A NOVEL NITRILE OXIDE PRECURSOR; 2-METHYL-4-NITRO-5(2H)-ISOXAZOLONE

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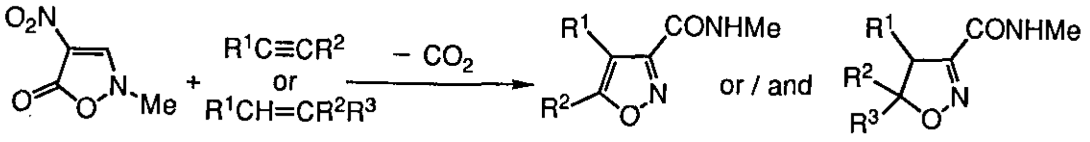
Abstract — 2-Methyl-4-nitro-5(2H)-isoxazolone (**1**) was found to be a versatile precursor for a functionalized nitrile oxide by reaction with dipolarophiles giving 3-(N-methylcarbamoyl)isoxazole (**2** or **3**) derivatives.

In our course of the study on reaction of electron-deficient pyridones with nucleophiles, we obtained 4-nitro-5(2H)-isoxazolone as pyridinium salt by ring transformation of 3,5-dinitro-1-(4-nitrophenyl)-4-pyridone with hydroxylamine.[1] This pyridinium salt was easily converted to 2-methyl-4-nitro-5(2H)-isoxazolone (**1**) by treating with dimethyl sulfate in good yield. Having a variety of functionalities such as β-nitroenamine, hetero-diene, and α-nitro-γ-lactone in its ring, **1** is anticipated to demonstrate various types of reactivity including ring transformation.

In the present paper we wish to report the utility of the isoxazolone (**1**) as a versatile precursor for nitrile oxide.

Treatment of **1** with 1.2 equiv. of phenylacetylene in DMF at 100 °C in the presence of a small amount of activated charcoal afforded 3-(N-methylcarbamoyl)-5-phenylisoxazole (**2a**)[2] in 66% yield after purification with column chromatography on silica gel.



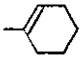
1

2a: R^1=H,R^2=Ph
2b: R^1=R^2=COOEt
2c: R^1=H,R^2=CH_2OAc
2d: R^1=Ph,R^2=H

3d: R^1=Ph,R^2=H,R^3=N O
3e: R^1=H,R^2=H,R^3=COOEt
3f: R^1=H,R^2=H,R^3=OEt
3g: R^1-R^2=$(CH_2)_4$,R^3=OMe

Reaction of **1** with ethyl vinyl ether also gave 3-(N-methylcarbamoyl)-5-ethoxy-2-isoxazoline (**3f**).[3] These results suggested that N-methylcarbamoylformonitrile oxide (**4**), MeNHCOC≡N→O, was intermediately derived from **1** by decarboxylation. When **1** was heated in ethanol 3,4-bis(N-methylcarbamoyl)froxane[4] was formed. This fact also supported the formation of **4**.[5] In order to investigate generality of reactivity of **1**, reactions with a various kind of 1,3-dipolarophiles containing acetylenes or olefins were carried out, and the results are summarized in Table 1.

Table 1 Reactions of **1** with dipolarophiles

Reagent	Reaction Conditions				Products (yield/%)	
	Equiv.	Solv.	Temp./°C	Time/h		
PhC≡CH	1.2	DMF	100	3	**2a** (66)	
EtOOCC≡CCOOEt	3.0	DMF	100	67	**2b** (61)	
HC≡CCH_2OAc	3.0	DMF	100	3	**2c** (95)	
PhCH=CHN O	1.2	MeCN	90	6	**2d** (10)	**3d**(71)
CH_2=CHCOOMe	2.2	DMF	100	6.5		**3e**(89)
CH_2=CHOEt	1.2	Pyridine	100	2		**3f**(69)
MeO— 	1.5	DMF	110	6		**3g**(55)

As shown in Table 1, **1** reacted effectively with both electron-rich and electron-deficient 1,3-dipolarophiles.

The isoxazolone (**1**) is enough stable on storage and can offer **4** on gentle heating without applying any particular conditions required in conventional methods[6] such as strong base,[7] silver nitrate,[8] uv light,[9] and high temperature.[10]

Though, the definitive mechanism for the formation of **4** was not evident, **1** was found to be a new and versatile precursor for a functionalized nitrile oxide.

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2. **2a:** mp 199.0-200.0 °C (ethanol). Ir(Nujol): 3340,1670 cm^{-1}. ^{1}H Nmr($CDCl_3$): δ 2.82(3H, d, J=4 Hz), 7.33(1H, s), 7.4-7.7 (3H, m), 7.8-8.1(2H, m), 8.71(1H,broad s).
3. **3f:** mp 97.0-98.0 °C (hexane). Ir: 3300, 1660, 1600 cm^{-1}. ^{1}H Nmr(acetone-d_6): δ 1.15(3H, t, J=7 Hz), 2.83(2H, d, J=5 Hz), 3.09 (1H, dd, J=2.5 and 19 Hz), 3.12(1H, dd, J=6 and 19 Hz), 3.7(2H, m), 5.69(1H, dd, J=2.5 and 6Hz), 7.50(1H, broad s). ^{13}C Nmr($CDCl_3$): δ 15.0, 26.0(C-4), 40.0, 64.3, 104.8(C-5), 154.7(C-3), 159.8.
4. The authentic sample was obtained by treatment of aqueous methylamine with diethyl 3,4-bis(ethoxycarbonyl)froxane prepared by the method of H. R. Synder and N. E. Boyer, J. Am. Chem. Soc., 1955, **77**, 4233.
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