Unusual ring transformation of 2-halogeno-*N*-phenacylpyridinium salts in reaction with secondary amines: a facile 'one-pot' route to 1-amino-4-(oxazol-2-yl)butadienes

Eugene V. Babaev * and Alexander A. Tsisevich

Chemistry Department, Moscow State University, 119899, Moscow, Russia

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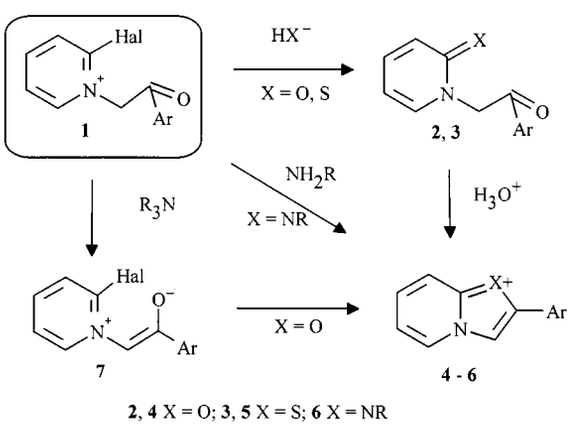
2-Halogeno-*N*-phenacylpyridinium salts **1** (Hal = Cl, Ar = *p*-NO_2Ph; Hal = Br, Ar = Ph) in reaction with aliphatic secondary amines undergo an unusual ring transformation to 1-amino-4-(5-aryloxazol-2-yl)buta-1,3-dienes **9** and **10**. The configuration of the products (1*E*,3*E* or 1*E*,3*Z*) depends on the reaction temperature. A suggested mechanism for the transformation involves intermediate formation of 2-aryloxazolo[3,2-*a*]pyridinium salt **4**.

Introduction

N-(Acylmethyl)-2-halogenopyridinium salts **1** are versatile intermediates useful in heterocyclic synthesis. The highly reactive halogen atom at the α-position of the pyridinium ring can be easily substituted by an appropriate nucleophile, and further cyclocondensation involving the acylmethyl (*e.g.* phenacyl) group and the inserted nucleophile may lead to bicyclic heterocycles with a bridgehead nitrogen atom (Scheme 1).



2, **4** X = O; **3**, **5** X = S; **6** X = NR

Scheme 1

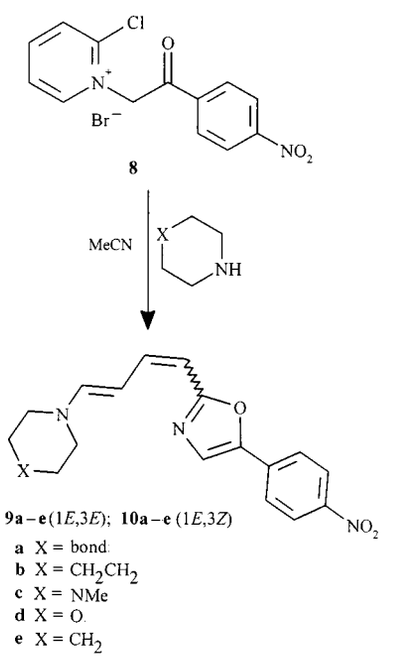
Thus, reactions of salts **1** with NaOH[1] and NaSH[2] lead to the intermediate *N*-(acylmethyl)-2-pyridones **2** and thiones **3** which may be further cyclized in acidic media to the oxazolo[3,2-*a*]pyridinium salts **4**[3] or their sulfur analogs **5**,[2,4] respectively. One-pot cyclizations to imidazo[1,2-*a*]pyridinium salts **6** (X = NAlk, NAr, NNHAc) and *N*-oxides (X = NO^-) were observed in the reactions of salts **1** with primary amines, acetylhydrazine and hydroxylamine.[5–7] Similar cyclizations of the salts **1** leading to other families of condensed heterocycles with *a*-fused pyridine rings (indolizines, pyrido[2,1-*c*][1,2,4]-triazines, pyrido[1,2-*a*:1′,2′-*c*]imidazoles) were reported.[1,5,8–10]

