Reactions of Pyridylnitrilimines with Dimethyl Acetylene Dicarboxylate

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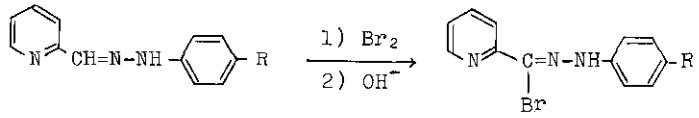
Abstract —— Reaction of 2-(1-bromo-1-phenylhydrazono)methylpyridines (2) with dimethyl acetylene dicarboxylate in the presence of triethylamine gave rise to dimethyl 1-phenyl-3-(2-pyridyl)-4,5-dicarboxylates (3) and dimethyl 1-phenylazoindolizine-2,3-dicarboxylates (4). The former is the usual 1,3-dipolar cycloaddition product of a nitrilimine, while the latter is an unusual cycloaddition product.

Studies of the 1,3-dipolar cycloaddition reaction of nitril-ylides[1], nitrilimines[2] and nitrile oxides[3] have been carried out previously by Huisgen and coworkers. Such 1,3-dipolar cycloaddition reactions are a potentially important synthetic method of five-membered heterocyclic compounds. In a previous paper[4], we reported an unusual intramolecular cyclization reaction of nitril-ylides having a pyridine ring. In a continuation of our studies on α-[4] and β-[5]substituted pyridine chemistry, the cycloaddition reaction of pyridylnitrilimines with dimethyl acetylene dicarboxylate was investigated.

The 2-(1-bromo-1-phenylhydrazono)methylpyridine derivatives, which served as the starting materials in our studies, were prepared by bromination of the corresponding picolinealdehyde phenylhydrazones in AcOH according to the reported method for the derivatization of benzaldehyde phenylhydrazone[6].
An acetic acid solution of bromine was added to an acetic acid solution of the picolinealdehyde phenylhydrazone at room temperature. After stirring for 1 h, the resulting precipitate was collected by filtration, washed with EtOH and recrystallized from EtOH to give the 2-(1-bromo-1-phenylhydrazono)methylpyridine as its hydrobromide salt. Neutralization with aqueous sodium bicarbonate afforded 2-(1-bromo-1-phenylhydrazono)methylpyridine (2). The results are summarized in Table I.

