

## SYNTHESIS OF 2,3,4,6-TETRA-SUBSTITUTED PYRIDINES FROM *N*-SILYL-1-AZA-ALLYL ANIONS AND 1,3-DIPHENYL- 2-PROPEN-1-ONE

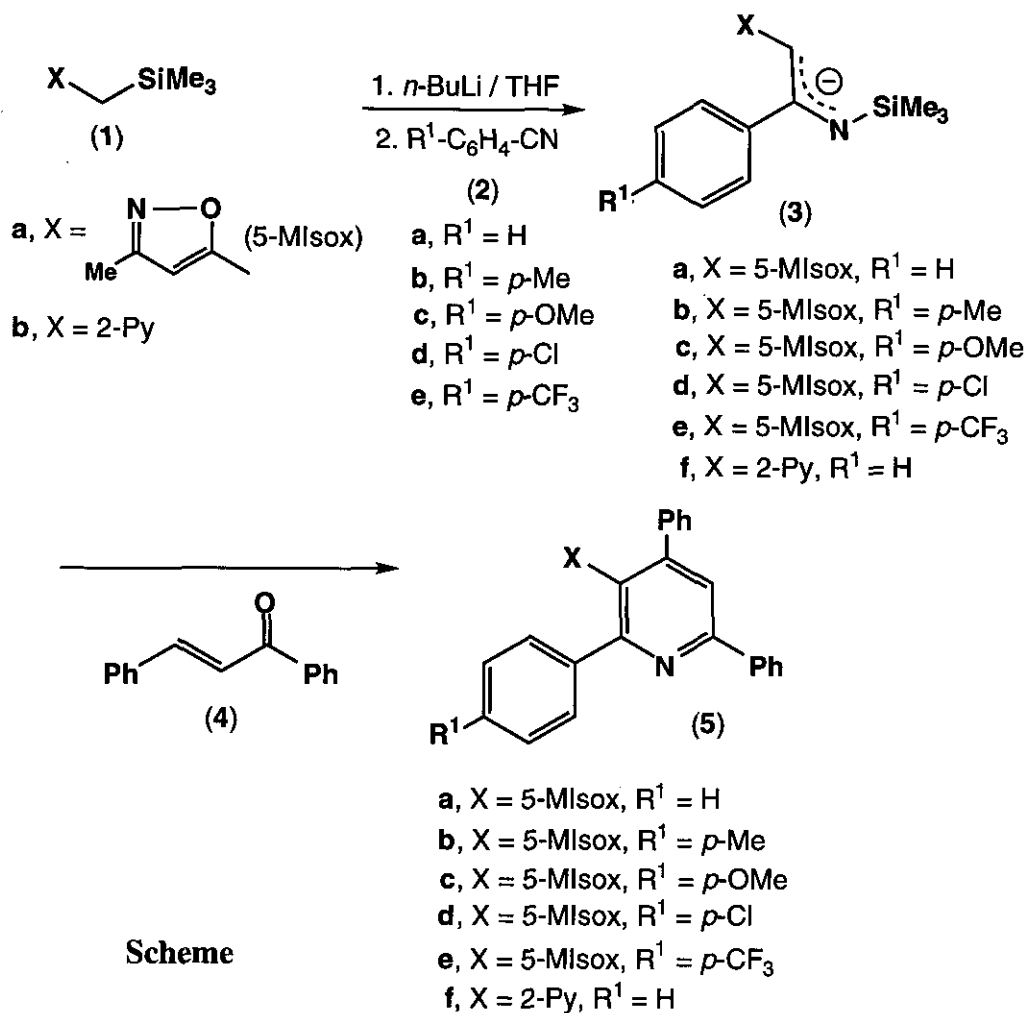
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**Abstract** - The reaction of *N*-silyl-1-aza-allyl anions (**3**) with 1,3-diphenyl-2-propen-1-one (**4**) is described. The anions (**3a-f**), which were prepared from an  $\alpha$ -silyl carbanion of 3-methyl-5-trimethylsilylmethylisoxazole (**1a**) [or 2-trimethylsilylmethylpyridine (**1b**)] and *p*-substituted benzonitriles (**2a-e**,  $R^1 = \text{H}$ , *p*-Me, *p*-OMe, *p*-Cl, *p*-CF<sub>3</sub>), reacted with a slightly excess amount of 1,3-diphenyl-2-propen-1-one (**4**) to afford 2,3,4,6-tetra-substituted pyridine derivatives (**5a-f**) in good yields. But the analogous reaction of the anion (**3e**) with cinnamaldehyde or methyl vinyl ketone did not give the corresponding pyridines.

