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A NOVEL SYNTHESIS OF 3- AND 4-ALKENYLPYRIDINES

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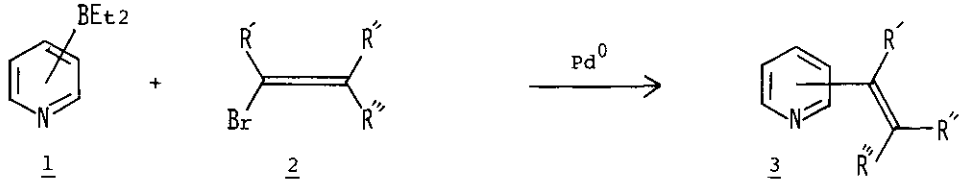
Abstract ——— A new approach for the simple preparation of 3- and 4-alkenylpyridines that relys upon the palladium catalyzed cross coupling reaction of diethylpyridylboranes with vinylic bromides is described.

In view of significance of alkenylpyridines as pharmacological interest and synthetic intermediates, much attention have been focused on this structural unit and a large number of synthetic routes have been described.[1]

Previously, we have reported that the palladium catalyzed cross coupling reaction of diethyl(3-pyridyl)borane(1a) with aryl and heteroaryl halides offers a potential and satisfactory means for the preparation of 3-aryl- and 3-heteroaryl-pyridines.[2]

In the present paper, we describe the extension of this methodology to the synthesis of 3- and 4-alkenylpyridines(3), as shown in Chart 1. Thus, diethyl-pyridylboranes(1), obtained by the reaction of lithiopyridines and diethylmethoxy-borane in high yields(1a, 80%; 1b, 71%),[3] could be smoothly converted to 3 by the palladium catalyzed coupling reaction with various vinylic bromides(2), and the results were summarized in Table 1.



a: 3-substituted
b: 4-substituted

Chart 1

The reactions were conducted in the presence of 1(1 mol eq.), 2(1.5 mol eq.), powdered KOH(5 mol eq.), Bu_4NBr(0.5 mol eq.) and $Pd(Ph_3P)_4$(0.05 mol eq.) in THF under nitrogen atmosphere at refluxing temperature. It is worthy to note that the reaction proceeded regioselectively and stereospecifically to give corresponding coupling products in good yields (Table 1).

Table 1 Reaction of 1 with $2^{a)}$

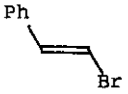
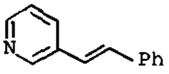
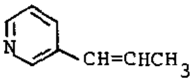
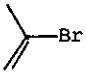
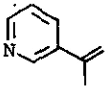
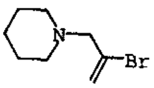
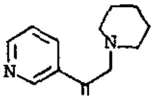
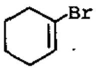
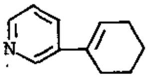
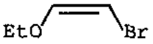
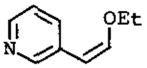
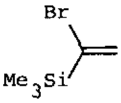
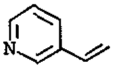
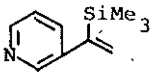
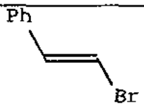
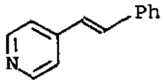
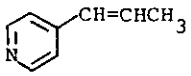
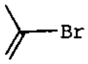
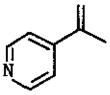
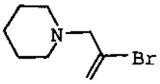
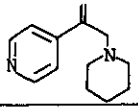
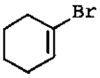
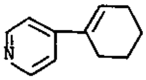
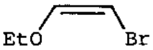
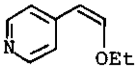
1	2	React. Time(h)	Yield$^{b)}$ of 3(%)	$3^{c)}$	mp (°C) or bp (°C/ mmHg)
1a		1	81		Picrate mp 174-175 (lit.[4] 171-172)
1a	$CH_3CH{=}CHBr$	1	74		Picrate$^{d)}$ mp 122-123.5
1a		2	60		Picrate mp 155.5-156 (lit.[5] 156)
1a		3	60		bp 120/18$^{d)e)}$
1a		1	70		Picrate$^{d)}$ mp 175.5-177
1a		1	70		Picrate$^{d)}$ mp 162-163
1a		1.5	57		Picrate mp 142.5-144.5 (lit.[6] 143-144)
			5		Picrate$^{d)}$ mp 149-151
1b		4	78		mp 124-126 (lit.[7] 127)
1b	$CH_3CH{=}CHBr$	1.5	71		Unstable viscous oil$^{d)}$

Table 1 (continued)

1	2	React. Time(h)	Yield[b] of 3(%)	3[c]	mp (°C) or bp (°C/ mmHg)
1b		1.5	65		Picrate[d)] mp 135-136
1b		2.5	70		bp 130/18[d)e)]
1b		2.5	76		Picrate[d)] mp 154-157
1b		4	55		Picrate[d)] mp 121-123

a) All products were fully characterized spectroscopically (^{1}H-NMR, MS).
b) Isolated yield c) Isolated by flash column chromatography (silica gel, hexane:AcOEt=2:1) d) All compounds gave satisfactory combustion or high-resolution mass spectral analysis. e) Kugelrohr distillation, bath temperature

Furthermore, vinylic bromides(4) substituted with 1-indolylmethyl groups also reacted with 1a under similar conditions to give the coupling products(5) in moderate yields (Chart 2, Table 2).

