A NOVEL SYNTHESIS OF 4-METHYL-, 4-OXO-, AND 4-AMINO-3-(3-METHYL-5-ISOXAZOLYL)PYRIDINE DERIVATIVES VIA N-SILYL-1-AZA-ALLYL ANION

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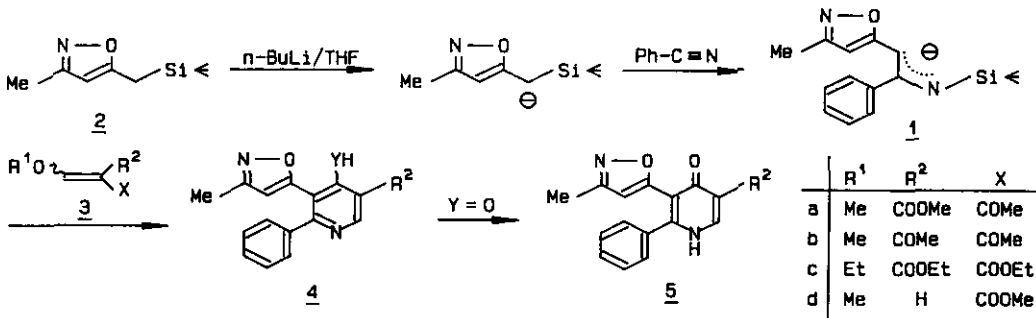
Abstract ——An N-silyl-1-aza-allyl anion (1) reacted with alkoxyalkenes (3a) - (3e) to afford the corresponding 4-methylpyridines (4a) and (4b), 4-pyridones (5c) and (5d), and 4-aminopyridine (4e), possessing a 3-methyl-5-isoxazolyl group on C-3 atom, in 91, 90, 62, 27, and 68% yields, respectively, whereas alkoxyalkenes (3f) and (3g) gave the corresponding N-adduct intermediates (6f) and (6g) in 46 and 60% yields.

It is well known that an α-silyl carbanion is frequently utilized in the Peterson olefination reactions.[1-4] In the course of our investigation of the reaction of the α-silyl carbanion with carbonyl compounds or with their analogs, we previously reported that the treatment of p-substituted benzonitriles or cyanopyridines with the α-silyl carbanions gave N-silyl-1-aza-allyl anions or the corresponding N-silyl-enamines in high yields,[5,6] and that the N-silyl-1-aza-allyl anion was a useful building block for the synthesis of N-heterocyclic compounds[7] and others.[8] The N-silyl-enamine, an ambident nucleophile possessing N and C atoms in the reaction center, is a stable, important equivalent of an unstable primary enamine.

As an extension of our investigation mentioned above, we now wish to report a reaction of the N-silyl-1-aza-allyl anion (1), generated from 3-methyl-5-trimethylsilylmethylisoxazole (2) and benzonitrile, with alkoxyalkenes (3) to afford the corresponding pyridine derivatives (4) or (5) in good yields (Scheme 1).

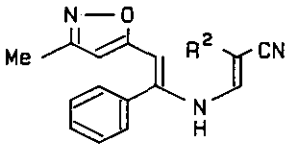
The results are shown in Table 1. Methyl 2-acetyl-3-methoxy-2-propenoate (3a) and 3-acetyl-4-methoxy-3-buten-2-one (3b) gave methyl 4-methyl-5-(3-



	R^1	R^2	X	Y
a	Me	COOMe	COMe	CH_2
b	Me	COMe	COMe	CH_2
c	Et	COOEt	COOEt	O
d	Me	H	COOMe	O
e	Et	COOEt	CN	NH
f	Me	H	CN	NH
g	Et	CN	CN	NH

Scheme 1

methyl-5-isoxazolyl)-6-phenylnicotinate (4a) and 5-acetyl-4-methyl-3-(3-methyl-5-isoxazolyl)-2-phenylpyridine (4b) in excellent yields (91 and 90%, respectively). Similarly, ethyl 3-ethoxy-2-ethoxycarbonyl-2-propenoate (3c) gave the corresponding 4-pyridone derivative (5c) in 62% yield, and methyl 3-methoxy-2-propenoate (3d) gave also the corresponding 4-pyridone (5d) but in a moderate yield (27% by ^{1}H nmr). In addition, ethyl 4-aminonicotinate (4e) was obtained from ethyl 2-cyano-3-ethoxy-2-propenoate (3e) in 68% yield by cyclization with the cyano carbon atom. Contrary to our expectations, both 3-methoxy-2-propenenitrile (3f) and 2-cyano-3-ethoxy-2-propenenitrile (3g) resisted stubbornly to construct the pyridine ring but formed the corresponding N-adduct intermediates (6f) and (6g), in 25 and 60% yields as major products. The yield of (4f) was only 2% even after refluxing the reaction mixture for 2 h in THF, whereas comparison of the yields of 6f before and after refluxing showed two-fold enhancement (25/46). Attempts at cyclization of both the pure adducts (6f and 6g) resulted in failure on heating in diglyme at 150 °C for 2 h.



