

PREPARATION OF 2,3,4,5-TETRAHYDROPYRIDINES FROM
5-ALKYNYLAMINES UNDER THE CATALYTIC ACTION OF Au(III)

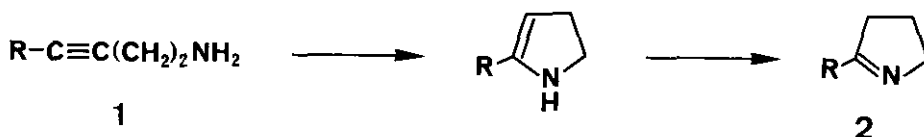
Yukitoshi Fukuda, Kiitiro Utimoto*, and Hitosi Nozaki

Department of Industrial Chemistry, Kyoto University, Yoshida,
Kyoto, 606, Japan

Dedicated to Professor Gilbert Stork on his 65th birthday

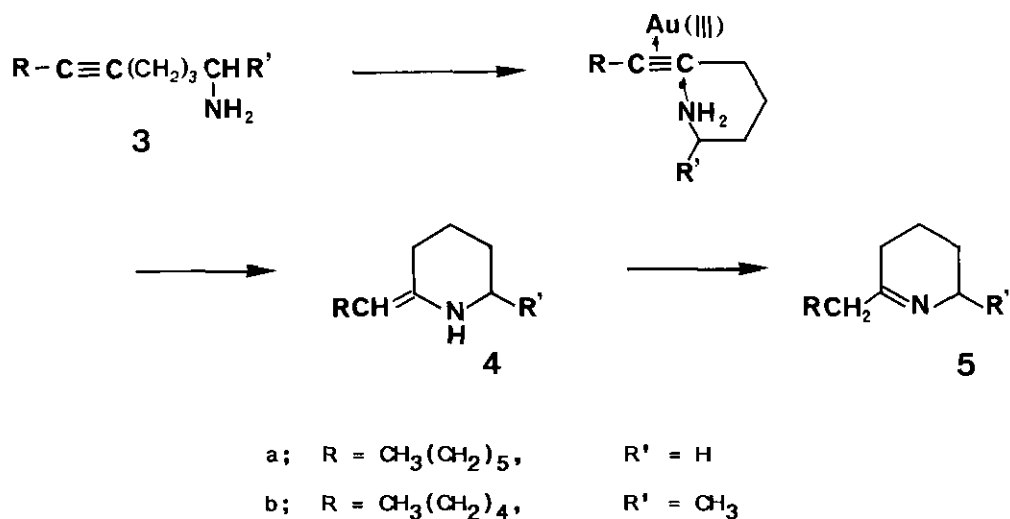
Abstract - Intramolecular addition of amine to acetylene moiety produces 2,3,4,5-tetrahydropyridines from 5-alkynylamines under catalytic action of Au(III).

The recent discovery of palladium catalyzed intramolecular addition of amine, alcohol, and carboxylic acid to acetylene moiety has opened novel syntheses of several heterocycles.^{1,2} Application to the synthesis of cyclic imines such as 1-pyrrolines and 2,3,4,5-tetrahydropyridines is expected to open novel approach to pyrrolidine and piperidine alkaloids isolated from the venoms of fire ants.³⁻⁵ We have found that 3-alkynylamines (**1**) cyclize in 5-Endo-Dig manner under the catalytic action of Pd(II) species to give 2-alkyl-1-pyrrolines (**2**) in good yields after isomerization of initially formed enamines to imines.⁶ This reaction can be applied to internal acetylenic amines.



Synthesis of 1- and 2-pyrrolines from 4-pentenylamines has been reported under the catalytic action of Pd(II) in the presence of oxidizing agent,^{7,8} internal olefinic amines gave unsatisfactory results. Application to the synthesis of tetrahydropyridines from 5-alkenylamines was fruitless either by the lack of

regioselectivity or by the recovery of starting materials. Under the circumstances, palladium catalyzed intramolecular reaction of 5-alkynylamines (**3**) was expected to open novel synthesis of tetrahydropyridines (**5**). In fact, 5-alkynylamines (**3**) regioselectively cyclized in 6-Exo-Dig manner and initially produced 2-alkylidenepiperidines (**4**), which isomerized to 6-alkyl-2,3,4,5-tetrahydropyridines (**5**). In contrast to the above described cyclization of alkenylamines, this reaction can be applied to internal acetylenic amines.⁶ Yields of tetrahydropyridines, however, were sometimes unsatisfactory. Therefore investigations to discover effective catalysts have been continued. After several attempts, Au(III) has been found effective under mild and neutral conditions. This paper discloses the formation of 2,6-dialkyl- and 6-alkyl-2,3,4,5-tetrahydropyridines (**5**) from the corresponding 5-alkynylamines (**3**).



