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HEXACARBONYLMOLYBDENUM-INDUCED FORMATION OF PYRIDINES FROM ISOXAZOLES AND ACETYLENIC ESTER

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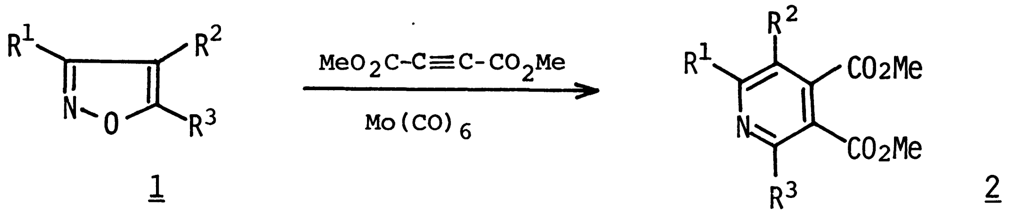
Upon treatment with $Mo(CO)_6$ in anhydrous benzene, substituted isoxazoles undergo a novel inclusion of dimethyl acetylenedicarboxylate across the C_4-C_5 bond and loss of an oxygen atom to lead to pyridines.

The thermal[1)] and photochemical[2)] reactions of isoxazole ring system have been shown to isomerize to the azirine derivatives. It has recently been shown that $Fe(CO)_5$, $Fe_2(CO)_9$, or $Mo(CO)_6$ causes an efficient reductive cleavage of the N-O bond of substituted isoxazoles to give β-aminoenones under mild conditions in the presence of water.[3,4)] The catalytic hydrogenation of isoxazoles also gives β-aminoenones which are widely applicable in synthesis.[5)] In contrast to the ring cleavage reactions, the cycloaddition of the simple isoxazole with olefins or acetylenic esters has not been accomplished,[6)] although only 2,1-benzisoxazole, which has an electron-withdrawing substituent is known to undergo Diels-Alder reaction with dimethyl acetylenedicarboxylate to lead to 1,4-epoxy-1,4-dihydroquinoline ring system.[7)]

We now report that $Mo(CO)_6$ effects a reaction of substituted isoxazoles to undergo a novel inclusion of dimethyl acetylenedicarboxylate (DMAD) across the C_4-C_5 bond and loss of an oxygen atom to lead to pyridine derivatives as shown in Scheme 1.

Thus the reactions of 2 mmol of the substituted isoxazoles (1a-e), 2 mmol of $Mo(CO)_6$, and 2 molar equivalent amount of DMAD in 10 cm^3 of anhydrous benzene were



a: $R^1 = R^3 = Ph$, $R^2 = H$
b: $R^1 = R^2 = R^3 = Ph$
c: $R^1 = Ph$, $R^2 = R^3 = H$
d: $R^1 = Ph$, $R^2 = H$, $R^3 = Me$
e: $R^1 = Me$, $R^2 = H$, $R^3 = Ph$

Scheme 1.

Table 1. Reaction Time, Yields, and Melting Points of Pyridines 2.

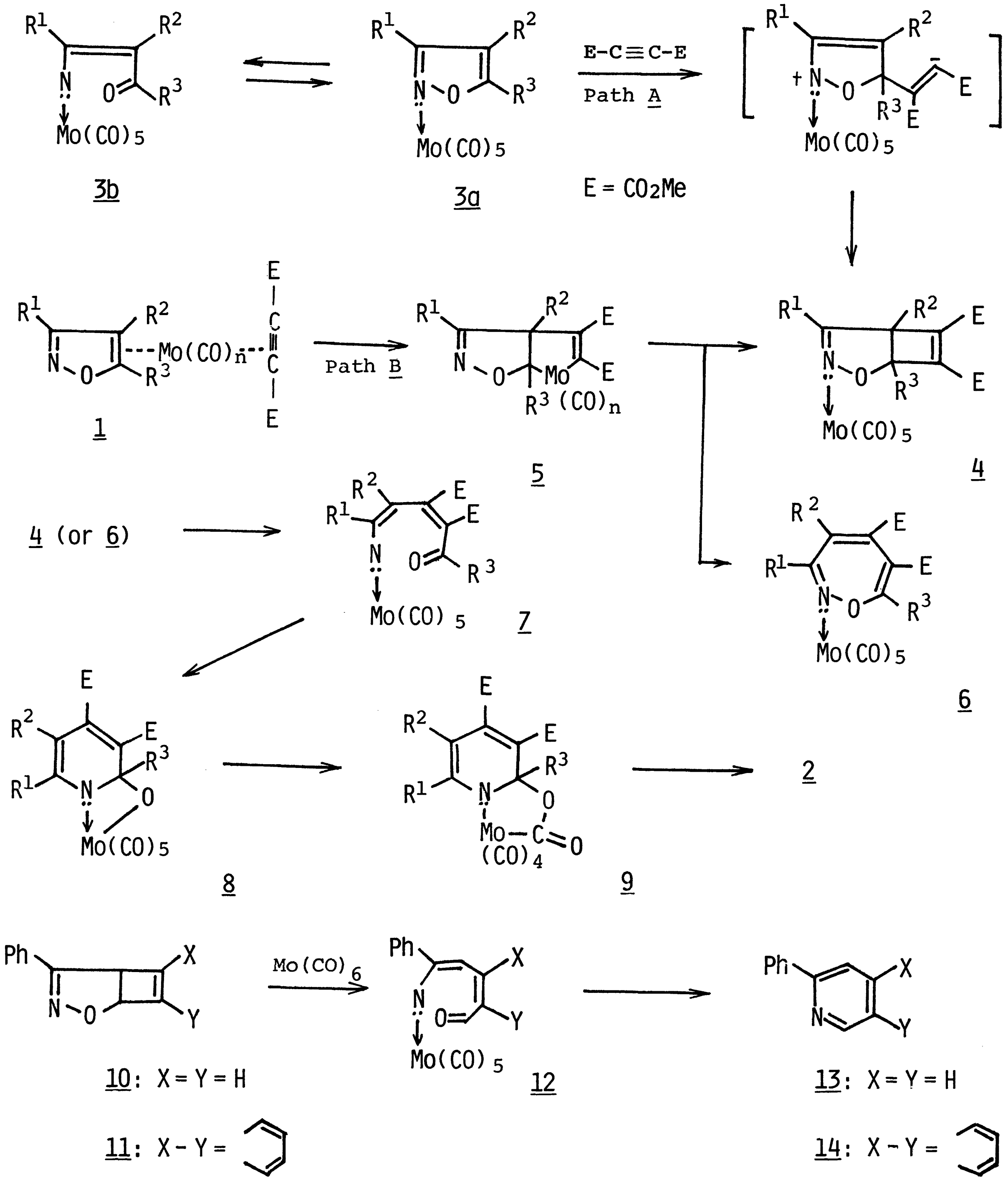
2	R^1	R^2	R^3	Reaction time/h	Yield/%	Mp/°C	Ref.
a	Ph	H	Ph	24	28	104-105	8
b	Ph	Ph	Ph	24	22	221-222	9
c	Ph	H	H	24	16	72-73	10
d	Ph	H	Me	24	26	(140-150)	11
e	Me	H	Ph	10	12	116-117	12

