1,3-Oxazines and Related Compounds. III.[1] Ring Contraction Reaction of 1,3-Oxazin-4-one Derivatives into 1,2,4-Oxadiazoles and Isoxazoles

Yutaka Yamamoto* and Yutaka Azuma

Tohoku College of Pharmacy, 4-4-1 Komatsushima, Sendai 983, Japan

Reaction of 2-phenyl-, 2-(2-pyridyl)-, 2-(3-pyridyl)- and 2-(2-quinolyl)-6-methyl-4H-1,3-oxazin-4-one (1a-d) with hydroxylamine hydrochloride in the presence of sodium acetate or sodium alkoxide led to a formation of the corresponding 1,2,4-oxadiazoles 4a-d in 72%, 65%, 80%, and 71% yield, respectively.

On the other hand, treatment of 1a-d with hydroxylamine hydrochloride in 95% ethanol gave rise to the corresponding isoxazoles 7a-d.

Analogously, the 2,3-dihydro-1,3-oxazine 1e underwent the ring contraction into the 1,2,4-oxadiazole 4e and isoxazole 7e in 32% and 56% yield, respectively.

In the previous papers 1,3-oxazin-4-one derivatives have been shown to be potentially useful for the synthesis of six-membered N-heterocycles such as pyridines[2], pyrimidines[3,4,5] and pyrindines[6] through the ring transformation. In addition, we have developed

the routes[1] for the preparation of 1,2,4-triazoles and pyrazoles which open pathway to further more N-heterocyclic systems. In this paper the ring contraction reaction of 1,3-oxazin-4-one derivatives into 1,2,4-oxadiazoles and isoxazoles is described.

The ring contraction into the 1,2,4-oxadiazoles was accomplished simply by treatment of 1a-e with hydroxylamine hydrochloride ($NH_2OH \cdot HCl$) in the presence of sodium acetate or sodium alkoxide.

When 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (1a)[1,3] was allowed to react with two molar equivalents of $NH_2OH \cdot HCl$ in the presence of sodium methoxide, there was obtained the oxime 4a of 5-acetonyl-3-phenyl-1,2,4-oxadiazole (3a) in 72% yield, which was identified by a comparison of the IR spectrum with that of an authentic sample.[7]

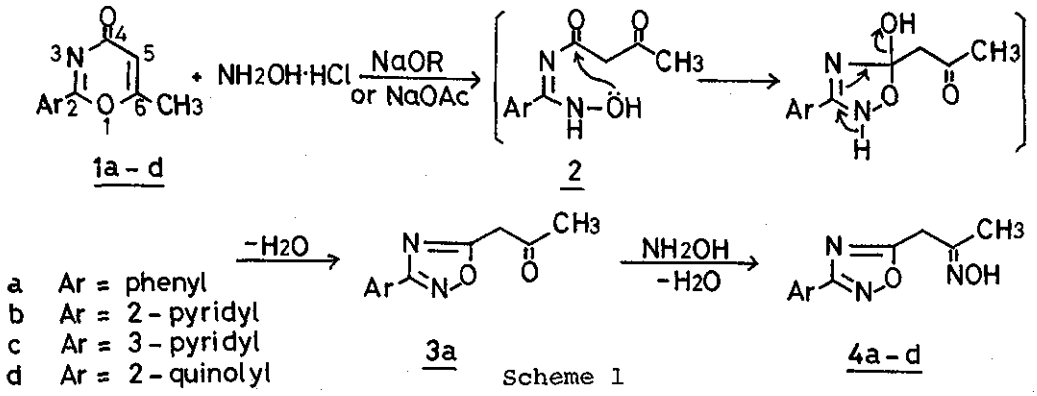
Treatment of 4a with sodium bisulphite furnished the ketone 3a in 67% yield, which was identical with an authentic sample.[7]

Similarly, reaction of 2-(2-pyridyl)-, 2-(3-pyridyl)- and 2-(2-quinolyl)-6-methyl-4H-1,3-oxazin-4-one (1b-d)[8] with $NH_2OH \cdot HCl$ afforded the corresponding 1,2,4-oxadiazoles in 65%, 80%, and 71% yield, respectively. Experimental and spectral data are summarized in Table 1 and 2.

