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REGIOSELECTIVE ALKYL GROUP INTRODUCTION AT THE 3-POSITION OF PYRIDINE VIA 1,4-BIS(TRIMETHYLSILYL)-1,4-DIHYDROPYRIDINE

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The reaction of 1,4-bis(trimethylsilyl)-1,4-dihydropyridine with aldehydes and ketones in the presence of tetrabutylammonium fluoride offers a convenient method for the preparation of 3-alkylpyridines.

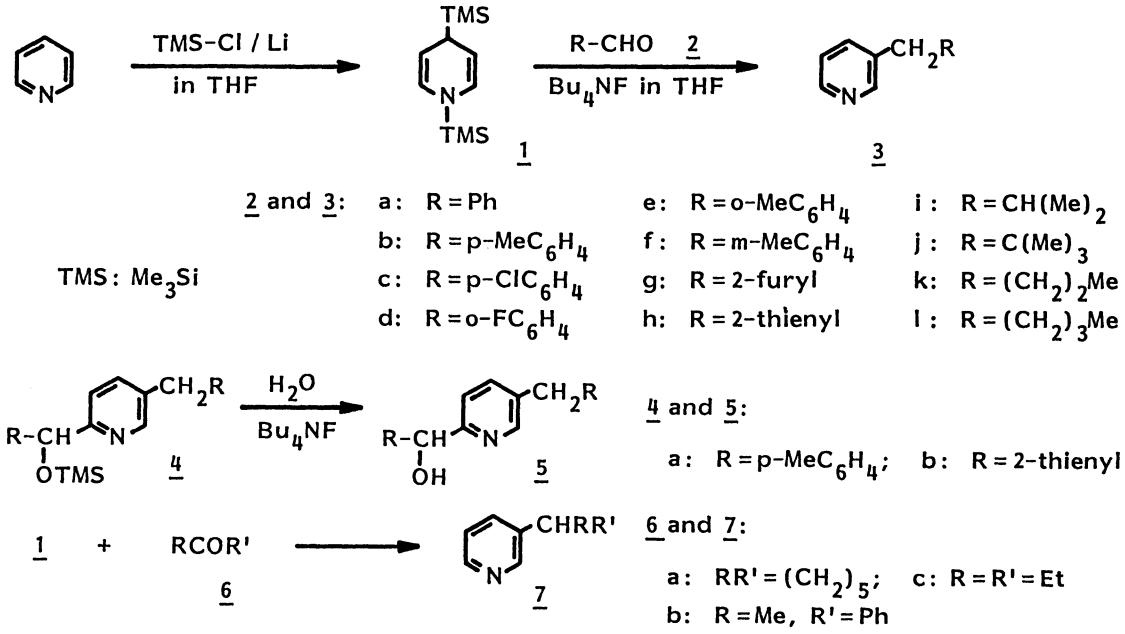
Regioselective introduction of substituents on the pyridine ring has long been an important subject in organic synthesis. Although the nucleophilic substitution onto the electron-poor aromatic ring of pyridine is useful as a preparative method for the 2- and 4-substituted pyridines,[1,2] the direct substitution at the 3-position is quite difficult.[3] Even the recently developed method, which introduces a substituent at the 3-position through the regioselective lithiation of a directing group-substituted pyridines, only provides 2,3- or 3,4-disubstituted pyridine derivatives.[4]

In the sence of organic synthesis, if the electron-poor aromatic ring of pyridine is metallated on the nitrogen forming the electron-rich nonaromatic ring, an electrophilic substitution at the 3-position of hydropyridine ring can be achieved. The only successful case according to this concept is the reaction of lithium tetrakis(N-dihydropyridyl)aluminate with alkyl halides leading to some 3-monosubstituted pyridines.[5] As 1,4-bis(trimethylsilyl)-1,4-dihydropyridine is readily available from the reaction of pyridine with chlorotrimethylsilane in the presence of lithium[6] and this includes a partial structure of N-silylenamine that acts as an effective nucleophile at the β-position,[7] the reaction of 1,4-bis-(trimethylsilyl)-1,4-dihydropyridine with electrophilic reagents will open a new route to 3-substituted pyridines.

