Formation of Oxazoles from 2-Methylsulfanyl-N-phenacylpiperidinium Salts

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Dedicated in honor of Prof. Fritz Sauter on his 70th Anniversary

Abstract
With piperidine reacting both as base and nucleophile 2-methylsulfanyl-N-phenacylpiperidinium salts 4a, b undergo ring transformation affording 2-[4-(1-piperidino)-(1Z,3E)-1,3-butadienyl]oxazoles 5a, b.

Keywords: 2-Methylsulfanyl-N-phenacylpiperidinium salts; 2-[4-(1-piperidino)-(1Z,3E)-1,3-butadienyl]oxazoles; ring transformation.

Introduction
A strategy to build oxazole rings is the closure of the chain Z–C–N–C–C–O upon attack of a nucleophilic O-atom at an electrophilic C-atom with Z as a leaving group (5-exo-tet) (eq. 1). This approach has been rarely used to obtain monocyclic oxazoles;1 nevertheless, it is a useful procedure to construct oxazoles in fused ring systems (eq. 2).

In particular, the oxazoloazinium salts of types III and VIII have been obtained by this strategy (Scheme 1).2 3 Tertiary amines induce the cyclization of N-phenacylpiperidinium salts bearing suitable leaving groups like the methylsulfanyl group as in pyrimidinium salts I,2 or halogen as in pyridinium salts IV.3 In both reactions the initial step was proposed to be the conversion of the phenacyl group into the enolates II and V, respectively. The betaine
intermediates II or V, in turn, undergo the oxazole ring closure affording the bicyclic heterocyclic salts III and VIII, respectively.

\[
\begin{align*}
\text{I, IV, VI} & \quad \text{Y} & \quad \text{Z} \\
\text{I, II} & \quad \text{N} & \quad \text{SMe} \\
\text{IV, V} & \quad \text{CH} & \quad \text{halogen} \\
\text{VI, VII} & \quad \text{CH} & \quad \text{SMe} \\
\text{II, V, VII} & \quad \text{- H}^+ & \quad \text{- Z}^- \\
\text{III, VIII} &
\end{align*}
\]

**Scheme 1**

The pyrido[2,1-b][1,3]oxazol-4-ium salts VIII are useful precursors for the preparation of other heterocycles because they provide both the oxazole and the pyridine fragment.\(^4,5\) On the other hand, 2-methylsulfanylpyridinium salts VI upon conversion into the enolate intermediates VII are considered to be suitable precursors of the salts VIII; up to now, there are no reports on the synthesis of salts VI and their reaction with bases and nucleophiles.

**Results and Discussion**

The starting materials 2-methylsulfanyl-\(N\)-phenacylpyridinium salts 4a, b can be readily obtained either by introducing phenacyl groups into 2-methylsulfanylpyridine (1) as well as by methylation of \(N\)-phenacylpyridine-2-thiones (3) with methyl iodide.
We found that in a one-pot reaction piperidine readily transformed the salts 4a, b into 2-[4-(1-piperidino)-1,3-butadienyl][1,3]oxazoles (5a, b) at room temperature (Scheme 2). The $^1$H NMR spectra of the products 5 are lacking the CH$_2$ singlet of the phenacyl group of 4, and only the signals of the piperidine fragment are displayed in the aliphatic region. The multiplets of proton signals in the aromatic region are typical for 4-substituted 1-azolylbutadienes, and the singlet of 4-H of the oxazole ring appears at δ 6.8–6.9. The coupling constants of the olefinic signals indicate the (1$Z$,3$E$)-configuration of the 1,3-butadienyl moiety of 5a, b. Spectral and physical properties of the diene 5b are identical with those of the (1$E$,3$Z$)-isomer described earlier. The mass spectrum of product 5a exhibits the most intensive peak at m/z = 195 (loss of the piperidine fragment, M-C$_5$H$_{10}$N), which is typical for 2-(4-amino-1,3-butadienyl[1,3]oxazoles.

