2-METHYL-4-NITROISOXAZOLIN-5-ONE:
RING TRANSFORMATION TO 3-NITOPYRROLES
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Abstract - Ring transformation of 2-methyl-4-nitroisoaxazolin-5-one with some enolate anions afforded 3-nitopyrroles. A ring-opened intermediate of the ring transformation was isolated.

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

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-sodium-3-oxobutanoate in pyridine at 70 °C gave ethyl 1,3-dimethyl-4-nitro-2-pyrrolecarboxylate (3a) as a major product (77.0%) and a trace of diethyl 1,3,5-trimethyl-2,4-pyrroleedicarboxylate (4a). The structure of 3a was assigned by its 1H nmr and ir spectra, and by comparison with those of an authentic sample, which was independently synthesized from ethyl 3-methylpyrrole-2-carboxylate by nitration, separation from 5-nitro isomer on silica gel column, and

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). The results are summarized in Table 1.

![Reaction Scheme](image)

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>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Products (Yield/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>1.2 Pyridine 70 5</td>
<td>3a (77.0) 4a (trace)</td>
</tr>
<tr>
<td>1</td>
<td>a</td>
<td>3.0 DMF 3, t</td>
<td>3a (48.0) 4a (36.0)</td>
</tr>
<tr>
<td>1</td>
<td>b</td>
<td>1.2 DMF 3, t</td>
<td>3b (56.6)</td>
</tr>
<tr>
<td>1</td>
<td>c</td>
<td>1.2 Pyridine 20 5</td>
<td>3c (5.8) 5c (10.4)</td>
</tr>
<tr>
<td>1</td>
<td>c</td>
<td>3.0 DMF 70 10</td>
<td>5c (64.2)</td>
</tr>
<tr>
<td>5c</td>
<td>(NH₄Cl)</td>
<td>3.0 Ethanol 80 10</td>
<td>3c (83.7)</td>
</tr>
</tbody>
</table>

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 β-diketone, yielded a similar ring transformed product (3e) in a low yield, and gave 5c as a major product. The ring-opened product (5c) presented in an equilibrium mixture of E- and Z-isomers in CDCl₃ solution in a ratio of about 4:3.

The product (5c) is a β-nitroenamine and has an electrophilic carbonyl carbon in the molecule. Cyclization of 5c to pyrrole (3e) 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 5e, 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 decarboxylation 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. There are also some precedents for the ring opening of isoxazole or isoxazolone followed by succeeding recyclization to an aziridine.

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 β-nitropyrrrole derivatives which were tediously obtainable by direct nitration.

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


4. Mp 143.0-145.0 °C. Ir: v 3140, 1690, 1550, 1340, 1100. 1H Nmr (CDCl3): δ 1.42 (t, J=7 Hz, 3H), 2.64 (s, 3H), 3.94 (s, 3H), 4.36 (q, J=7 Hz, 2H), 7.60 (s, 1H).

5. 1H Nmr (CDCl3): 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).


7. Mp 88.0-89.0 °C. Ir: v 3130, 1720, 1700, 1550, 1346. 1H Nmr (CDCl3): δ 1.27 (t, J=7 Hz, 3H), 1.37 (t, J=7 Hz, 3H), 3.96 (s, 3H), 4.18 (q, J=7 Hz, 2H), 4.28 (s, 2H), 4.34 (q, J=7 Hz, 2H), 7.64 (s, 1H).

8. Mp 133.5-134.5 °C. Ir: v 1655, 1550, 1310. 1H Nmr (CDCl3): 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: v 1610, 1560, 1310. 1H Nmr(CDCl3): 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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