The present communication describes a facile synthesis of 3-alkylpyridines by the reaction of 1,4-bis(trimethylsilyl)-1,4-dihydropyridine with aldehydes and ketones in the presence of tetrabutylammonium fluoride.

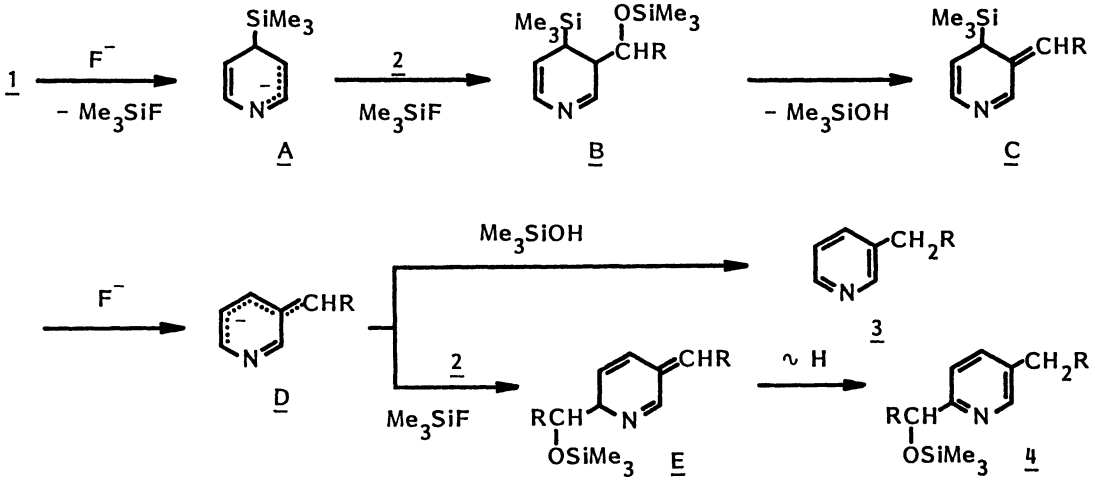
The typical procedure to 3-alkylpyridines is presented as follows: each equivalent mixture of freshly prepared 1,4-bis(trimethylsilyl)-1,4-dihydropyridine 1[8] and benzaldehyde 2a in anhydrous tetrahydrofuran (THF) was treated with a cata-

lytic amount of tetrabutylammonium fluoride (10 mol%) at room temperature under argon atmosphere for 15 h. The crude product obtained from the usual hydrolytic work-up was purified by a chromatography over silica gel using hexane-ether (5:1) to give 72% of 3-benzylpyridine 3a (Scheme 1 and Table 1). Its structure was based on the ^{1}H-NMR,[9] ^{13}C-NMR, other spectral data, and the elemental analysis.[10]



Scheme 1.

Some other substituted benzaldehydes 2b to 2f reacted with 1 as well under the reaction conditions shown in Table 1 giving 3b to 3f in moderate yields. As the major route to 3-benzylpyridines is the reduction of 3-benzoylpyridines which are



Scheme 2.

Table 1. Synthesis of 3-Alkylpyridines 3 and 7

Product	Conditions[a]		Yield/%[b]	^{1}H-NMR (in $CDCl_3$, δ ppm)[c]			M^+
	Temp	Time/h		3-CH_2	2- and 6-H	Others	m/e
3a	room temp	15	72	3.92^s	8.31-8.49^m		169
3b	room temp	14	58[d]	3.86^s	8.31-8.50^m	2.26^s (p-Me)	183
3c	room temp	15	62	3.83^s	8.21-8.40^m		203
3d	room temp	17	47	3.92^s	8.24-8.51^m		187
3e	room temp	18	63	3.88^s	8.19-8.48^m	2.17^s (o-Me)	183
3f	room temp	17	68	3.85^s	8.29-8.51^m	2.26^s (m-Me)	183
3g	room temp	13	48	3.90^s	8.35-8.52^m		159
3h	room temp	16	52[e]	4.09^s	8.30-8.54^m		175
3i	reflux	7	69	2.39^d	8.20-8.38^m	0.82^d, 1.81^m (i-Pr)	
3j	reflux	8	56	2.46^s	8.27-8.46^m	0.89^s (t-Bu)	
3k	reflux	10	23	2.53^t	8.32-8.51^m	0.90^t, 1.12-1.73^m (Pr)	
3l	reflux	6	35	2.43^t	8.21-8.44^m	0.85^t, 1.05-1.70^m (Bu)	149
7a	reflux	5	64	2.43^m(CH)	8.26-8.48^m	1.03-2.08^m (CH_2)	161
7b	reflux	5	13	4.12^q(CH)	8.28-8.54^m	1.63^d (Me)	183
7c	reflux	10	33	2.32^m(CH)	8.28-8.55^m	0.83^t, 1.57^m (Et)	