Quite another reactivity pattern of the salts **1** is displayed in their reaction with sterically hindered tertiary amines. In these cases, the action of a base caused deprotonation of the methylene group leading to ylides **7** which, like many other pyridinium ylides, may be involved in 1,3-dipolar cycloaddition reactions.[11] The intermediate enol betaines **7**, however, were unstable and underwent thermal intramolecular closure of the oxazole ring leading to the cations **4**.[1,5]

Although the salts **1** react with primary and tertiary amines in quite different manners, no attention has been paid to their reaction with secondary amines.

Results

We found that in reactions with secondary amines, 2-chloro-*N*-(*p*-nitrophenacyl)pyridinium bromide **8** undergoes an unusual ring transformation to 1-amino-4-(oxazol-2-yl)buta-1,3-dienes **9a**–**e** and **10a**–**e** (Scheme 2).



9a–**e** (1*E*,3*E*); **10a**–**e** (1*E*,3*Z*)

a X = bond
b X = CH_2CH_2
c X = NMe
d X = O
e X = CH_2

Scheme 2

The reaction between salt **8** and aliphatic secondary amines proceeds smoothly in high yield in refluxing acetonitrile, leading to deep purple compounds insoluble in water. According to the mass spectra and elemental analysis data (Table 1), the constitution of the products corresponds to the addition of a secondary amine molecule to the initial salt **8** with simultaneous elimination of HCl and HBr from such adducts. In the ^{1}H NMR spectra of the products only the signals of NR_2 groups are observed in the aliphatic region. The multiplets in the aromatic region are typical for 4-substituted 1-azolylbuta-1,3-dienes,[12–14] and the singlet of the oxazole ring proton appears at

Table 1 Characteristics of aminooxazolylbutadienes **9** and **10**

Compound (Formula)	Yield (%)	Mp/°C (decomp.)	Found (%) (required)		
			C	H	*m/z* (%)
9a, **10a** ($C_{17}H_{17}N_3O_3$)	85	171–173	65.1 (65.6)	5.0 (5.5)	311 (M^+, 30), 241 (100), 195 (47)
9b, **10b** ($C_{19}H_{21}N_3O_3$)	93	131–133	67.1 (67.3)	6.5 (6.2)	339 (M^+, 52), 241 (100), 195 (26)
9c, **10c** ($C_{18}H_{20}N_4O_3$)	95	203–205	63.3 (63.5)	5.7 (5.9)	340 (M^+, 49), 241 (100), 195 (21)
9d, **10d** ($C_{17}H_{17}N_3O_4$)	95	204–206	62.0 (62.4)	5.2 (5.2)	327 (M^+, 32), 241 (100), 195 (35)
9e	97	179–181 [a]			
10e	83	156–158 [b]			

[a] Lit.,[14] 179–180 °C. [b] Lit.,[14] 160–161 °C.

Table 2 ^{1}H NMR spectra of 1*E*,3*E*-butadienes **9** (400 MHz, $CDCl_3$, Me_4Si)

Molecule	δ_H							$J_{1,2}$, $J_{2,3}$, $J_{3,4}$/Hz
	1-H	2-H	3-H	4-H	$H_{oxazole}$	Ar	NR_2	
9a	6.90	5.18	7.30	5.94	7.48	7.71, 8.24	1.96, 3.30	12.1, 11.3, 15.6
9b	6.71	5.23	7.31	5.94	7.48	7.71, 8.24	1.59, 1.74, 3.30	12.4, 11.6, 15.0
9c	6.55	5.36	7.27	6.01	7.48	7.71, 8.24	2.32, 2.45, 3.21	12.2, 11.0, 16.2
9d	6.54	5.39	7.26	6.04	7.49	7.72, 8.24	3.17, 3.75	12.2, 11.0, 15.6
9e [a]	6.59	5.34	7.30	5.98	7.49	7.72, 8.24	1.60, 3.15	12.2, 11.6, 15.1

[a] Ref. 14.