5-Dodecynylamine (**3a**, $R = n\text{-Hex}$, $R' = H$; 80 mg, 0.44 mmol) was added to a solution of 8 mg (0.020 mmol, 5 mol%) of $NaAuCl_4 \cdot 2H_2O$ in 4 ml of acetonitrile and the whole was stirred at room temperature for 12 h. The reaction mixture was diluted with ether and washed with aqueous ammonia and brine. The ethereal solution was dried (Na_2SO_4) and concentrated to afford 6-heptyl-2,3,4,5-tetrahydropyridine (**5a**)⁹ in quantitative yield. Cyclization under the action of $PdCl_2(MeCN)_2$ (5 mol%) in refluxing propionitrile for 20 h gave the same product in 70% yield.

1-Methyl-5-undecynylamine (**3b**, R = n-Pent, R' = Me; 96 mg, 0.53 mmol) afforded 2-methyl-6-hexyl-2,3,4,5-tetrahydropyridine (**5b**)¹⁰ quantitatively by the action of 5 mol% of NaAuCl₄·2H₂O in refluxing acetonitrile (5 ml, 4 h).

Though stereoselective reduction of 2,6-dialkyl-2,3,4,5-tetrahydropyridines (**5**) to either trans-2,6-dialkylpiperidines or cis-isomers has been reported,³⁻⁵ the above described reaction opens novel approach to piperidine alkaloids including solenopsin A and B.

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REFERENCES AND NOTES

1. Y. Wakabayashi, Y. Fukuda, H. Shiragami, K. Utimoto, and H. Nozaki, Tetrahedron, **41**, 3655 (1985) and references cited therein.
2. N. Yanagihara, C. Lambert, K. Iritani, K. Utimoto, and H. Nozaki, J. Am. Chem. Soc., **108**, 2753 (1986).
3. A. B. Attygalle and E. D. Morgan, Chem. Soc. Rev., **13**, 245 (1984).
4. T. H. Jones, M. S. Blum, and H. M. Fales, Tetrahedron, **38**, 1949 (1982).
5. Y. Matsumura, K. Maruoka, and H. Yamamoto, Tetrahedron Lett., **23**, 1929 (1982). Solenopsin A and B were prepared from the corresponding 2,3,4,5-tetrahydropyridine precursors by stereoselective reduction.
6. Reaction of 3-alkynylamines has been reported in preliminary form; K. Utimoto, Pure Appl. Chem., **55**, 1845 (1983). Palladium catalyzed reaction of 1-alkyl-3-alkynylamines also gave 2,6-dialkyl-1-pyrrolines. For example, 1-methyl-3-undecynylamine gave 2-heptynyl-6-methylpyrrolidine; ir (neat), 1630, 1360, 1180, 1100; ¹H nmr (CDCl₃) 0.89 (3H, t, J = 6.0 Hz), 1.25 (3H, d, J = 6.2 Hz), 1.20-1.83 (10H, m), 2.14 (2H, m), 2.36 (2H, t, J = 7.0 Hz), 2.50 (2H, m), 4.06 (1H, m). Anal. Calcd for C₁₂H₂₃N, C, 79.46; H, 12.79. Found C, 79.26; H, 12.95. Detailed descriptions; K. Utimoto, Y. Fukuda, C. Lambert, K. Imai, and H. Nozaki, to be published.

7. L. S. Hegedus and J. M. McKearin, J. Am. Chem. Soc., **104**, 2444 (1982) and references cited therein.
8. B. Pugin and L. M. Venanzi, J. Am. Chem. Soc., **105**, 6877 (1983) and references cited therein.
9. ir (neat), 1700, 1260, 1110, 1060 cm^{-1} ; ^1H nmr (CDCl_3 , 200 MHz), 0.89 (3H, t, $J = 6.4$ Hz), 1.23-1.71 (10H, m), 2.05-2.20 (4H, m), 5.54 (2H, m).
10. ir (neat), 1640, 1360 cm^{-1} ; ^1H nmr (CDCl_3 , 200 MHz), 0.88 (3H, t, $J = 7.6$ Hz), 1.23 (3H, d, $J = 6.9$ Hz), 1.24-1.75 (8H, m), 2.12 (2H, m), 3.45 (1H, m); MS, Calcd for $\text{C}_{12}\text{H}_{23}\text{N}$, 181.1832. Found 181.1808.

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