a) All the reactions were carried out between each equivalent of 1 and 2 in the presence of tetrabutylammonium fluoride (10 mol%) in anhydrous tetrahydrofuran (10 ml/5 mmol of 1) under argon. b) Isolated yield. c) ^{13}C-NMR (in $CDCl_3$, δ ppm) are given for the following products: 3a: 149.99^d (2-C), 147.46^d (6-C), 139.66^s (3-C), 136.25^d (4-C), 123.34^d (5-C), 28.65^t (CH_2). 3i: 150.38^d (2-C), 147.11^d (6-C), 136.64^s (3-C), 136.34^d (4-C), 123.04^d (5-C), 42.30^t (CH_2), 29.97^d, 22.17^q (i-Pr). 3j: 151.18^d (2-C), 147.13^d (6-C), 137.44^d (4-C), 134.74^s (3-C), 122.59^d (5-C), 47.09^t (CH_2), 31.59^s, 29.06^q (t-Bu). d) The 1:2 adduct 4a was also obtained in 31% yield. e) 5b was also yielded (28%).

available from the Friedel-Crafts acylation between pyridine-3-carbonyl chloride and substituted benzenes, our reaction leading to the ortho- and meta-substituted benzylpyridines 3d to 3f is of great value.

Similarly, 1 reacted with heterocyclic aldehydes 2g and 2h, aliphatic aldehydes 2i to 2l, and ketones 6a to 6c providing a variety of 3-alkylpyridines 3g to 3l and 7a to 7c, while the reactions with aliphatic aldehydes and ketones required somewhat harder conditions (Scheme 1 and Table 1).

Although similar side products were formed more or less in most reactions,[11] the reaction of 1 with 2b isolated a side product 4a which was desilylated into 5a in a quantitative yield. The spectral data indicate that 4a has two substituents at the 2- and 5-positions.[12]

The reaction paths to 3-alkylpyridines 3 and 2,5-disubstituted pyridines 4 are illustrated in Scheme 2. Of the two silyl moieties of 1, the one on the nitrogen is removed by the attack of silylophile (F^-) generating an anionic intermediate A.

Its nucleophilic addition to an aldehyde 2 forms B which then looses trimethylsilanol giving C. The silyl group is again eliminated forming a pentadienyl anion D. The major path is the abstraction of proton leading to the 3-alkylpyridine 3 and the minor one is the addition of the second molecule of 2 giving E which is aromatized into the stable 2,5-disubstituted pyridine 4.[13)]

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8) This compound 1 is readily oxidized into 4-trimethylsilylpyridine in the air. The freshly prepared 1 according to the reported method (Ref. 5) is contaminated with less than 10% of 4-trimethylsilylpyridine.

9) The ^{1}H-NMR spectrum of 3a was identical with the reported one (Ref. 5).

10) Analytical samples were prepared by the purification through a gas chromatography. All the new compounds reported herein gave satisfactory high-mass spectra or elemenatl analyses.

11) The ^{1}H-NMR spectra of crude products show that the 3-alkylpyridines 3 and 7 are contaminated with the 2,5-disubstituted pyridines 4 which show the characteristic signals at 5.5-6.0 (CH) and 0 ppm (TMS). However, they are usually too little to be isolated.

12) 4a: ^{1}H-NMR ($CDCl_3$) 0.16 (9H, s, TMS), 2.34 (6H, s, p-Me), 3.89 (2H, s, CH_2), 5.89 (1H, s, CH), 7.01-7.58 (10H, m, 3-H, 4-H, and p-tolyl), and 8.37 ppm (1H, s, 6-H); M^+ m/e 375.

13) In order to increase the opportunity of reaction between D and 2, 1 was allowed to react with excess of 2b under the same conditions, but the ratio of 3b to 4b was about the same.

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