Some Reactions of 1-Lithio-2-*n*-butyl-1,2-dihydropyridine. VI. Synthesis of β-Substituted Pyridines

E. E. Knaus and T. A. Ondrus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2H7

and

C. S. Giam

Department of Chemistry, Texas A & M University, College Station, Texas 77843

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Reaction of the ambident anion 1-lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) with several electrophilic reagents has been investigated. Direct methods for the introduction of amino, bromo, β-pyridyl, arylselenyl, alkanesulfonyl and methyl substituents into the β-position of pyridine are described.

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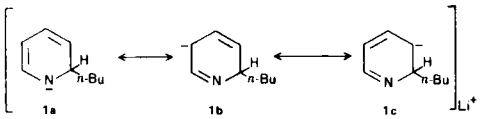
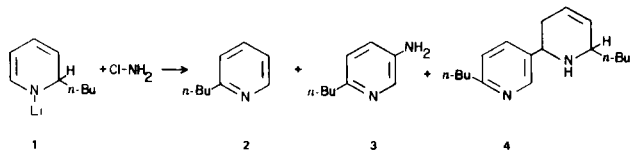
The reaction of *N*-lithio-1,2-dihydropyridines, obtained from the reaction of organolithium reagents and pyridines (1), with suitable electrophiles is a useful procedure for the synthesis of 3-substituted pyridines which are otherwise difficult to prepare (2). In this way, arylalkylation (2,3) alkylation (3), hydroxyalkylation (2), aminoalkylation (2), and acylation (4,5) were conveniently effected. We now wish to describe reactions of 1-lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) with electrophiles which provide methods for direct β-amination, sulfonation, bromination, methylation, selenation, and dimerization.

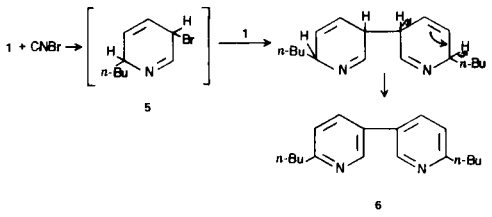
The reaction of alkyllithium reagents with haloamines is a convenient method for the synthesis of alkylamines (6). It was therefore of interest to study the reaction of **1** with electrophiles which would lead to 3-aminopyridines. Treatment of 1-lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) (3 equivalents) with one equivalent of chloramine afforded **2** (2.7%), 2-*n*-butyl-5-aminopyridine (**3**) (57.4%) as well



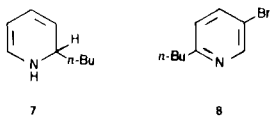


as the tetrahydro product **4** (30.3%). When equimolar amounts of **1** and chloramine were utilized, **2** (7.9%), **3** (23%) and **4** (36.1%) were isolated. It is believed that **4** arises from the reaction of **1a** with **2** (some of which is always obtained) in view of the known reaction of 1-lithio-2-phenyl-1,2-dihydropyridine with 2-phenylpyridine (2). There was no evidence of any product resulting from the action of chloramine as a chlorinating agent.

The reaction of **1** with cyanogen bromide was examined since it could be a useful procedure to prepare 3-bromo- and/or 3-cyanopyridine derivatives depending on the polarizability of cyanogen bromide. Treatment of **1** with cyanogen bromide gave rise to **2** (22.2%) and 6,6′-di-*n*-butyl-3,3′-dipyridyl (**6**) (26.4%). The formation of **6** likely involves the reaction of **1** with 2-*n*-butyl-5-bromo-2,5-dihydropyridine (**5**) and subsequent aromatization.



The reaction of 2-*n*-butyl-1,2-dihydropyridine (**7**) with cyanogen bromide also afforded **2** (27.1%) and **6** (7.2%). In order to prevent the reaction of **1** with **5** an inverse addition procedure was employed using a large excess of cyanogen bromide. Thus, addition of one equivalent of **1** to five equivalents of cyanogen bromide afforded **2** (32.5%) and 2-*n*-butyl-5-bromopyridine (**8**) (14.9%). Similarly, treatment of excess *N*-bromosuccinimide with **1** gave **2** (8.2%) and **8** (10.5%). The presence of **6** could not be detected in either reaction.