Table 3 ^{1}H NMR spectra of 1*E*,3*Z*-butadienes **10**[a]

Molecule	δ_H			Ratio **9**:**10** [b]
	1-H, 2-H, 3-H	4-H	$H_{oxazole}$	
10a	6.30, 6.94, 6.53	5.63	7.57	5:1
10b [c]	6.41, 6.74, 6.52	5.62	7.56	6:1
10c	6.58–6.60	5.69	7.56	7:1
10d [c]	6.55–6.65	5.74	7.56	9:1
10e [d]	6.53–6.58	5.64	7.56	5:1 [e,f]

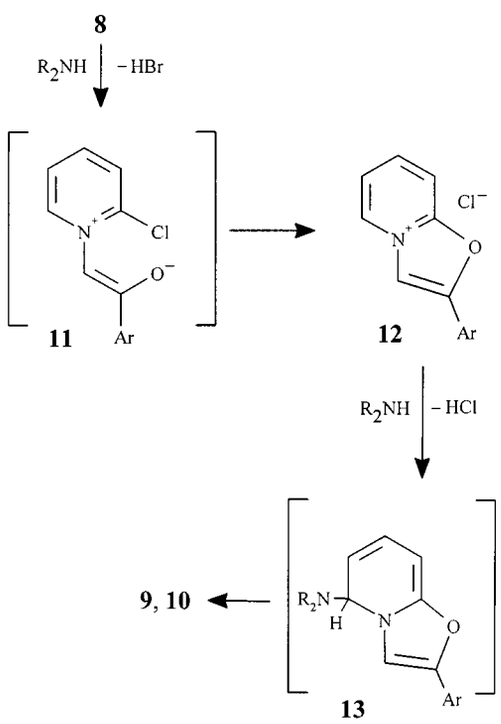
[a] Signals of the groups *p*-$NO_2C_6H_4$ and NR_2 overlap with that for the 1*E*,3*E* isomers. [b] The ratio of isomers obtained by general method (3 h, 82 °C). [c] Ref. 15. [d] Ref. 14. [e] The ratio **9e**:**10e** = 1:10 if reagents were kept for 1 h at 20 °C. [f] The ratio was 1:2 if the mixture obtained initially was refluxed for a further 1 h at 82 °C.

7.5 ppm. The intense bands in the UV spectra of the products (λ_{max} = 455–465 nm) typical for conjugated dienes with intramolecular charge transfer, and the diene band (ν = 1625 cm^{-1}) in their IR spectra also confirm the structure of the 1-amino-4-(oxazol-2-yl)butadienes. In the mass spectra the peak *m/z* 241 (loss of NR_2 fragment) was the most intense one for all the products, and it may be associated with the probable closure of the pyridinium ring in the molecular ion.

According to their ^{1}H NMR spectra the butadienes are formed as mixtures of 1*E*,3*E*-(**9**) and 1*E*,3*Z*-isomers (**10**), with a clear predominance (85–90%) of the stereoisomers **9** in all cases. The chromatographic properties of the isomeric pairs were identical. The configuration of each isomer clearly follows from the coupling constants in the ^{1}H NMR spectra and was additionally confirmed by NOESY measurements. Spectral characteristics of the products **9** and **10** are shown in Tables 2 and 3.

Discussion

There are two possible mechanisms for the transformation of the pyridinium salt **8** to oxazoles **9** and **10**. The first one, involving initial opening of the pyridinium ring followed by cyclization of the open chain to the oxazole ring, looks improbable. Much more probable is the alternative mechanism, which involves intermediate formation of the oxazolo[3,2-*a*]pyridinium cation **12** followed by further opening of the six-membered fragment (Scheme 3).