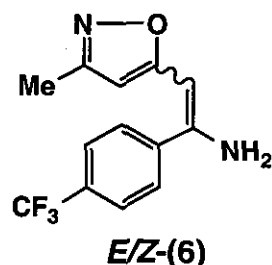
The reaction of enamines with  $\alpha,\beta$ -unsaturated carbonyl compounds (Hantzsch reaction) has been utilized in the synthesis of 1,4-dihydropyridine derivatives.<sup>1,2</sup> The 1,4-dihydropyridine nucleus is a fundamental structure of NADPH and easily oxidized to afford the corresponding pyridine derivative. Recently, we have reported a useful general method for the synthesis of 2,3,4,5-tetra-substituted pyridine derivatives<sup>3</sup> from *N*-silyl-1-aza-allyl anions<sup>4-6</sup> and 2-acetyl-3-methoxy-2-propenoate in the course of our investigation on the synthesis of heterocyclic compounds using organosilicon reagents. As the *N*-silyl-1-aza-allyl anion is an ambident nucleophile possessing nitrogen and carbon atoms as a reaction center, it can be utilized as an versatile building block for the synthesis of *N*-heterocyclic compounds such as 2-(2-pyridyl)ethenyl-carbamates,<sup>7</sup> pyrroles,<sup>8</sup> perfluoroalkylpyridines,<sup>9</sup> furans,<sup>10</sup> and  $\beta$ -lactams.<sup>11</sup>

As an extension of this study, we now wish to report a synthesis of 2,3,4,6-tetra-substituted pyridine derivatives (**5**) from the *N*-silyl-1-aza-allyl anion (**3**) and 1,3-diphenyl-2-propen-1-one (**4**).



A solution of 3-(3-methyl-5-isoxazolyl)-2-phenyl-*N*-trimethylsilyl-1-aza-allyl anion (**3a**), generated from 3-methyl-5-trimethylsilylmethylisoxazole (**1a**) and benzonitrile (**2a**) (Scheme),<sup>6</sup> was treated with a slightly excess of 1,3-diphenyl-2-propen-1-one (**4**) to give 3-(3-methyl-5-isoxazolyl)-2,4,6-triphenylpyridine (**5a**) in 40% yield under the optimized reaction conditions, as shown in Experimental section. Similarly, the reaction of **3b-e** with **4** afforded the corresponding pyridine derivatives (**5b-e**) in 62, 52, 51 and 70% yields, respectively.

The *N*-silyl-1-aza-allyl anion (**3f**), derived from 2-trimethylsilylmethylpyridine (**1b**), also gave the corresponding 2,4,6-triphenylpyridine derivative (**5f**) in 52% yield. Thus, the anion (**3e**) acts as the best nucleophile in this reaction. Contrary to our expectation, the reaction of **3e** with cinnamaldehyde was so



complex that any product was hardly isolated from the reaction mixture. In the case of methyl vinyl ketone, a mixture of (*E*) and (*Z*)-1-amino-2-(3-methyl-5-isoxazolyl)-1-(*p*-trifluoromethylphenyl)ethene (**6**) was obtained in 67% yield, by hydrolysis of the unreacted **3e** during the work-up.

The structures of the products (**5a-f** and **6**) were determined by both their spectroscopic properties and elemental analyses. For example, the ms of **5e** showed a molecular ion peak at  $m/z$  456 ( $M^+$ ), and the ir spectrum suggested the presence of aryl groups and the C-F functional group (1400-1130  $\text{cm}^{-1}$ ). In addition, there are three singlet signals at  $\delta$  2.00, 5.84, and 7.83 for the methyl protons, the isoxazole-ring proton, and the pyridine-ring proton, respectively, accompanied with one multiplet signal at 7.00-8.00 for the protons of three benzene-rings, in the  $^1\text{H}$  nmr spectrum.