We suppose that the conversion of the pyridinium salt 4 to oxazoles 5 is initiated by piperidine causing deprotonation and conversion of the salt 4 to the enol betaine 6; this intermediate 6, in turn, undergoes ring closure to give the pyrido[2,1-b][1,3]oxazol-4-ium intermediate 7 (Scheme 3). In a subsequent step, piperidine acting as a nucleophile adds to the pyridinium ring of 7 forming the adduct 5-piperidino-5$H$-pyrido[2,1-b][1,3]oxazole 8. Eventually, intermediate 8 undergoes ring-opening (cycloreversion) furnishing the final product 5. This type of reactivity of salts 7 with secondary amines is well known.
Thus, the strategy utilized for the synthesis of bicyclic oxazoles can also be applied for the preparation of monocyclic oxazoles (cf. eq. 2).

Dienes of type 5 have been previously reported to possess antimicrobial activity.\textsuperscript{5b} The ring transformation reaction reported here offers a novel route to these compounds. Presently, we are investigating analogous ring transformation reactions with other azinium salts containing a 2-methylsulfanyl group (e.g. I, Scheme 1).

**Experimental**

**General Remarks.** The starting compounds 2-methylsulfanylpyridine (1),\textsuperscript{8} N-phenacylpyridine-2-thiones (3)\textsuperscript{9} were synthesized using previously described procedures. GLC-MS spectra were obtained from a HP 5989 (with SE 30 column; EI 70 eV). NMR spectra were measured with a Bruker AM-300 (300 MHz) or with a Bruker AC-200 (200 MHz).

**Preparation of $N$-phenacylpyridinium salts (4a, b):**

(a) **From 2-methylsulfanylpyridine (1) and phenacylbromides 2a,b.** A mixture of 2-methylsulfanylpyridine (1) (2.8 g, 22.4 mmol) and the phenacylbromide 2a,b (22.4 mmol) in acetonitrile (45–56 mL) was stirred at room temperature for 10 days. The white precipitate formed was filtered off, and the filtrate was refluxed for 1 h, cooled, and the resulting precipitate was filtered off. An additional crop separated from the filtrate after prolonged standing.

1-(4-Bromophenyl)-2-[2-(methylsulfanyl)-1-pyridiniumyl]-1-ethanone bromide (4a, $X = \text{Br}$): Colorless crystals. Yield: 4.24 g (47%); mp (decomp.) 200–201 °C. $^1$H NMR (CD$_3$OD): $\delta$ 2.9 (s, 3H), 6.4 (s, 1.5 H, deuterium exchange$^{10}$), 7.80–7.85 (m, 3H), 8.03–
8.15 (m, 3H), 8.50 (t, 1H), 8.79 (d, 1H). Anal. calcd. for C\textsubscript{14}H\textsubscript{13}Br\textsubscript{2}NOS (403.14): C, 41.69; H, 3.23; N, 3.47. Found: C, 41.33; H, 3.23; N, 3.37.

2-[(2-Methylsulfanyl)-1-pyridiniumyl]-1-(4-nitrophenyl)-1-ethanone bromide (4b, X = Br): Colorless crystals. Yield: 5.37 g (65%); mp (decomp.) 204–206 °C. \textsuperscript{1}H NMR (CD\textsubscript{3}OD): \(\delta\) 3.06 (s, 3H), 6.66 (s, 0.46 H, deuterium exchange\textsuperscript{10}), 8.05 (dd, 1H), 8.34 (d, \(J = 8.3\) Hz, 1H), 8.56 (d, \(J = 9.3\) Hz, 2H), 8.64–8.75 (m, 3H), 9.01 (d, \(J = 9.4\) Hz, 1H). Anal. calcd. for C\textsubscript{14}H\textsubscript{13}BrN\textsubscript{2}O\textsubscript{3}S (369.24): C, 45.53; H, 3.52; N, 7.59. Found: C, 45.57; H, 3.45; N, 7.50.