Mechanistic consideration provides that the initial attack of NH_2OH takes place preferentially at the 2-position of the 1,3-oxazine ring, leading to the intermediate 2, which undergoes ring closure by loss of water to yield the oxadiazole 3. Successively, another mole of NH_2OH reacts with 3 to afford 4.

In fact, using an equimolar of $NH_2OH \cdot HCl$ in the reaction of

1a resulted in the formation of 3a (yield: >30%) along with a small amount of 4a.

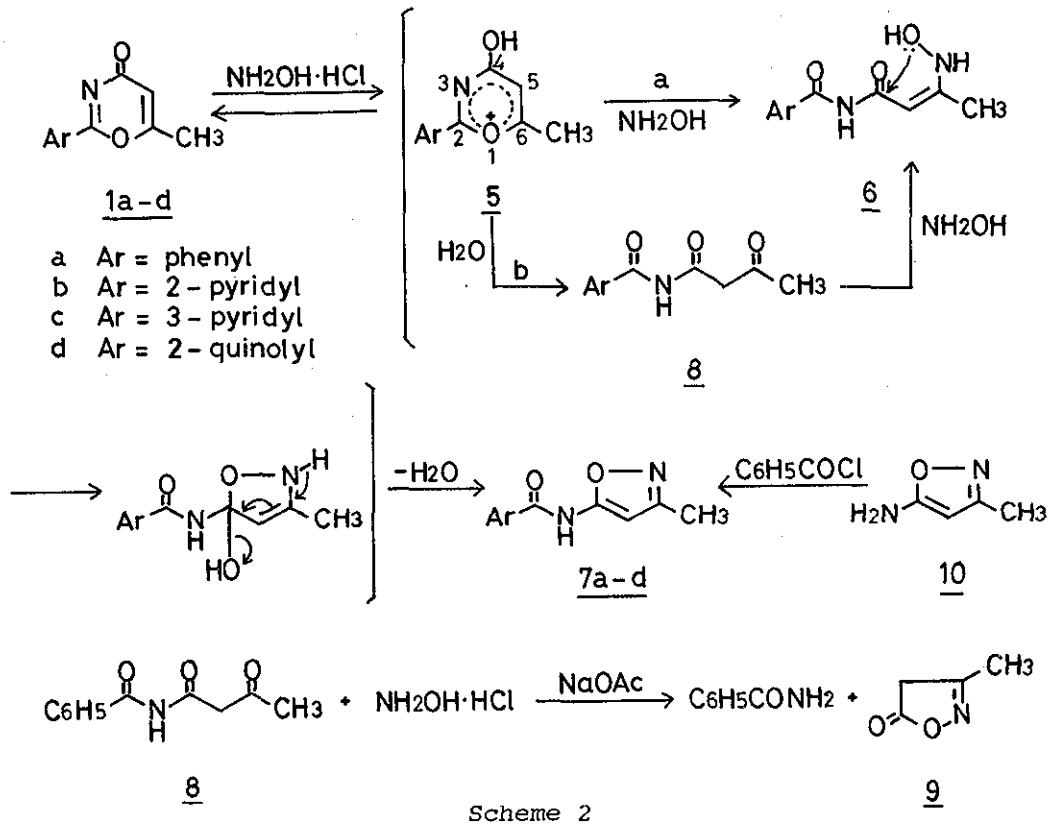


Scheme 1

On the other hand, refluxing of a solution of 1a and $NH_2OH \cdot HCl$ in 95% ethanol gave rise to 5-benzamido-3-methylisoxazole (7a), whose structure was determined by a comparison of the IR spectrum with that of an authentic sample prepared by benzoylation of 5-amino-3-methylisoxazole (10).[9]

Similar treatment of 1b, 1c and 1d with $NH_2OH \cdot HCl$ afforded the corresponding isoxazole 7b, 7c, and 7d in 28%, 16%, and 37% yield, respectively, together with the respective carboxamide (from 12% to 72%), which resulted from hydrolysis of the oxazine 1b-d followed by deacetoacetylation.