As described above, this reaction was not applicable to both cinnamaldehyde and methyl vinyl ketone. That is to say, it appears to be characteristic for 1,3-disubstituted 2-propen-1-one derivatives. Recently, Poindexter and his coworkers have reported Hantzsch condensation reaction of heterocyclic enamines to afford 1,4-dihydropyridines.<sup>12</sup> An analogous 1,4-dihydropyridine, however, did not formed in our reaction. It should be oxidized by air during work-up to give **5**. As previously reported for the synthesis of pyrroles from **3a** with  $\alpha$ -diketones, the first step of the cyclization is the nucleophilic attack of the nitrogen atom in **3a** on the carbonyl group as demonstrated by the reaction of **3a** with benzaldehyde to give an *N*-adduct.<sup>8</sup> Corriu and his coworkers also reported that *N,N*-bis(silyl)enamines reacted with carbonyl compounds to give substituted 2-aza-1,3-dienes in the presence of cesium fluoride.<sup>13</sup> For this reason, the reaction in the present work may also proceed in the same manner by a nucleophilic attack of the intrinsic anionic nitrogen atom in **3** on the carbonyl group of the compound (**4**).<sup>14</sup>

## EXPERIMENTAL

All melting points, measured using a Mitamura Micro-Melting Point Apparatus, were uncorrected. Ir spectra were recorded on a Hitachi Model 260-50 or JEOL JIR-5300 spectrophotometer.  $^1\text{H}$  Nmr or  $^{19}\text{F}$  nmr spectra were obtained using a JEOL PMX-60SI, JNM FX-90Q, or JNM EX-400 spectrometer for solutions in  $\text{CDCl}_3$ ,  $\text{CCl}_4$  or acetone- $d_6$  as shown below. The chemical shifts are reported in  $\delta$  values (internal standard  $\text{Me}_4\text{Si}$ , unless otherwise indicated). Mass spectra were obtained with a Hitachi M-80 at 70 eV. Elemental Analyses were performed at Faculty of Pharmaceutical Sciences, Science University of Tokyo.

### Materials.

3-Methyl-5-trimethylsilylmethylisoxazole and 2-trimethylsilylmethylpyridine were prepared by the method

reported previously.<sup>5,6</sup> Benzonitriles and 1,3-diphenyl-2-propen-1-one were used after distilling or recrystallizing commercial products, and tetrahydrofuran (THF) was distilled from Na-benzophenone ketyl before use.

### Syntheses of the pyridines (5a-f); General procedure.

All pyridines of formula (5) were prepared according to the procedure given below. As an example, the synthesis of the pyridine (5a) was described.

**3-(3-Methyl-5-isoxazolyl)-2,4,6-triphenylpyridine (5a):** To a THF (50 ml) solution of **1a** (1.69 g, 10 mmol) was added a hexane solution of *n*-butyllithium (4.30 g of 15 % solution, 10 mmol) at -80 °C, and the mixture was stirred for 1 h under oxygen-free dry nitrogen. To this solution, **2a** (1.03 g, 10 mmol) was added slowly and stirred for an additional 1 h at -80 °C and then for 2 h at room temperature to give the *N*-silyl-1-aza-allyl anion (**3a**). After re-cooling to -80 °C, a THF solution of **4** (2.29 g, 11 mmol) was added dropwise to the solution of **3a**, and the mixture was stirred for 3 h at -80 °C and then for 15 h at room temperature. The reaction mixture was quenched with 30 ml of a saturated aqueous ammonium chloride solution at -5-0 °C, then extracted with ether. The ether layer was dried with Na<sub>2</sub>SO<sub>4</sub> overnight and worked up as usual to give **5a** (1.55 g, 40%) as yellow needles after recrystallization from hexane. 145.6-146.8 °C; ir (KBr)  $\nu$  3050, 2940, 1605, 1580, 1540, 1500 cm<sup>-1</sup>; <sup>1</sup>H nmr (CCl<sub>4</sub>)  $\delta$  2.00 (3H, s, Me), 5.30 (1H, s, isoxazolyl H), 7.45 (1H, s, Py-H), 7.00-8.00 (15H, m, Ph-H); ms *m/z* 388 (M<sup>+</sup>); Anal. Calcd for C<sub>27</sub>H<sub>20</sub>N<sub>2</sub>O: C, 83.48; H, 5.19; N, 7.21. Found: C, 83.15; H, 5.42; N, 6.97.

**3-(3-Methyl-5-isoxazolyl)-4,6-diphenyl-2-(*p*-tolyl)pyridine (5b):** 62%; 181.4-182.4 °C (from ethyl acetate); ir (KBr)  $\nu$  3050, 1605, 1580, 1540, 1500 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  2.01 (3H, s, isoxazolyl Me), 2.34 (3H, s, Me), 5.43 (1H, s, isoxazolyl H), 7.53 (1H, s, Py-H), 7.00-8.00 (14H, m, Ph-H); ms *m/z* 402 (M<sup>+</sup>); HRms Calcd for C<sub>28</sub>H<sub>22</sub>N<sub>2</sub>O: 402.1734. Found: 402.1739.

