Formation of oxazoles from 2-methylsulfanyl-*N*-phenacylpyridinium salts

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

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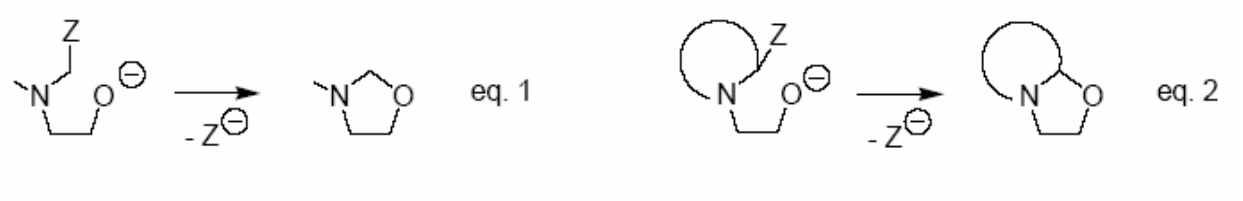
Abstract

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

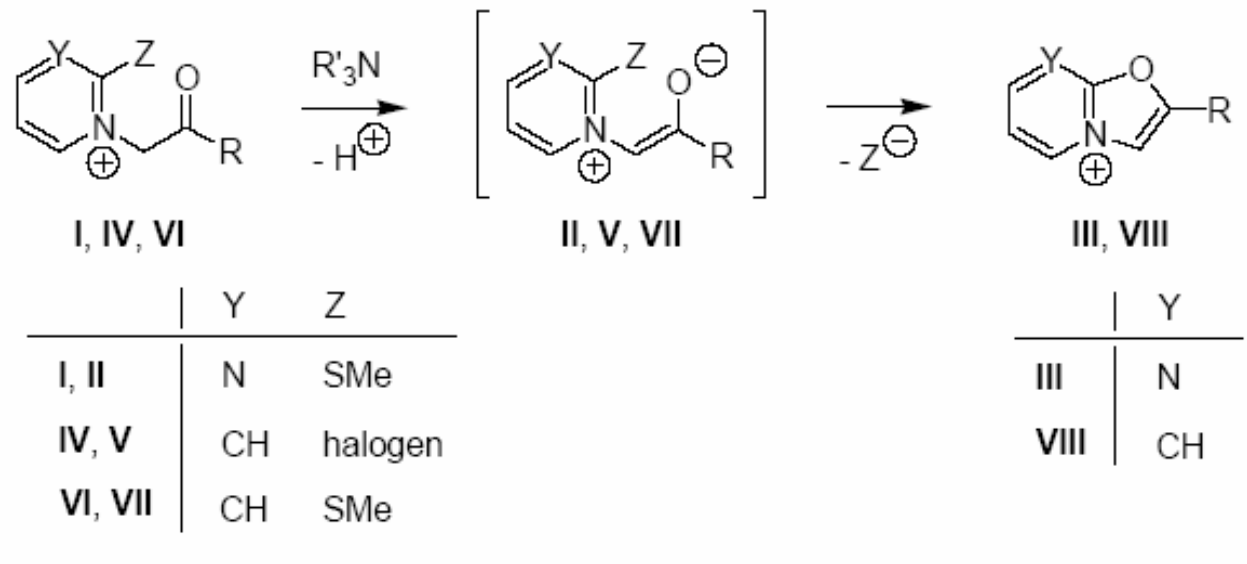
Keywords: 2-Methylsulfanyl-*N*-phenacylpyridinium salts, 2-[4-(1-piperidino)-(1*Z*,3*E*)-1,3-butadienyl]oxazoles, ring transformation

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*-phenacylazinium 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.