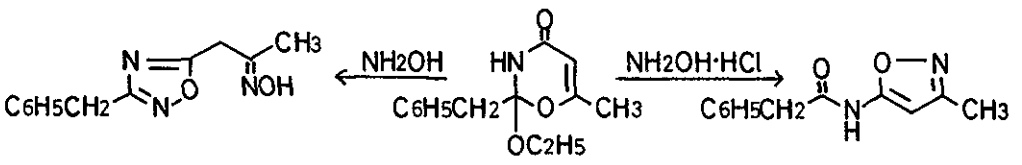
For the ring contraction into the isoxazole, two possible routes (a and b) are speculative as shown in Scheme 2. However, route b seems reasonable to be excluded, since heating a solution of N-benzoylacetoacetamide 8 and $NH_2OH \cdot HCl$ in 95% ethanol in the presence of sodium acetate led to the isolation of benzamide and the isoxazolone 9;[10] no evidence for formation of the expected isoxazole could be found.



Scheme 2

Thus, a probable route for the conversion into the isoxazole is as follows: the nucleophilic attack of NH_2OH takes place predominantly at the 6-position of the 1,3-oxazinium salt 5,[11] which must be in equilibrium with the 1,3-oxazine 1 in the presence of $NH_2OH \cdot HCl$, and subsequently causes the cleavage of $C_{(6)}$-O bond leading to the intermediate 6. Recyclization of 6 with elimination of water affords the isoxazole 7.

Analogously, 2-benzyl-2-ethoxy-2,3-dihydro-6-methyl-2H-1,3-oxazin-4-one (1e)[3] underwent the ring contraction to provide the 1,2,4-oxadiazole 4e and isoxazole 7e in 32% and 56% yield, respectively.



4e Scheme 3 1e 7e

Table 1. Reaction of 1a-e with Hydroxylamine and Its Hydrochloride

1,3-Oxazine 1 (g)	Reaction Condition Method,[a]	Temp.,	Time(hr)	Product	Mp & Bp(°C) (Solvent)	Yield g (%)
1a (1)	A	r.t.	6	4a	87 (n-pentane)	0.84(72)
1a (1)	B	refl.	1	4a		0.8 (69)
1b (0.4)	A	r.t.	6	4b	110 (ether)	0.3 (65)
1c (0.4)	B	refl.	3	4c	132-135 (benzene)	0.37(80)
1d (0.5)	A[b]	refl.	2	4d	128 (benzene)	0.4 (71)
1d (0.4)	B	refl.	2	4d		0.18(40)
1e (2)	A	r.t.	6	4e	160 (0.2 Torr)	0.6 (32)
1a (1)		refl.	1	7a	147 (ether)	0.7 (65)
1b (0.4)		r.t.	8	7b	135 (benzene)	0.12(28)
1c (0.3)		r.t.	8	7c	205(dec) (ethyl acetate)	0.05(16.2)
1d (0.4)		refl.	0.5	7d	188-190(dec) (benzene)	0.2 (37)
1e (1.3)		r.t.	8	7e	111 (ether)	0.64(56)

a) Method A and B are described in Experimental Section.

b) Ethanol was used instead of methanol.

Abbreviation used: r.t.= room temperature, refl.= reflux.

EXPERIMENTAL SECTION

General Procedure for the Oxime 4——— Method A: The amount of sodium metal equivalent to 1 was dissolved in methanol. To the resulting solution was added a solution of 96% $NH_2OH \cdot HCl$ (an equiv-

alent amount to 1) in methanol. The precipitates appeared were filtered off. The filtrate was added dropwise to a solution of 1 in methanol with stirring. The reaction solution was allowed to stir at room temperature or heated under reflux and condensed under reduced pressure by an aspirator. The residue was extracted with chloroform. The chloroform was evaporated. The residual product was purified by recrystallization or distillation to give 4. Method B: To a solution of 1 and 96% $NH_2OH \cdot HCl$ (2.1 equivalent amounts to 1) in 95% ethanol was added a solution of sodium acetate (2.2 equivalent amounts to 1) in a small amount of water. The resulting solution was heated under reflux, and condensed under reduced pressure. The residue was made alkaline with 10% sodium carbonate aq. solution, and then extracted with chloroform. Evaporation of the chloroform followed by recrystallization gave 4. The experimental and spectral data were summarized in Table 1 and 2.