Scheme 3

Both steps of such a mechanism have parallels in heterocyclic chemistry. At the first step, secondary amine acts as the base, converting the salt **8** to the enol betaine **11** followed by intramolecular ring closure to the stable aromatic cation **12**. This step is completely parallel to the cyclization of salts **1** under the action of tertiary amines to cations **4** *via* intermediates **7**.[1,5] At the second step, the molecule of amine acts as the nucleophile, transforming the cation **12** to the ring opening products **9** and **10** *via* the adduct **13**. This step also has direct experimental evidence: conversion of cations **4**–**6** to various 1-amino-4-azolylbutadienes is well known.[12–15] In our experiments we found that the reactions of morpholine with either salt **8** or 2-(*p*-nitrophenyl)oxazolo[3,2-*a*]pyridinium perchlorate **14** under the same conditions (82 °C, MeCN, 3 h) lead to the same product.

A specific feature of the ring-opening reactions of various pyrrolopyridinium cations to azolylbutadienes is that the configuration of the dienes depends dramatically on the reaction temperature.[12–15] One would expect an analogous influence of the temperature on the ratio of the products **9**:**10** formed from the salt **8** *via* oxazolopyridinium cation **12**. Indeed, when the salt **8** was allowed to react with piperidine at room temperature, the ratio **9e**:**10e** was 1:10, whereas this ratio was changed to 5:1 in refluxing acetonitrile (see Table 3).

Previously, only the 1*E*,3*Z*-isomer **10d** had been obtained by the ring opening of the perchlorate **14** with morpholine at 20 °C.[15] We found that the complementary isomer **9d** (almost free from **10d**) may be obtained in refluxing acetonitrile by reaction of morpholine with either perchlorate **14** (90% yield) or the pyridinium salt **8** (yield 95%).

Theoretical calculations confirmed that all-(*E*) isomers **9** are more stable than the 1*E*,3*Z*-isomers **10**. According to MNDO calculations[15] the difference in energy between isomers **9e** and **10e** is 5.7 kcal mol^{-1}. We found that no isomerization of butadiene **10e** to **9e** was observed at room temperature (keeping in CH_3CN for 3 days). However, such isomerization readily occurred in refluxing acetonitrile: after 1 h of heating the ratio **9e**:**10e** is changed from 1:10 to 1:2.

Azolyldienes are widely used in heterocyclic synthesis.[16,17] The specific practical importance of the discussed class of oxazolylbutadienes **9** and **10** is their recently-found antimicrobial activity[15] and also the possibility of their utilisation as non-linear optic materials. The discovered 'one-pot' ring transformation, therefore, opens a novel route to this class of dienes starting from easily available pyridinium salts **1**. In order to expand the series of 1-(acylalkyl)-2-halopyridinium salts involved in such reactions, we investigated the reaction of 1-acetonyl-2-bromo- and 2-bromo-1-phenacylpyridinium bromides with piperidine. In the first case only an unstable oily product was obtained, whereas for the second case, the desired 1-(4-phenyloxazol-2-yl)-4-piperidinobuta-1,3-diene with all-(*E*) configuration was formed in moderate yield.

Experimental

General

2-Chloro-*N*-(*p*-nitrophenacyl)pyridinium bromide **8**,[15] 2-bromo-1-phenacylpyridinium bromide[6] and 2-(*p*-nitrophenyl)-oxazolo[3,2-*a*]pyridinium perchlorate **14**[14] were obtained according to published data.

Reaction of 2-chloro-*N*-(*p*-nitrophenacyl)pyridinium bromide with secondary amines (general method)

A mixture of 0.5 g (1.4 mmol) of the pyridinium salt **8** in 25 ml of anhydrous CH_3CN and 5.6 mmol of secondary amine was refluxed for 3 h, cooled and poured into water (100 ml). The deep purple precipitate was filtered, washed with water (3 × 50 ml) and dried at 20 °C. The properties of oxazolylbutadienes **9** and **10** are given in Tables 1–3.

