Tetrahedron Letters No.55, pp.4875-4878, 1969. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF 4-ISOXAZOLINES AND THEIR THERMAL CONVERSION INTO PYRROLES

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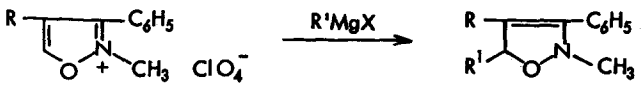
Received in Japan 11 October; received in the U K for publication 28 November 1969.

Among the three types of dihydro derivatives of isoxazoles, 2-isoxazolines have been studied in detail but only recently have a limited number of 4-isoxazolines become available. The latter system has been synthesized mainly by the 1,3-dipolar cycloaddition reaction of nitrones with acetylene carboxylates (1). Little was known about the 3-isoxazoline system prior to our proceeding paper (2), in which we reported that some 5-unsubstituted isoxazolium salts (1) react with Grignard reagents to give 5-substituted 3-isoxazoline derivatives (2).



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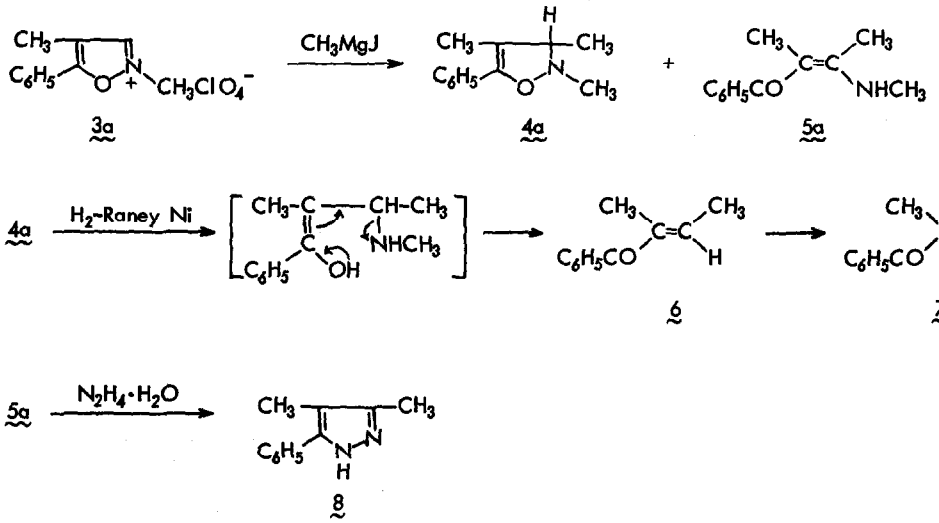
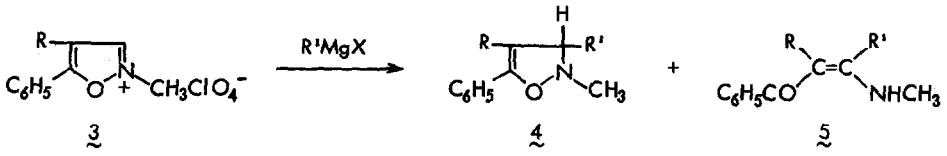
We now wish to report a new synthesis of 4-isoxazoline derivatives (4) from 3-unsubstituted isoxazole quaternary salts (3); and the thermal conversion of 3-benzyl-4-isoxazoline derivatives into pyrrole derivatives.

Reaction of 2,4-dimethyl-5-phenylisoxazolium perchlorate (3a) with methylmagnesium iodide in ether at 0° gave an oil (4a) together with the ring cleavage product, 2-benzoyl-3-methylamino-2-butene (5a). The oily product 4a was purified only by chromatography through alumina because of its instability. Formulation of 4a as 2,3,4-trimethyl-5-phenyl-4-isoxazoline follows from its elementary analysis (3) and spectral data (see TABLE I). Further evidence for the structure of 4a was obtained by catalytic reduction with Raney nickel, which afforded a mixture of 2-benzoyl-2-butene (6) and α-ethylpropiophenone (7). The structure assignment for 5a was supported by its elementary analysis (3), spectral properties and reaction with hydrazine hydrate, which gave 3,4-dimethyl-5-phenylpyrazole (8).



Similary, the reaction of 3a with benzylmagnesium chloride gave 2,4-dimethyl-3-benzyl-5-phenyl-4-isoxazoline (4b) and reactions of 2-methyl-5-phenylisoxazolium perchlorate (3b) with several Grignard reagents gave the corresponding 3-substituted 2-methyl-5-phenyl-4-isoxazolines (4c-g) (see TABLE I). Their elementary analyses (3) and spectral data are all in accord with the structures assigned.



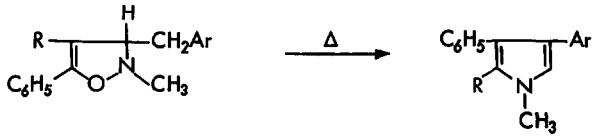
a: R = CH_3, R' = CH_3
b: R = CH_3, R' = $CH_2C_6H_5$
c: R = H, R' = C_2H_5
d: R = H, R' = $CH_2C_6H_5$
e: R = H, R' = $CH_2C_6H_4CH_3$(p)
f: R = H, R' = $CH_2C_6H_4Cl$(p)
g: R = H, R' = $CH_2CH{=}CH_2$

Heating a solution of 4d in xylene under reflux for 2.5 hours resulted in the formation of a brown resinous product, from which a crystalline solid, $C_{17}H_{15}N$, was isolated. Spectral feature (see TABLE II) indicated that the product was 1-methyl-3,4-diphenylpyrrole (9d); this was confirmed by comparison with an authentic sample obtained by the literature method (4). Similary, 1,2-dimethyl-3,4-diphenyl-, 1-methyl-3-tolyl-4-phenyl-, and 1-methyl-3-p-chlorophenyl-4-phenylpyrroles (9b, 9e and 9f) were obtained from the corresponding 4-isoxazolines (TABLE II).