General Procedure for the Isoxazole 7 ——— A mixture of 1 and 96% $NH_2OH \cdot HCl$ (1.2 equivalent amounts of 1) in 95% ethanol was allowed to stir at room temperature or heated under reflux, and condensed under reduced pressure by an aspirator. The residue was made alkaline with 10% sodium carbonate aq. solution, and then extracted with chloroform. The chloroform was evaporated. The resulting solid was purified by recrystallization to give 7. The experimental and spectral data were summarized in Table 1 and 2.

Table 2. Spectral Data of The Oxadiazole 4 and Isoxazole 7.

Product	Formula	Elemental Analysis Calcd. (Found) C	H	N	IR ($CHCl_3$) cm^{-1}	NMR($CDCl_3$) δ (ppm)
4a	$C_{11}H_{11}N_3O_2$	60.83 (60.96)	5.07 (5.08)	19.35 (19.08)	3320, 1600.	2.02 (3H,s), 3.85 (2H,s), 7.3-8.2 (5H,m), 8.9 (1H,b).
4b	$C_{10}H_{10}N_4O_2$	55.05 (55.04)	4.59 (4.68)	25.69 (25.70)	3250, 1585.	2.02 (3H,s), 3.89 (2H,s), 7.3-8.9 (4H,m), 9.1 (1H,b).
4c	$C_{10}H_{10}N_4O_2$	55.05 (54.81)	4.59 (4.49)	25.69 (25.45)	3400, 1590.	2.01 (3H,s), 3.92 (2H,s), 7.3-9.3 (4H,m), 10.1 (1H,b).
4d	$C_{14}H_{12}N_4O_2$	62.69 (62.41)	4.48 (4.53)	20.90 (20.63)	3230, 1585.	2.03 (3H,s), 3.93 (2H,s), 7.5-8.5 (6H,m), 9.6 (1H,b).
4e	$C_{12}H_{13}N_3O_2$	62.34 (62.18)	5.63 (5.93)	18.18 (18.27)	3250, 1580.	1.92 (3H,s), 3.72 (2H,s), 4.01 (2H,s), 7.25 (5H,s), 8.6 (1H,b).
7a	$C_{11}H_{10}N_2O_2$	65.35 (65.60)	4.95 (5.24)	13.86 (13.99)	3300, 1670.	2.23 (3H,s), 6.35 (1H,s), 7.3—8.0 (5H,m), 9.6 (1H,b).
7b	$C_{10}H_9N_3O_2$	59.11 (58.98)	4.43 (4.37)	20.69 (20.66)	3330, 1710.	2.29 (3H,s), 6.36 (1H,s), 7.4-8.7 (4H,m), 10.5 (1H,b).
7c	$C_{10}H_9N_3O_2$	59.11 (58.67)	4.43 (4.53)	20.69 (20.13)	3400, 1695.	2.25 (3H,s), 6.28 (1H,s), 7.3-9.2 (4H,m),11.9 (1H,b).
7d	$C_{14}H_{11}N_3O_2$	66.40 (66.11)	4.35 (4.50)	16.60 (16.50)	3320, 1710.	2.31 (3H,s), 6.38 (1H,s), 7.4-8.3 (6H,m), 10.8 (1H,b).
7e	$C_{12}H_{12}N_2O_2$	66.67 (66.84)	5.56 (5.53)	12.96 (12.68)	3370, 1705.	2.22 (3H,s), 3.72 (2H,s), 6.18 (1H,s), 7.3 (5H,s), 8.7 (1H,b).

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