	Y	Z
I, **II**	N	SMe
IV, **V**	CH	halogen
VI, **VII**	CH	SMe

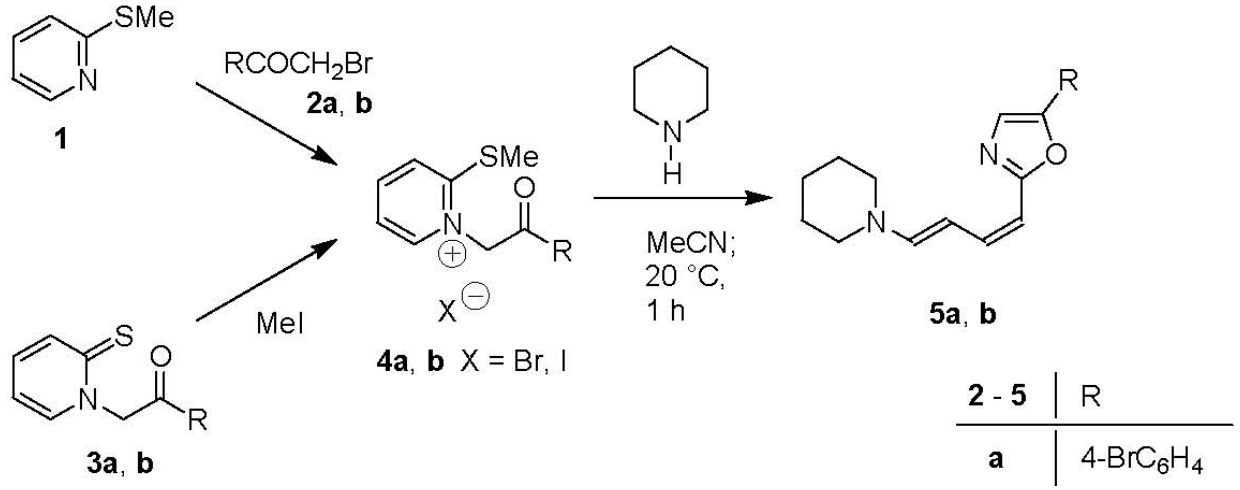
	Y
III	N
VIII	CH

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

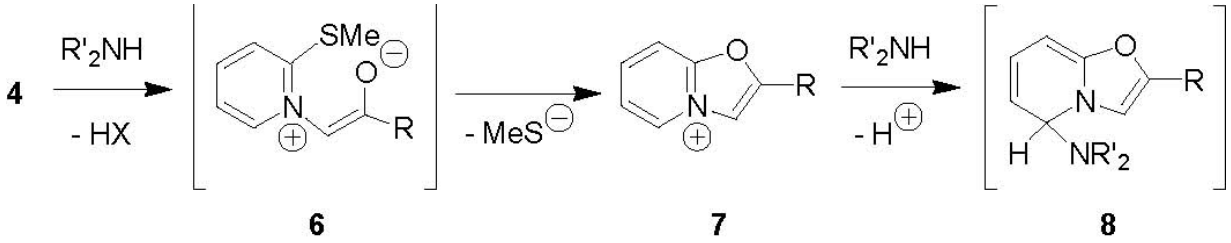
The starting materials 2-methylsulfanyl-*N*-phenacylpyridinium salts **4a**, **b** can be readily obtained either by introducing phenacyl groups into 2-methylsulfanylpyridine (**1**) as well as by methylation of *N*-phenacylpyridine-2-thiones (**3**) with methyl iodide.



Scheme 2

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,[6] 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.[5a] The mass spectrum of product **5a** exhibits the most intensive peak at *m*/*z* = 195 (loss of the piperidine fragment, M-$C_5H_{10}N$),which is typical for 2-(4-amino-1,3-butadienyl[1,3]oxazoles.[7]

We suppose that the conversion of the pyridinium salt **4** to oxazoles **5** is initiated by piperidine causing deprotonation and convertion 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.[5]



Scheme 3

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.[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 Section

General Procedures. The starting compounds 2-methylsulfanylpyridine (**1**),[8] *N*-phenacyl-pyridine-2-thiones (**3**)[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 = Br): Colorless crystals. Yield: 4.24 g (47%); mp (decomp.) 200–201 ºC. ^{1}H NMR (CD_3OD): δ 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 $C_{14}H_{13}Br_2NOS$ (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 ºC. ^{1}H NMR (CD_3OD): δ 3.06 (s, 3H), 6.66 (s, 0.46 H, deuterium exchange[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 $C_{14}H_{13}BrN_2O_3S$ (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 ºC.

***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-[(1*Z*,3*E*)-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.[5b] Orange solid **5a** (74 mg, 68.5%), mp 101–103 °C. ^{1}H NMR (DMSO-d_6): δ 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, 5H); MS: m/z (%) 358 (13.8, M^+), 274 (100, M –$C_5H_{10}N$), 195 (26.3, M – $C_5H_{10}N$, –Br), 183 (27.4, COC_6H_4Br), 155 (31,6, C_6H_4Br). [13]

4-[5-(4-Nitrophenyl)-2-[(1*Z*,3*E*)-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). ^{1}H NMR (DMSO-d_6): 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 $C_{18}H_{19}N_3O_3$ (325.37): N, 12.9. Found: N, 12.4.

References and Notes

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10. The spectra have been measured immediately after dissolving the compound in the solvent; after 3 h this signal exhibited a lower intensity.
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13. The isolated product contains beside (1*Z*,1*E*)-**5a** as small amount (< 10%) of the (1*E*,1*E*)-**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.