(1*E*,3*Z*)-4-[5-(*p*-Nitrophenyl)oxazol-2-yl]-1-piperidylbuta-1,3-diene 9e

A mixture of 0.2 g (0.56 mmol) of the pyridinium salt **8** in 25 ml of anhydrous CH_3CN and 2 ml of piperidine was stirred at 20 °C for 1 h, poured into water (100 ml) and the precipitate was filtered, washed with water (3 × 50 ml) and dried at 20 °C.

(1*E*,3*E*)-1-Morpholino-4-[5-(*p*-nitrophenyl)oxazol-2-yl]buta-1,3-diene 10d

A mixture of perchlorate **14** (2 mmol) in 20 ml of anhydrous CH_3CN and 1.7 ml of morpholine was refluxed for 3 h, cooled and poured into water (100 ml). The precipitate was filtered, washed with water (3 × 50 ml) and dried at 20 °C giving 0.59 g (90%) of butadiene **10d**. The product was identical (mp, TLC, ^1H NMR spectra) with the compound obtained by the general method from the pyridinium salt **8** and morpholine.

(1*E*,3*E*)-1-Piperidino-4-(5-phenyloxazol-2-yl)buta-1,3-diene

The product was obtained according to the general method from 2-bromo-1-phenacylpyridinium bromide and piperidine. The product (early described[19] as a yellow oil) was an amorphous dark yellow solid (56%); mp 104–106 °C. ^1H NMR and IR spectra were identical with the authentic sample.

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References

1 H. Pauls and F. Krohnke, *Chem. Ber.*, 1976, **109**, 3653.
2 B. Blank, N. W. DiTullio, A. J. Krog and H. L. Saunders, *J. Med. Chem.*, 1978, **21**, 489.
3 C. K. Bradsher and M. Zinn, *J. Heterocycl. Chem.*, 1967, **4**, 66.
4 H. Pauls and F. Krohnke, *Chem. Ber.*, 1976, **109**, 3646.
5 C. K. Bradsher, R. D. Brandau, J. E. Boilek and T. L. Hough, *J. Org. Chem.*, 1969, **34**, 2129.
6 E. S. Hand and W. W. Paudler, *J. Org. Chem.*, 1978, **43**, 658.
7 A. M. Demchenko, V. A. Chumakov, K. G. Nazarenko, A. N. Krasovskii, V. V. Pirozhenko and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 1995, **5**, 644.
8 R. A. Nugent and M. Murphy, *J. Org. Chem.*, 1987, **52**, 2206.
9 H. Pauls and F. Krohnke, *Chem. Ber.*, 1977, **110**, 1294.
10 E. V. Babaev, S. V. Bozhenko and D. A. Maiboroda, *Russ. Chem. Bull.* (*Engl. Transl.*), 1995, **44**, 2203 (Original: *Izv. Akad. Nauk*, *Ser. Khim.*, 1995, **11**, 2298, in Russian).
11 P. B. Terent'ev, S. M. Vinogradova and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1980, **5**, 651.
12 Gy. Hajos and A. Messmer, *J. Heterocycl. Chem.*, 1984, **21**, 809.
13 A. Messmer, Gy. Hajos and G. Timari, *Tetrahedron*, 1992, **48**, 8451.
14 E. V. Babaev, A. V. Efimov, D. A. Maiboroda and K. Jug, *Eur. J. Org. Chem.*, 1998, **1**, 193.
15 D. A. Maiboroda, E. V. Babaev and L. V. Goncharenko, *Khim.-Farm. Zh.* (*Russ.*), 1998, **6**, 24.
16 Z. Reidl, Gy. Hajos, A. Messmer and G. Kollenz, *J. Heterocycl. Chem.*, 1993, **30**, 819.
17 A. Gelleri and A. Messmer, *Tetrahedron*, 1973, **44**, 4295.
18 D. A. Maiboroda and E. V. Babaev, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1995, **11**, 1251.
19 E. V. Babaev, D. A. Maiboroda and K. Yu. Pasichnichenko, *Khim. Geterotsikl. Soedin.*, 1997, **3**, 397.

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