

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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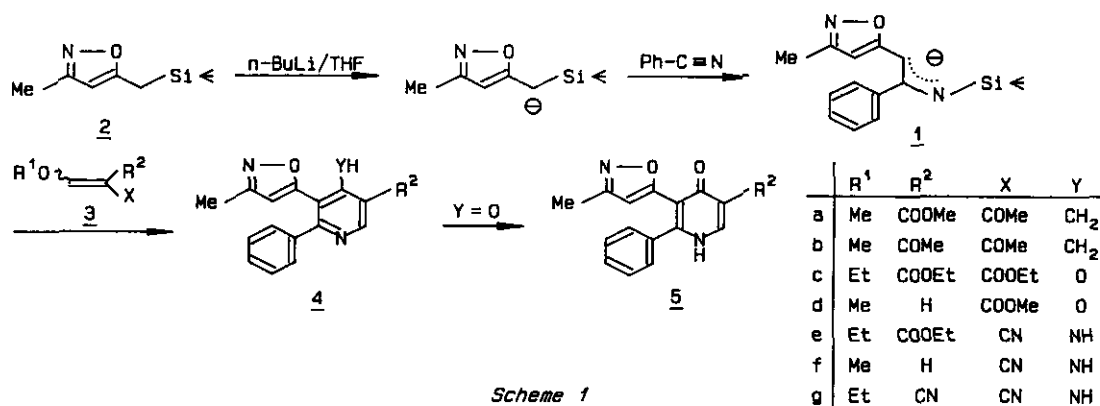
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Abstract — An N-silyl-1-aza-allyl anion (1) reacted with alkoxyalkenes (3a) - (3e) to afford the corresponding 4-methylpyridines (4a) and (4b), 4-pyridones (5c) and (5d), and 4-amino-pyridine (4e), possessing a 3-methyl-5-isoxazolyl group on C-3 atom, 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 compounds⁷ 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-



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 ¹H 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.

The structures of the products (**4**) or (**5**) were determined not only by their spectral properties⁹ 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).

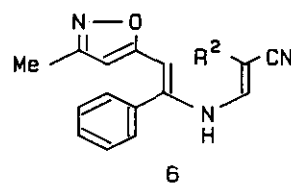


Table 1. Reaction of 1 with 3^{a)}

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

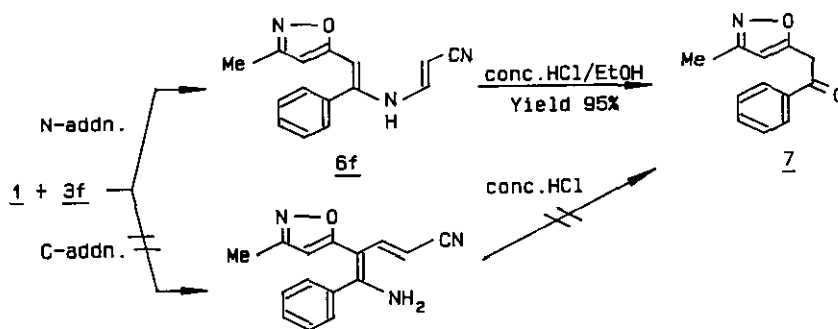
b) Determined by ¹H nmr in parentheses.

c) Yield of the corresponding intermediate (6) in brackets.

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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9. All new compounds gave satisfactory ^1H nmr, ir, mass spectra and elemental analysis: for example, for **4e**: ^1H nmr(CDCl_3): δ 1.36(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 $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$: C, 66.86; H 5.30; N, 13.00.
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