b**); in this case, the additional (saturated or aromatic) ring is annelated at the CN bond of oxazole. The list of substrates and nucleophiles for the generation of these phenacylides is now small (Schemes 53–58), but the novelty of both the intermediates and the products (not accessible by other methods) of their transformations stimulates further studies in this direction.

This review will be helpful in choosing a reliable route to desired salt **1** or its analog and seeking new strategies for their synthesis. From a preparative viewpoint, salts **1** and their analogs, as well as phena-

cylides, are very interesting multifunctional synthons. The second part of this review will therefore be devoted to the use of these reagents in organic synthesis.

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