refluxed under a nitrogen atmosphere until all of 1a-e were consumed. The reaction mixture was carefully filtered through Celite and the filtrates were purified by TLC on silica gel to give pyridine derivatives 2a-e as summarized in Table 1. The yields of pyridines are rather poor. Each of the reaction accompanied the formation of hexamethyl mellitate (10-20% based on DMAD used)13) and a mixture (ca. 8%) of more than three products. The latter mixture seemed to contain no methoxycarbonyl group and it is not separated, thus the structures have not been determined at the present stage.

The structures of pyridines were confirmed by the studies of the spectral data (NMR, IR, and mass spectra) and by the comparison of the physical data (mp and bp) of the authentic materials. Since the thermal reaction of 1a and DMAD in refluxing benzene for 24 h did not afford any adducts and 1a was recovered quantitatively, therefore $Mo(CO)_6$ is indispensable for the present reactions.

Possible mechanistic pathways for the formation of pyridines are outlined in Scheme 2. This mechanism is speculative since no intermediates have been isolated. Initial complexation of the isoxazole to $Mo(CO)_6$ would give 3a, which has been shown to undergo the N-O bond cleavage to give the complexed nitrene intermediate 3b14) collapsing to the corresponding β-aminoenones in the presence of water.4) The factor allowing facile N-O bond cleavage of 3a could be ascribed to the delocalization of π-d electrons from the molybdenum to the π* orbital of the isoxazole. In the presence of DMAD, 3a could undergo cycloaddition to give the complex 4 (Path A). An alternative possibility may be the [2 + 2] cross-addition of DMAD with the C_4-C_5 bond of 1 to give metallocycle such as 5,15) and the subsequent ligand migration to lead to 4 or the complexed 1,2-oxazepine16) derivative 6 (Path B). However, the facile N-donor complexation of the isoxazole to give 3a4) seems to prefer Path A to Path B.

The N-O and C_4-C_5 bond cleavage of the 3,5-disubstituted isoxazolines affording the corresponding aldehydes and the complexed nitrene intermediates in the presence of $Fe(CO)_5$, $Fe_2(CO)_9$,17) or $Mo(CO)_6$18) has previously been shown. In a similar fashion, the complex 4 (or 6) would give the complexed nitrene intermediate 7. A species similar to 7 has also been proposed as an intermediate of the $Mo(CO)_6$- or $Fe_2(CO)_9$-induced transformation of ketovinylazirine to pyrrole derivatives and/or pyridine derivatives.19) Thus the cyclization of 7 to give the complex 8 and the subsequent ligand migration could then lead to 9 which could collapse to give pyridines 2 by elimination of CO_2 and $Mo(CO)_4$.19)



Scheme 2.

Support for the mechanistic aspect was obtained from the following fact. Heating of benzene solution of 10[20] or 11[21] in the presence of an equivalent amount of $Mo(CO)_6$ for 6-18 h under a nitrogen atmosphere resulted in the formation of 2-phenylpyridine (13) or 3-phenylisoquinoline (14)[22] in 76 or 65% yield after purification by TLC. The complexed nitrene intermediate, such as 12, would intervene in the reaction. Thus the intermediacy of 4 and 7 seems to be plausible. Further confirmation of the mechanistic pathways and studies under this program are now in progress.

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