Table I



1 2

2	R	Yield (%)	mp (°C)
a	Cl	87	147-149 (238-240)*
b	CH_3O	57	113-115 (212-213)
c	NO_2	81	258-260 (261-263)

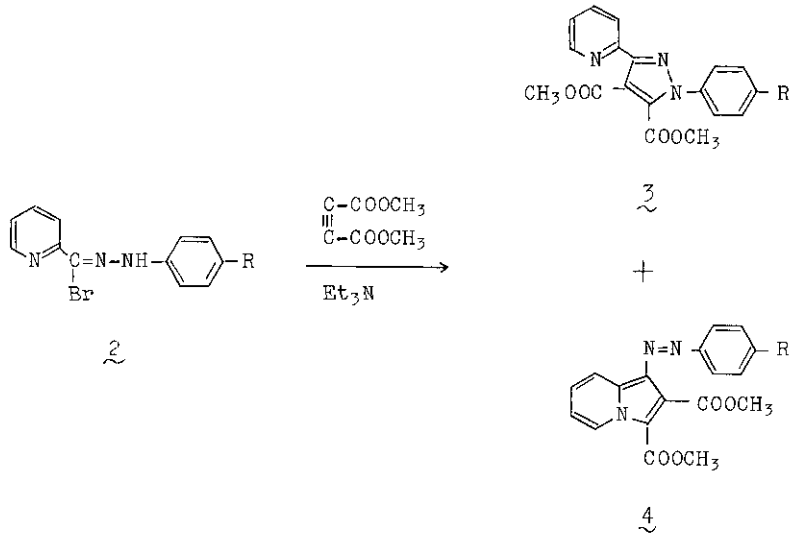
* : hydrobromide

Treatment of 2a (0.05 M) with dimethyl acetylene dicarboxylate (0.06 M) in the presence of three drops of triethylamine in CH_3CN (50 ml) for 5 h, followed by careful silica gel chromatography, gave two products (3a and 4a). The first reaction product (3a), which was obtained in 35% yield, was determined to be dimethyl 1-(p-chlorophenyl)-3-(2-pyridyl)-pyrazole-4,5-dicarboxylate, the expected 1,3-dipolar cycloaddition product of nitrilimine (2a). 3a : mp 149-151°. Anal. Calcd. for $C_{18}H_{14}ClN_3O_4$: C,58.12; H,3.76; N,11.30; Cl,9.55. Found: C,58.23; H,3.79; N,11.30; Cl, 9.53. ir max (nujol): 1740 and 1736 cm^{-1}. nmr δ ($CDCl_3$): 3.90(3H, s, $-COOCH_3$), 4.03 (3H, s, $-COOCH_3$), 7.32-8.55(8H, m, aromatic H).

The second reaction product (4a), obtained in 2 % yield, was determined to be dimethyl 1-(p-chlorophenylazo)indolizine-2,3-dicarboxylate, an unusual 1,3-dipolar cycloaddition product of nitrilimine (2a). 4a :mp 158-160°. Anal. Calcd. for $C_{18}H_{14}ClN_3O_4$: C,58.12; H,3.76; N,11.30; Cl,9.55. Found: C,57.91; H,3.61; N,11.09; Cl,9.89. ir max (nujol): 1730 and 1698 cm^{-1}. uv λ_{max}(EtOH): 407(4.37), 325(4.22), 244(4.45) and 237(4.44). nmr δ ($CDCl_3$): 4.03(3H, s, $-COOCH_3$), 4.10(3H, s, $-COOCH_3$), 7.13(1H, dd, J=9 Hz, J=7 Hz), 7.47(1H, m), 7.57(2H, d, J=9 Hz), 7.93(2H, d, J=9 Hz), 8.49(1H, d, J=9 Hz), 9.67(1H, d, J=7 Hz)[7].

Likewise, the p-methoxy- and p-nitro-substituted compounds (2b and 2c) were treated with dimethyl acetylene dicarboxylate under the same reaction conditions. As in the case of 2a, the corresponding pyrazole and indolizine derivatives were obtained. The results are summarized in Table II.

These findings suggest that the reaction products, 3 and 4, might be formed



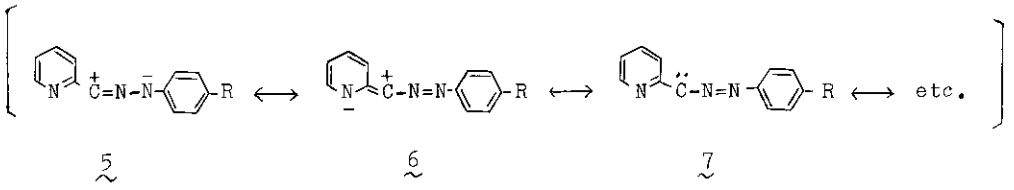


Table II

	R	3 mp(°C)	3 Yield(%)	4 mp(°C)	4 Yield(%)
a	Cl	149-151	35	158-160	2
b	CH_3O	133-135	47	136-137	0.6
c	NO_2	175-176	33	247-248	2

by the 1,3-dipolar cycloaddition reaction of 5 and 6, respectively, (two possible intermediates of the equilibrium mixture of the initially formed nitrilimine) with dimethyl acetylene dicarboxylate.

We attempted the reaction of 2 with other dipolarophiles such as ethyl propiolate, ethyl acrylate and diethyl maleate in hopes of obtaining other unusual 1,3-dipolar cycloaddition products. However, in all three of these cases no unusual products were obtained.

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7) In the literature[8], C-5 proton of indolizine ring possessing the electron withdrawing substituent such as ethoxycarbonyl or benzoyl group at C-3 position was shifted to down field by its anisotropy in the nmr.

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