

FACILE SYNTHESIS OF 4-SUBSTITUTED PYRIDINES USING GRIGNARD REAGENTS

Kin-ya Akiba*, Yuji Iseki, and Makoto Wada

Department of Chemistry, Faculty of Science, Hiroshima University

Higashisenda-machi, Hiroshima 730, Japan

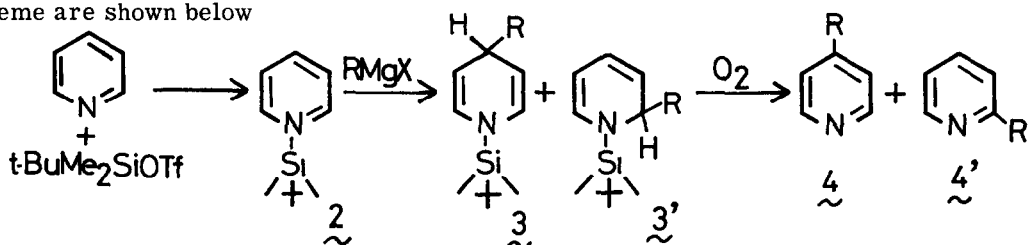
Abstract N-t-Butyldimethylsilylpyridinium triflate (**2**) reacted with Grignard reagents at 4-position with almost complete regioselectivity ($\geq 99\%$) to afford the corresponding 1,4-dihydropyridine derivatives (**3**), which are easily oxidized by oxygen to give 4-substituted pyridines (**4**, 58 - 70%)

In spite of considerable investigation to introduce substituents at 4-position of pyridine, it still remains unsolved satisfactorily. Katritzky and co-workers have been challenging this problem and reporting successful examples by employing specially prepared pyridinopyridone as their starting material.¹⁾ In relation to this subject, recently we proposed two new methods starting from N-ethoxycarbonylpyridinium chloride (**1**), i.e., 1) synthesis of diisopropyl 1-ethoxycarbonyl-1,4-dihydropyridine-4-phosphonate and its alkylation,²⁾ 2) reaction of **1** with RCu BF_3 .³⁾ Here we report the third and more facile and probably the most handy method for this problem by using Grignard reagent as a nucleophile.

First, phenetylmagnesium bromide in tetrahydrofuran (THF) was added to the suspension of trimethylsilylpyridinium triflate in THF at room temperature. After standard work-up, phenetylpyridine was obtained in 29% yield where the ratio of 4- to 2- derivative was 99 to 1. Trimethylphenetylsilane and pyridine were the major products. Encouraged by the result in the literature that reaction of t-butyldimethylsilyl chloride with nucleophiles is slower by 10^4 times to that of trimethylsilyl chloride,⁴⁾ we used t-butyldimethylsilyl triflate as a quartermizing reagent.

A standard procedure is shown. t-Butyldimethylsilylpyridinium triflate (**2**) was prepared from t-butyldimethylsilyl triflate (4.69 mM) and pyridine (4.70 mM) in dichloromethane (5 ml) and the solvent was evaporated under reduced pressure. Butylmagnesium bromide (5.77 mM) in THF (5 ml) was added to the suspension of **2** in THF (7 ml) and the mixture was stirred for 2 - 3 h at room temperature under nitrogen atmosphere. Neat product (**3** containing 20 - 30% of **4** produced by air oxidation, total yield 90 - 100%) was obtained by ether extraction after quenching the mixture with 5% aq. NaHCO_3 (30 ml). Oxygen was bubbled through the neat product to afford 4-butylpyridine (**4a**, 79%) after extraction with hydro-

chloric acid (1N) and neutralization with aq NaOH (3N, up to pH 11) Pure product was obtained by Kugel-Rohr distillation (68%, b p 105 - 115 °C / 17 mmHg) ³⁾ The results and the scheme are shown below



Regioselective Synthesis of 4-Alkylpyridines (**4**)

R	Yield (%)	Ratio (3 : 3') ^{iv)}
a $\text{CH}_3(\text{CH}_2)_3-$	68 ⁱ⁾ (79) ⁱⁱⁱ⁾	99 : 6 : 0.4
b $\text{CH}_3(\text{CH}_2)_5-$	62 ⁱ⁾ (72) ⁱⁱⁱ⁾	99 : 5 : 0.5
c $\text{PhCH}_2\text{CH}_2-$	64 ⁱⁱ⁾ (71) ⁱⁱⁱ⁾	98 : 9 : 1.1
d $\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_3 \end{array} \text{CH}-$	58 ⁱ⁾ (72) ⁱⁱⁱ⁾	98 : 8 : 1.2
e $\text{Ph}-$	59 ⁱⁱⁱ⁾	99.7 : 0.3

i) Isolated yield based on pyridine after Kugel-Rohr distillation

ii) Isolated yield after TLC (SiO_2 , MeCO_2Et) purification iii) Yield after ether extraction (pure by ^1H NMR) iv) Determined by GLC

(5% Apiezon Grease L on Chromosorb WAW DMCS, 150 - 200 °C)

When all the process is carried out in one-pot, i.e., oxygen was bubbled through a mixture of THF and aq NaHCO_3 solution, the yields of 4-substituted pyridines were 10 - 20% lower than the results shown in the Table

It should be noted here that there is definitely a limitation to this method according to the nature of nucleophiles. When butyllithium was used instead of butylmagnesium bromide, total yield of butylpyridines was 58% according to the standard procedure and the ratio of 4- to 2- substitution was 85 to 15, showing poorer selectivity. Lithium enolate of acetophenone and Grignard type reagent of ethyl 2-mercaptoacetate attacked the silicon of **2** almost exclusively. On the other hand, no reaction took place with **2** when dibutylboron and trimethylsilyl enol ethers of acetophenone, Reformatsky reagent of ethyl bromoacetate, and RCu BF_3 were used.

References and Notes

- 1) A. R. Katritzky, H. Beltrami, J. G. Keay, D. N. Rogers, M. P. Sammes, C. W. G. Leung, and C. M. Lee, Angew. Chem. Intern. Ed., **18**, 792 (1979), A. R. Katritzky, H. Beltrami, and M. P. Sammes, J. Chem. Res. (S), **1981**, 133. 2) K. Akiba, H. Matsuoka, and M. Wada, Tetrahedron Lett., **1981**, 4093. 3) K. Akiba, Y. Iseki, and M. Wada, ibid., **1982**, 429. 4) E. Akerman, Acta Chem. Scand., **10**, 298 (1956), **11**, 373 (1957). 5) Partial support by Grant-in-aid for Special Project Research (No. 56109002) and kind gift of t -butyldimethylsilyl chloride from Chisso Co. Ltd. are acknowledged.

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