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THE SYNTHESIS OF N-SUBSTITUTED-2-PHENYL-1,2-DIHYDROPYRIDINES[1]

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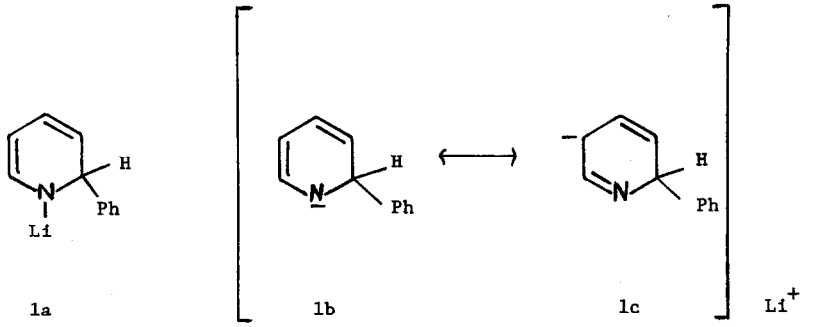
Dihydropyridines and their derivatives find important applications, e.g., as hydride donors in biological[2,3] and in non-enzymatic reduction systems,[4-6] as intermediates in organic synthesis,[7-10] and in mechanistic investigations.[11] However, the preparation of these compounds has been a problem. The competition between hydrogenation and disproportionation, the separation of product mixtures, and the instability of 1,2-dihydropyridines has made their synthesis and characterization particularly difficult.[11]



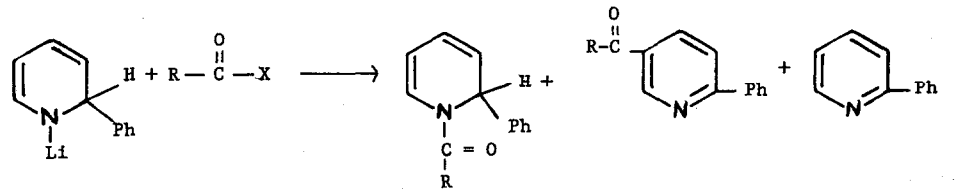
1a 1b 1c

Recently we isolated and characterized the highly reactive intermediate, 1-lithio-2-phenyl-1,2-dihydropyridine (1a) from the reaction of phenyllithium with pyridine. Structures 1b-c suggest that the intermediate is capable of undergoing electrophilic attack at either the carbon or nitrogen atoms or at both. C-substitutions were observed,[7] however C-versus N-substitutions in this or other structurally related cyclic dienamines have not been reported. We now have evidence of N-substitution and we also wish to report a new and simple preparation of N-substituted-2-phenyl-1,2-dihydropyridines.

The yellow crystalline adduct (1), prepared by adding pyridine dropwise to an ethereal solution of phenyllithium, was isolated,[12] washed with anhydrous ether, and taken up in dry tetrahydrofuran. One equivalent of the acid chloride was carefully added to this solution[13] at -65°. After 1 hr, the reaction mixture was worked up and analyzed by column or gas chromatography.

Acetylation occurred preferentially at the nitrogen atom to yield N-acetyl-2-phenyl-1,2-dihydropyridine (2a) (34.2%), some C-substitution product 2-phenyl-5-acetylpyridine (3a)[14] (1.7%), mp 118°, and 2-phenylpyridine (4) (7.1%). Inverse addition also gave predominantly 2a; when 1 was added to two equivalents of acetyl chloride, a very high yield of 2a (68.5%) and 4(13%) was obtained, but 3a was not detected. 2a had the correct elemental composition and spectral data consistent with the assigned structure: bp 118°/1.5 mm; ν_{max}^{FILM} 1640 cm^{-1} (C = 0); nmr ($CDCl_3$) δ 7.38 (5H, m, phenyl), 6.53 (1H, d($J_{5,6}$ = 7.5H_z) of d($J_{4,6}$ = 0.75Hz), C_6-H), 6.26 (1H, d($J_{2,3}$ = 5.5Hz), C_2-H), 6.08 (1H, d($J_{3,4}$ = 8.75H_z) of d($J_{4,5}$ = 5.75Hz), C_4-H), 5.79 (1H, d($J_{3,4}$ = 8.75Hz) of d($J_{2,3}$ = 5.5Hz) of d($J_{3,5}$ = 1.5Hz), C_3-H), 5.36 (1H, d($J_{5,6}$ = 7.5Hz) of d($J_{4,5}$ = 5.75Hz) of d($J_{3,5}$ = 1.5Hz), C_5-H), 2.17 (3H, s, CH_3).