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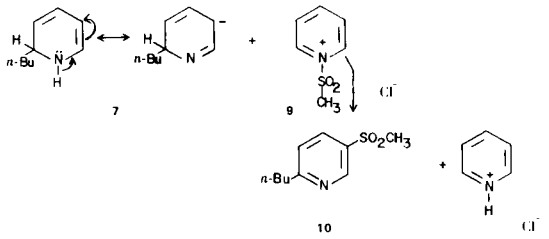
The reaction of **1** with *N*-methanesulfonylpyridinium chloride (**9**) was examined with the intention of preparing sulfonamide derivatives. However, reaction of **1** with **9** gave rise to **2** (20%) and the unexpected dimer **6** (6.9%). When **7** was allowed to react with **9**, 2-*n*-butyl-5-methanesulfonylpyridine (**10**) (11.2%) was obtained which indicates that the nitrogen atom free electron pair is not sufficiently nucleophilic to displace pyridine from **9**. In a related study it was shown that reaction of **7** with methanesulfonyl chloride affords a mixture of *N*-methanesulfonyl-2-*n*-butyl-1,2,5,6-tetrahydropyridine and **10** (7).



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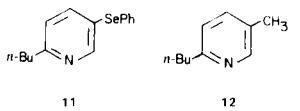
Treatment of **1** with phenylselenyl chloride gave **2** (12.2%) and 2-*n*-butyl-5-phenylselenylpyridine (**11**) (16.3%). Similarly reaction with 2-*n*-butyl-1,2-dihydropyridine (**7**) also afforded **2** (13.4%) and **11** (17.8%).



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The reaction of **1** with methylsulfonates was investigated as a method to introduce a methyl substituent into the β-position of pyridine since β-methylpyridines are useful precursors for the synthesis of pharmacological active nicotinic acid derivatives (8). Reaction of **1** with methyl *p*-toluenesulfonate afforded **2** (5.9%) and **12** (54.7%) while the reaction with **7** gave **2** (14.8%) and **12** (16.1%). The reaction of **1** and **7** with methyl trifluoromethanesulfonate afforded **12** in yields of 42.7 and 19.7% respectively. Further studies of organolithium-pyridine adducts and their derivatives are in progress in these laboratories.

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nmr spectra were determined for solutions of deuteriochloroform unless otherwise noted with TMS as the internal standard with a Varian A-60 or HA-100 spectrometer. Infrared spectra (in potassium bromide unless otherwise noted) were taken on a Unicam SP-1000 spectrometer. Mass spectra were measured with an AEI-MS-9 mass spectrometer and these exact mass measurements are used in lieu of elemental analyses. Quantitative analysis were effected with a Hewlett-Packard 5710 A dual column gas chromatograph.

2-*n*-Butyl-5-aminopyridine (**3**) and 6,6′-Di-*n*-butyl-1,2,3,6-tetrahydro-2,3′-dipyridyl (**4**).

General Procedure.