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The structures of the products (4) or (5) were determined not only by their spectral properties[9] but also by transformation of the intermediate 6f into a known compound. On hydrolysis in ethanolic hydrochloric acid, 6f quantitatively gave 3-methyl-5-isoxazolylmethyl phenyl ketone (7), which was identified by comparison with an authentic sample.[6] The result implies that the nitrogen atom of 1 attacks to the 3-positioned carbon atom in 3f to give 6f (Scheme 2).

Table 1. Reaction of 1 with 3[a)]

Entry	3	Product	Yield (%)	mp/°C
1	a	4a	91	137.7-138.3
2	b	4b	90	154.6-155.1
3	c	5c	62	207.0-207.9
4	d	5d	11 (27)[b)]	215.1-215.3
5	e	4e	68	171.1-172.3
6	f	4f	trace [25][c)]	—
7[d)]	f	4f	2 [46][c)]	—
8	g	4g	[60][c), e)]	—

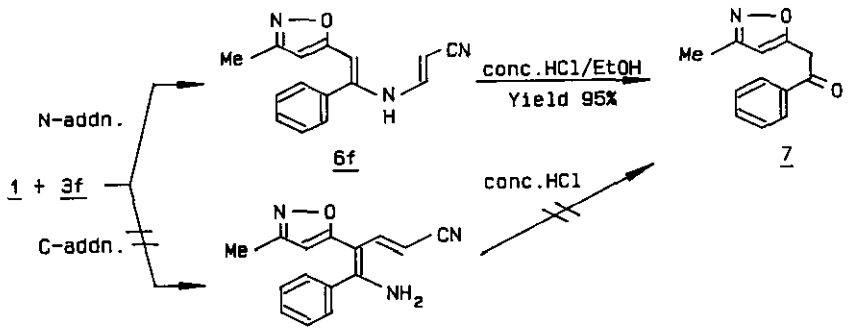
a) Molar ratio, 1 : 3 = 1 : 1; Stirred for 1 h at -80 °C and then for 2 h at room temperature.

b) Determined by ^{1}H nmr in parentheses.

c) Yield of the corresponding intermediate (6) in branckets. mp: 6f 145.3-147.3 °C, 6g 172.9-174.4 °C.

d) Refluxed for 2 h after stirring for 1 h at -80 °C.

e) Yield of 4g was not determined.



Scheme 2

Miyajima and his co-workers have reported that N-t-butylimine derivatives of ketones cyclize with 3c, 3e or 3g at elevated temperature to give the corresponding 2-pyridone or 2-aminopyridines in poor to good yields.[10] In comparison with their method, the present method has the advantages of the lower reaction temperatures, the shorter reaction times, the higher yields, and high selectivity for the synthesis of 4,5-functionalized pyridines such as 4 or 5. The present method, however, is of no advantage to the reaction with 3f or 3g. Further investigation is now in progress.

In a typical procedure, a 15% solution of n-butyllithium (20 mmol) in hexane was added to a solution of 2 (20 mmol) in THF at -80 °C with stirring under nitrogen. After an additional 1 h stirring at that tem-

perature, benzonitrile (20 mmol) was slowly added to the solution, and the mixture was stirred for 1 h at -80 °C and for 2 h at room temperature to give the N-silyl-1-aza-allyl anion (1). After cooling at -80 °C, 3a (20 mmol) was slowly added to the solution of 1, and the mixture was stirred for 1 h at -80 °C and for 2 h at room temperature. The resulting mixture was finally quenched with saturated aqueous ammonium chloride solution (50 ml) at 0 °C, and worked up as usual to give 4.91 g (91%) of 4a as yellow needles after recrystallization from acetone-ether.

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REFERENCES AND NOTES

1. D. J. Ager, Organic Reactions, Wiley, New York, Vol. 38, 1990, Chapt. 1.
2. T. Konakahara and Y. Takagi, Synthesis, 1979, 192.
3. T. Konakahara and Y. Takagi, Tetrahedron Lett., 1980, 21, 2073.
4. T. Konakahara, H. Nishigaki, A. Watanabe, and K. Sato, Heterocycles, 1984, 22, 2765.
5. T. Konakahara and K. Sato, Bull. Chem. Soc. Jpn., 1983, 56, 1241.
6. T. Konakahara and Y. Kurosaki, J. Chem. Res(M)., 1989, 1068.
7. T. Konakahara, M. Sato, T. Haruyama, and K. Sato, Nippon Kagaku Kaishi, 1990, 466 (Chem. Abstr., 1990, 113, 171837j).
8. T. Konakahara, A. Watanabe, and K. Sato, Heterocycles, 1985, 23, 383.
9. All new compounds gave satisfactory ^{1}H nmr, ir, mass spectra and elemental analysis: for example, for 4e: ^{1}H nmr($CDCl_3$): δ1.36(t,J=6.8 Hz, 3H), 2.07(s,3H), 4.12(q,J=6.8 Hz,2H), 5.01(s,1H), 6.42(br,2H), 7.07(m, 5H), 8.21(s,1H); ir(KBr): ν/cm^{-1} 3415, 3274, 1699; ms(m/z): 323(M^+); Anal. Found: C, 66.90; H, 5.35; N, 12.97. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H 5.30; N, 13.00.
10. K. Ito, S. Yokokura, and S. Miyajima, J. Heterocycl. Chem., 1989, 26, 773.

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