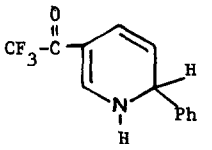
Similarly, when 1a was treated with benzoyl chloride, it gave as isolable products N-benzoyl-2-phenyl-1,2-dihydropyridine (2b) (26.6%), bp 170°/1.0 mm, 2-phenyl-5-benzoylpyridine (3b) (8.9%), mp 85-5° (lit.[15] 89°) and 4(16.5%). Considerable intractable tar was also obtained in this and the reaction below. With trifluoroacetylchloride, 1 gave almost exclusive C- rather than N-acylation to yield 2-phenyl-5-trifluoroacetyl-1,2-dihydropyridine (5) (13.2%): mp 121-3°; ν_{max}^{KBr} 1600 cm^{-1} (C = 0); nmr ($CDCl_3$) δ 7.74 (1H, d($J_{1,6}$ = 7.5Hz), C_6-H),[16] 7.40 (5H, m, phenyl), 6.70 (1H, broad d($J_{1,6}$ = 7.5Hz), -NH),[17] 6.56 (1H, d($J_{3,4}$ = 9.75Hz), C_4-H), 5.41 (1H, d($J_{2,3}$ = 5.5Hz), C_2-H), 5.36 (1H, d($J_{3,4}$ = 9.75Hz) of d($J_{2,3}$ = 5.5Hz), C_3-H); Anal. calcd for $C_{13}H_{10}NOF_3$: C, 61.67; H, 3.98; N, 5.53. Found: C, 61.69; H, 3.85; N, 5.51; 2-phenyl-5-trifluoroacetylpyridine (3c) (5%), mp 72-3°, 2-phenylpyridine (17.1%), and some N-trifluoroacetyl-2-phenyl-1,2-dihydropyridine (2c) (1.1%).



a, R=Me
b, R=Ph
c, R=CF_3
d, R=OEt

2 3 4

a, R=Me
b, R=Ph
c, R=CF_3
d, R=OEt



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Thus, the overall yield of isolable products of the above reactions ranged from 36-82%; however, the ratio of N/C-substitution dropped significantly in going from the weaker electrophilic reagent acetyl chloride to the stronger electrophilic reagent benzoyl or trifluoroacetyl chloride. The mechanism of the above reaction is not known but the ratio of N/C products appears to be very sensitive to the electrophilicity of the reagent.

We have also prepared compounds 2 using other reagents. Acylation with ethyl acetate and ethyl chloroformate occurred exclusively at nitrogen to give high yields of 2a (55.6%) and N-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (2d) (77%), bp 118°/0.6 mm, respectively.

Since other organolithium-pyridine intermediates can also be prepared,[7,18] the above reaction should pave the way to the synthesis of a wide variety of dihydro compounds with a wide selection of substituents in the 2-and N-positions. While 2a-d did undergo some decomposition during distillation, the dihydro compounds are remarkably stable to air and heat. For example, compounds 2 can be purified by column, thin layer or gas chromatography. Moreover, 2a,b and d can be separated from the other reaction products (3a, b, d)[19] by ethereal extraction of the strongly acidic reaction mixture. 2a, 2d and 5 remain unchanged after prolonged (2 weeks) exposure to oxygen although 2b did undergo slow polymerization.

The scope of this N-acylation, the mechanism of the substitution reaction, the photochemistry and biological screening of compounds 2 are presently under study.

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