(b) From N-phenacyl-1,2-dihydropyridine-2-thiones (3a,b). To a solution of N-phenacylpyridine-2-thione (3a, b) (2 mmol) in acetonitrile (5 mL) was added iodomethane (284 mg), and the resulting solution was stirred at room temperature for 2 days. The yellow precipitate formed was filtered off, washed with acetonitrile and dried.

1-(4-Bromophenyl)-2-[(2-(methylsulfanyl)-1-pyridiniumyl)-1-ethanone iodide (4a, X = I): Yield: 604 mg (67%) of 4a, mp (decomp.) 184 °C.

N-2-(4-Bromophenyl)oxazolo[3,2-a]pyridinium perchlorate (7a, X = ClO\(_4\)). N-2-(4-1-(4-Bromophenyl)-2-[2-(methylsulfanyl)-1-pyridiniumyl]-1-ethanone bromide 4a (X=Br) (200 mg, 0.5 mmol) was dissolved in acetonitrile (15 ml), and after addition of triethylamine (0.2 mL) the mixture was refluxed for 3 h. Upon cooling the resulting precipitate was collected by filtration and dissolved in water. Addition of 70% perchloric acid (10- to 12-fold excess) afforded a white precipitate, which was filtered off, washed with water and dried affording the perchlorate 7a (X = ClO\(_4\)); yield: 117 mg (63%).

4-[5-(4-Bromophenyl)-2-[(1Z,3E)-4-(1-piperidino)-1,3-butadienyl]oxazole (5a). To a solution of the pyridinium bromide 4a (121 mg, 0.3 mmol) in acetonitrile (15 mL) was added piperidine (1.2 mL, 12 mmol), and the mixture was stirred at room temperature for 1 h. To the resulting orange solution was added water (60 mL), and the precipitate thus formed was collected, washed with water and dried at room temperature.\textsuperscript{5b} Orange solid 5a (74 mg, 68.5%), mp 101–103 °C. \textsuperscript{1}H NMR (DMSO-\textsubscript{d}\(_6\)): \(\delta\) 1.58 (m, 4H), 3.22 (m, 6H), 5.53, (d, \(J = 10.4\) Hz, 1H), 6.33–6.55, (m, 2H), 6.79 (d, \(J = 12.4\) Hz, 1H), 7.34–7.96 (m, 2H).
5H); MS: m/z (%) 358 (13.8, M⁺), 274 (100, M –C₅H₁₀N), 195 (26.3, M –C₃H₁₀N, –Br), 183 (27.4, COC₆H₄Br), 155 (31.6, C₆H₄Br).¹³

4-[5-(4-Nitrophenyl)-2-[(1Z,3E)-4-(1-piperidino)-1,3-butadienyl]oxazole (5b). To a solution of pyridinium bromide 4b (65 mg, 0.176 mmol) in acetonitrile (8.5 mL) was added piperidine (0.7 mL), and the mixture was stirred at room temperature for 1 h. To the resulting purple solution was added water (35 mL), and the precipitate thus formed was collected, washed with water and dried at room temperature. Dark-violet solid 5b (42 mg, 71%), mp 170–171 °C (lit.⁵a mp 160–161 °C). ¹H NMR (DMSO-d₆): δ 1.57 (m, 4H), 3.24 (m, 6H), 5.54 (d, J = 10,5 Hz, 1H), 6.36–6.62 (m, 2H), 6.88 (d, J = 12,4 Hz, 1H), 7.83, 7.88 (AA', 2H), 7.95 (s, 1H), 8.26, 8.30 (BB', 2H). Anal. calcd. for C₁₈H₁₉N₃O₃ (325.37): N, 12.9. Found: N, 12.4.

References and Notes


10. The spectra have been measured immediately after dissolving the compound in the solvent; after 3 h this signal exhibited a lower intensity.


13. The isolated product contains beside (1Z,1E)-5a as small amount (< 10%) of the (1E,1E)-5a isomer as indicated by NMR signals in the olefinic region [δ 5.86 (d) and 7.20 (dd)] as well as by additional GC peak.