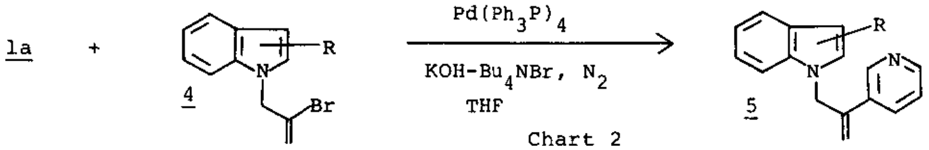


Chart 2

Table 2 Reaction of 1a with 4[a)]

4; R	Catalyst (mol %)	React. Time(h)	Yield of 5[b)]	4; R	Catalyst (mol %)	React. Time(h)	Yield of 5[b)]
H	5	3	51	3-Me	5	2	72
H	10	2	68	3-$(CH_2)_2$OTHP	10	2	68
2-Me	5	6	49	3-$(CH_2)_2OCH_2OCH_3$	10	3	70

a) All products were obtained as a viscous syrup after flash column chromatography(silica gel, hexane:AcOEt=1:1.5), and gave satisfactory spectrometric(IR, NMR, MS) data and high-resolution mass spectral analysis.
b) Isolated yield

Likewise, treatment of 1 with *phenylbromoethyne under similar conditions also* gave phenylethynylpyridines(6)(6a, 70%; 6b, 63%)(Chart 3).[8] The catalytic hydrogenation of 6 in the presence of 5% Pd-$BaSO_4$ under atmospheric pressure in EtOH gave cis-stilbazoles(7)(7a, 75%; 7b, 80%).[8]

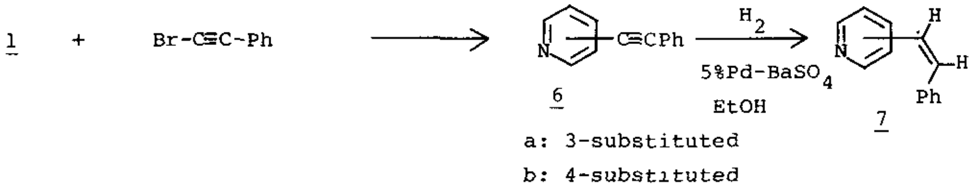


Chart 3

The present method for the synthesis of alkenylpyridines(3) is experimentally simple and good in the yield, and particularly seems to be available for the ready introduction of additional vinylic groups with various substituents to 3- or 4-position of pyridine.

REFERENCES AND NOTES

1. R. C. Micetich, "The Chemistry of Heterocyclic Compounds", R. A. Abramovitch, *ed., John Wiley & Sons, Inc., New York, 1974, Supplement part 2, p 326.*
   W. C. Frank, Y. C. Kim and R. F. Heck, J. Org. Chem., 1978, **43**, 2947.
2. M. Ishikura, M. Kamada and M. Terashima, Heterocycles, 1984, **22**, 265.
   M. Ishikura, M. Kamada and M. Terashima, Synthesis, in press.
3. M. Ishikura, T. Mano, I. Oda and M. Terashima, preceding communication in this issue.
4. G. Galiazzo, Gazz. Chim. Ital., 1965, **95**, 1322.
5. M. D. Oparina, J. Russ. Phys. Chem. Soc., 1925, **57**, 319.
6. H. A. Iddles, E. H. Lang and D. C. Gregg, J. Am. Chem. Soc., 1937, **59**, 1945.
7. C. E. Kaslow and R. D. Stayner, J. Am. Chem. Soc., 1945, **67**, 1716.
8. 6a; picrate mp(from EtOH) 155-156°C (high-resolution MS m/z Calcd for $C_{13}H_9N$ 179.0753, Found 179.0748). 6b; picrate mp(from EtOH) 168-170°C (high-resolution MS m/z Calcd for $C_{13}H_9N$ 179.0753, Found 179.0761). 7a; hydrochloride mp(from EtOH) 150-152°C (lit.[9] 148-150°C). 7b; picrate mp(from EtOH) 129-130°C (high resolution MS m/z Calcd for $C_{13}H_{11}N$ 181.0891, Found 181.0906).
9. F. H. Clarke, G. A. Felock, G. B. Silverman and C. M. Watnik, J. Org. Chem., 1962, **27**, 533.

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