2-METHYL-4-NITROISOXAZOLIN-5-ONE: RING TRANSFORMATION TO 3-NITROPYRROLES

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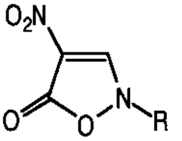
Abstract - Ring transformation of 2-methyl-4-nitroisoxazolin-5-one with some enolate anions afforded 3-nitropyrroles. A ring-opened intermediate of the ring transformation was isolated.

In our course of the study on electron deficient pyridones, 4-nitroisoxazolin-5-one was obtained.[1] Functional varieties of the isoxazolone such as heterodiene, α-nitrolactone, and β-nitroenamine suggest us that it may undergo various types of reactions. We already reported 2-methyl-4-nitroisoxazolin-5-one (**1**) acted as a precursor of a nitrile oxide in the reaction with various dipolarophiles to give isoxazoles.[2] Availability of 2-acetyl-4-nitroisoxazolin-5-one (**2**) as an acetylating reagent also was revealed.[3]



1: R = Me
2: R = Ac

Here, we wish to deal a new ring transformation of **1** with enolate anions of β-keto esters and β-diketones. Treatment of 1 with 1.2 equiv. of ethyl 2-sodio-3-oxobutanoate in pyridine at 70 °C gave ethyl 1,3-dimethyl-4-nitro-2-pyrrolecarboxylate (**3a**)[4] as a major product (77.0%) and a trace of diethyl 1,3,5-trimethyl-2,4-pyrroledicarboxylate (**4a**).[5] The structure of **3a** was assigned by its ^{1}H nmr and ir spectra, and by comparison with those of an authentic sample, which was independently sythesized from ethyl 3-methylpyrrole-2-carboxylate[6] by nitration, separation from 5-nitro isomer on silica gel column, and

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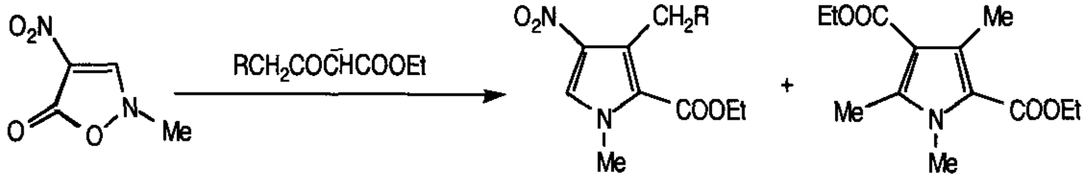
Dedicated to Dr. Shigeru Oae on the occasion of his 77th birthday.

N-methylation. The similar reaction with diethyl 2-sodio-3-oxopentanedioate yielded ethyl 3-ethoxycarbonylmethyl-1-methyl-4-nitro-2-pyrrolecarboxylate (**3b**).[7] The results are summarized in Table 1.



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3a: R = H
3b: R = COOEt

4a

It is clear that the C(2)-C(3) part of the obtained pyrrole (**3**) is derived from the reagent and the rest arises from the N(2)-C(3)-C(4) moiety of the isoxazolone (**1**). Formation of **4a** must involve the condensation of two molar ethyl 3-oxobutanoate during the ring transformation, but the detail is in progress.

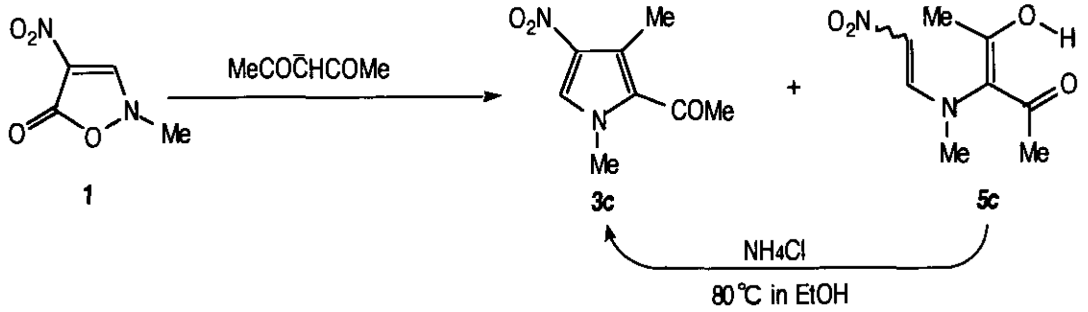
Table 1 Ring transformation of 2-methyl-4-nitroisoxazoloin-5-one (**1**)

Substrate	Reagent[a)]	Reaction Conditions				Products (Yield/%)		
		equiv.	Solvent	Temp./℃	Time/h			
1	**a**	1.2	Pyridine	70	5	**3a** (77.0)	**4a** (trace)	
1	**a**	3.0	"	"	"	**3a** (48.0)	**4a** (36.0)	
1	**a**	1.2	DMF	"	"	**3a** (56.8)		
1	**b**	1.2	"	"	"	**3b** (56.6)		
1	**c**	1.2	Pyridine	20	"	**3c** (5.8)		**5c** (10.4)
1	**c**	3.0	DMF	70	"			**5c** (64.2)
5c	(NH_4Cl)	3.0	Ethanol	80	10	**3c** (83.7)		