**3-(3-Methyl-5-isoxazolyl)-4,6-diphenyl-2-(*p*-methoxyphenyl)pyridine (5c):** 52%; 187.0-188.5 °C (from acetone); ir (KBr)  $\nu$  3050, 1600, 1580, 1540, 1500 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  2.00 (3H, s, Me), 3.73 (3H, s, MeO), 5.45 (1H, s, isoxazolyl H), 7.50 (1H, s, Py-H), 7.00-8.00 (14H, m, Ph-H); ms *m/z* 418 (M<sup>+</sup>); Anal. Calcd for C<sub>28</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.75; H, 5.23; N, 7.04.

**3-(3-Methyl-5-isoxazolyl)-4,6-diphenyl-2-(*p*-chlorophenyl)pyridine (5d):** 51%; 195.0-196.1 °C (from benzene-hexane); ir (KBr)  $\nu$  3050, 1605, 1585, 1540 1500 cm<sup>-1</sup>; <sup>1</sup>H nmr (CCl<sub>4</sub>)  $\delta$  2.01 (3H, s, Me), 5.3 (1H, s, isoxazolyl H), 7.50 (1H, s, Py-H), 7.00-8.00 (14H, m, Ph-H); ms *m/z* 422 (M<sup>+</sup>); Anal. Calcd for C<sub>27</sub>H<sub>19</sub>N<sub>2</sub>OCl: C, 76.68; H, 4.53; N, 6.62. Found: C, 76.24; H, 4.92, N, 6.79.

**3-(3-Methyl-5-isoxazolyl)-4,6-diphenyl-2-(p-trifluoromethylphenyl)pyridine (5e):** 70%; 187.3-187.9 °C (from ethyl acetate); ir (KBr)  $\nu$  3050, 1605, 1580, 1540, 1500, 1400, 1130  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (acetone- $d_6$ )  $\delta$  2.00 (3H, s, Me), 5.84 (1H, s, isoxazolyl H), 7.83 (1H, s, Py-H), 7.00-8.00 (14H, m, Ph-H); ms  $m/z$  456 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{19}\text{N}_2\text{OF}_3$ : C, 73.67; H, 4.20; N, 6.14. Found: C, 73.58; H, 4.29; N, 5.67.

**3-(2-Pyridyl)-2,4,6-triphenylpyridine (5f):** 52%; 139.7-140.2 °C (from hexane); ir (KBr)  $\nu$  3050, 1600, 1580, 1540, 1500  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  7.72 (1H, s, Py-H), 6.78-8.37 (19H, m, Ph-H and 2-Py-H); ms  $m/z$  384 ( $\text{M}^+$ ); HRms Calcd for  $\text{C}_{28}\text{H}_{20}\text{N}_2$ : 384.1628. Found: 384.1635.

**Reaction of 3e with cinnamaldehyde or methyl vinyl ketone:** The reaction was performed by the same method described above for the synthesis of **5**. To a solution of **3e**, generated from **1a** (1.69 g, 10 mmol) and **2e** (1.71 g, 10 mmol), cinnamaldehyde (1.45 g, 11 mmol) or methyl vinyl ketone (0.77 g, 11 mmol) was added slowly at -80 °C. The reaction of cinnamaldehyde was so complex that any product was hardly isolated from the mixture whereas the reaction of methyl vinyl ketone gave a mixture of (*E*)- and (*Z*)-1-amino-2-(3-methyl-5-isoxazolyl)-1-(p-trifluoromethylphenyl)ethene (**6**) (1.80 g, 67%). 125.5-127.2 °C (from hexane); ir (KBr)  $\nu$  3480, 3400, 3330, 3220, 1630, 1615, 1580  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  2.20 (3H, s, Me), 4.95 (2H, br,  $\text{NH}_2$ ), 5.20 (1H, s, =CH), 5.56 (1H, s, isoxazolyl H), 7.39 (4H, s-like, Ph);  $^{19}\text{F}$  nmr (84.25 MHz,  $\text{CDCl}_3$ ,  $\text{CFCl}_3$ )  $\delta$  -63.25 (s,  $\text{CF}_3$ ); ms  $m/z$  268 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_2\text{OF}_3$ : C, 58.21; H, 4.13; N, 10.44. Found: C, 58.14; H, 4.17; N, 10.33.

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