TABLE I

	Yield %	$\nu_{C=C}^{film}$ cm^{-1}	λ_{max}^{EtOH} mμ (log ε)	τ (multiplicity,[d] J = Hz) in $CDCl_3$ (60 MHz) C_3-H	C_4-H or CH_3	N-CH_3
4a	41.4	1681	224(3.95), 275(3.79)	6.34(qq, 6.2, 1.1)	8.14(d, 1.1)	7.23(s) [a]
4b	81.2	1670	222(4.31), 279(3.88)	6.24(m)	8.18(d, 1.1)	7.37(s)
4c	14.9	1682	226(3.92), 275(3.80)	6.34(td, 6.5, 2.7)	4.77(d, 2.7)	7.18(s) [b]
4d	95.5	1649	222(4.17), 279(3.90)	6.07(td, 7.0, 2.4)	4.87(d, 2.4)	7.29(s)
4e	65.9	1646	223(4.16), 276(3.88)	6.07(td, 7.0, 2.4)	4.85(d, 2.4)	7.27(s)
4f[c]	98.4	1646	223(4.34), 276(3.97)	6.08(td, 6.6, 2.8)	4.86(d, 2.8)	7.28(s)
4g	85.0	1649	223(4.12), 276(3.91)	6.22(td, 6.6, 2.5)		7.21(s)

a) 5a: 21.3% yield, mp. 70-71°. b) 5c: 75.2% yield, mp. 59-60°. c) Colorless prisms, mp. 76-77°. d) Abbreviation: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.



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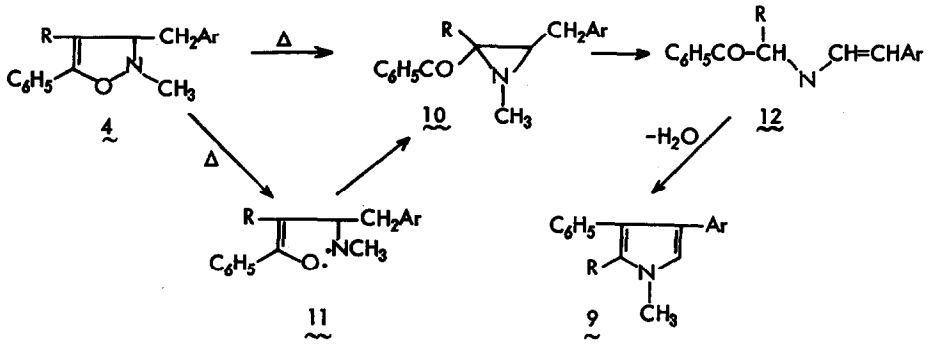
b: R = CH_3, Ar = C_6H_5
d: R = H, Ar = C_6H_5
e: R = H, Ar = $C_6H_4CH_{3(p)}$
f: R = H, Ar = $C_6H_4Cl_{(p)}$

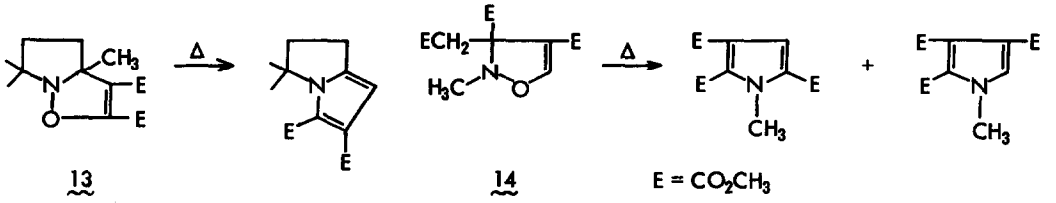
TABLE II

	Yield %	M.p. °C	λ_{max}^{EtOH} mμ (log ε)	τ (multiplicity) in $CDCl_3$ (60 MHz)
9b	60.6	92-93	244(4.31), 266(sh)	7.88(s, 3H), 6.60(s, 3H), 3.37(s, 1H), 2.84-2.94(m, 10H)
9d	59.0	127-128	244(4.34), 265(sh)	6.47(s, 3H), 3.39(s, 2H), 2.71-2.96(m, 10H)
9e	67.0	88-90	244(4.35), 264(sh)	7.70(s, 3H), 6.37(s, 3H), 3.35(s, 2H), 2.80-2.94(m, 9H)
9f	74.1	135-137	247(4.34), 271(sh)	6.38(s, 3H), 3.35(s, 2H), 2.80-2.86(m, 9H)

A plausible mechanism for the formation of 9 from 4 (R' = $ArCH_2$) is given as follows:



The thermal valence rearrangement of 4 to the 2-acylaziridine (10) may involve either a one step concerted process or initial homolysis of 4 into a biradical (11) followed by recombination (5). The intermediate 10 would undergo cleavage of the C-C bond to give the aminoketone (12), dehydrative ring closure of which would give the final product 9. An analogous thermal rearrangement of some 4-isoxazolines to 2-acylaziridines has been described by Baldwin et al. (6). However, their final products are the corresponding 4-oxazolines. Only two examples (13 and 14) of pyrrole formation similar to our present case have been reported by Aceson et al. (7) and Winterfeldt et al. (8).



The scope and limitations of the new reaction described in this paper are under investigation.

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