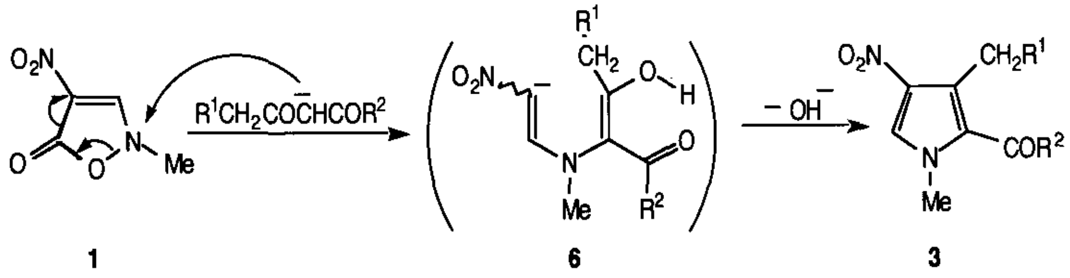
a) **a**: ethyl 2-sodio-3-oxobutanoate; **b**: diethyl 2-sodio-3-oxo-pentanedioate;
c: 3-sodiopentane-2,4-dione

2,4-Pentanedione, a kind of ß-diketone, yielded a similar ring transformed product (**3c**)[8] in a low yield, and gave **5c**[9] as a major product. The ring-opened product (**5c**) presented in an equilibrium mixture of *E*- and *Z*-isomers in $CDCl_3$ solution in a ratio of about 4:3.[10,11]

The product (**5c**) is a β-nitroenamine and has an electrophilic carbonyl carbon in the molecule. Cyclization of **5c** to pyrrole (**3c**) could be achieved in good yield by heating **5c** at 80 °C for 10 h in ethanol containing a small amount of ammonium chloride as an acid catalyst.

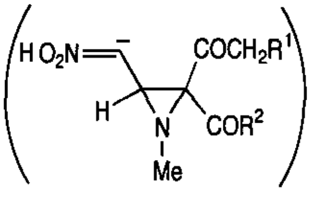


In the present reaction, a new C-N bond is formed between the active methylene carbon of the reagent and the ring nitrogen of isoxazolone (**1**). Taking account of isolation of **5c**, one of a plausible course of the reaction is proposed as that direct nucleophilic attack of the enolate anion to the nitrogen atom of **1** accompanied by decarboxylation to form **6**, then intermediate anion (**6**) recyclized to nitropyrrole (**3**).



We, however, can not neglect that the intramolecular attack of the enolate anion introduced at the 3-position of **1** to the ring nitrogen atom caused the N-O bond cleavage and decarboxylatiton to give aziridine (**7**), and successive ring opening of the aziridine ring forms intermediate (**6**).

Since, it is not likely known that the C-anion of the reagent attacks directly at the ring nitrogen of an isoxazolone before ring cleavage. It has been well known that the nucleophilic attack at the 3-position of 5-isoxazolone resulted in the N-O bond cleavage and decarboxylation.[12-15] There are also some precedents for the ring opening of isoxazole or isoxazolone followed by succeeding recyclization to an aziridine.[16]



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Though more examples with a variety of carbonyl compounds are necessary to show the general utility of the reaction, the ring transformation furnishes a convenient route for synthesis of functionalized ß-nitropyrrole derivatives which were tediously obtainable by direct nitration.

In conclusion, this new ring transformation suggests that 2-methyl-4-nitroisoxazol-5(2*H*)-one (**1**) behaves as a masked ß-nitroenamine besides a precursor of nitrile oxide.[2]

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5. Ir: ν 1690, 1540, 1350. ^{1}H Nmr ($CDCl_3$): δ 1.37 (t, *J*=7 Hz, 3H), 1.38 (t, *J*=7 Hz, 3H), 2.51 (s, 3H), 2.55 (s, 3H), 3.78 (s, 3H), 4.28 (q, *J* =7 Hz, 2H), 4.30 (q, *J*=7 Hz, 2H).
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8. Mp 133.5-134.5 °C. Ir: ν 1655, 1550, 1310. ^{1}H Nmr ($CDCl_3$): δ 2.52 (s, 3H), 2.69 (s, 3H), 3.90 (s, 3H), 7.63 (s, 1H).
9. Mp 125.0-128.0 °C. Ir: ν 1610, 1560, 1310. ^{1}H Nmr($CDCl_3$): *E*-**5c**: δ 2.10 (s, 6H), 3.29 (s, 3H), 6.46 (d, *J*=11 Hz, 1H), 8.16 (d, *J*=11 Hz, 1H), 15.71 (s, 1H); *Z*-**5c**: δ 2.10 (s, 6H), 3.03 (s, 3H), 6.72 (d, *J*=11 Hz, 1H), 7.92 (d, *J*=11 Hz, 1H), 15.53 (s,1H).
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