A solution of 1-lithio-2-*n*-butyl-1,2-dihydropyridine (4.29 g., 0.03 mole) in 50 ml. of anhydrous ether was added slowly with stirring to a solution of chloramine (0.515 g., 0.01 mole) in 200 ml. of dry ether under a nitrogen atmosphere at -65°. The temperature was maintained at -65° for 1 hour and after warming to room temperature, water (50 ml.) was added. Extraction with chloroform (3 x 20 ml.), drying (sodium sulfate) and removal of the solvent gave a yellow oil which was subjected to preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, with benzene-methanol (7:1 v/v) as the developing solvent. Extraction with warm methanol (50 ml.) of the fraction with R_f of 0.36 gave **3** (0.861 g., 57.4%); ir (neat): 3200 and 3320 cm^{-1} (NH_2); nmr: δ 0.9 (t (J = 7 Hz), 3, CH_3), 1.1-2.0 (m, 4, $-CH_2CH_2CH_2CH_3$), 2.67 (t (J = 7 Hz), 2, $-CH_2-CH_2-CH_2CH_3$), 3.46 (br s, 2, NH_2, exchanges with deuterium), 6.86 (m, 2, C_3-H, C_4-H), 8.0 (m, 1, C_6-H); mass calcd. for $C_9H_{14}N_2$, 150.11570; found, 150.11615. Extraction of the band with R_f 0.62 afforded **4** (1.238 g., 30.3%); ir (neat): 3260 cm^{-1} (NH); nmr: δ 0.9 (t (J = 7 Hz), 6, CH_3), 1.1-2.0 (m, 10, $C_6-CH_2CH_2CH_2-CH_3$ and $C_6'-CH_2CH_2CH_2CH_3$), 2.2 (m, 2, C_3-H), 2.6 (br s, 1, NH, exchanges with deuterium), 2.76 (t (J = 7 Hz), 2, $C_6'-CH_2CH_2CH_2-CH_3$), 3.35 (m, 1, C_6-H), 4.0 (t (J = 7 Hz), 1, C_2-H), 5.8 (m, 2, C_4-H, C_5-H), 7.08 (d ($J_{4',5'}$ = 8 Hz), 1, C_5'-H), 7.62 (d ($J_{4',5'}$ = 8 Hz), of d ($J_{2',4'}$ = 2.5 Hz), C_4'-H), 8.3 (d ($J_{2',4'}$ = 2.5 Hz), 1, C_2'-H); mass calcd. for $C_{18}H_{28}N_2$, 272.22525; found, 272.22517. Extraction of the fraction having R_f 0.75 gave rise to **2** (0.108 g., 2.7%) which showed ir and nmr spectra identical to those of an authentic sample. Reaction of **1** (2.86 g., 0.02 mole) with chloramine (1.03 g., 0.02 mole) as described above afforded **2** (0.212 g., 7.9%), **3** (0.69 g., 23%) and **4** (0.981 g., 36.1%).

6,6′-Di-*n*-butyl-3,3′-dipyridyl (**6**).

(a) From 1-Lithio-2-*n*-butyl-1,2-dihydropyridine.

Cyanogen bromide (1.06 g., 0.01 mole) in 10 ml. of dry ether was added dropwise with stirring to a solution of 1-lithio-2-*n*-butyl-1,2-dihydropyridine (1.43 g., 0.01 mole) in 50 ml. of dry ether under a nitrogen atmosphere at -65°. The resulting solution containing the precipitated lithium bromide was maintained at -65° for 1 hour and after warming to room temperature water (20 ml.) was added. Extraction with chloroform (3 x 20 ml.), drying (sodium sulfate) and removal of the solvent gave a brown oil which was separated by preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene-ether (2:1 v/v) as the development solvent. Extraction of the band having R_f 0.32 using warm methanol (50 ml.) afforded **6** (0.422 g., 26.4%), m.p. 5-8°; nmr: δ 0.9 (t (J = 7 Hz), 6, CH_3), 1.1-2.1 (m, 8, $-CH_2CH_2CH_2CH_3$), 2.8 (t (J = 7 Hz), 4, $-CH_2CH_2CH_2CH_3$), 7.14 (d ($J_{4,5}$ = $J_{4',5'}$ = 8 Hz), 2, C_5-H, C_5'-H), 7.68 (d ($J_{4,5}$ = $J_{4',5'}$ = 8 Hz) of d ($J_{2,4}$ = $J_{2',4'}$ = 2.5 Hz), 2, C_4-H, C_4'-H), 8.61 (d ($J_{2,4}$ = $J_{2',4'}$ = 2.5 Hz), 2, C_2-H, C_2'-H); mass calcd. for $C_{18}H_{24}N_2$, 268.1940; found, 268.1932. Extraction of the band with R_f 0.56 gave rise to **2** (0.3 g., 22.2%).

(b) From 2-*n*-Butyl-1,2-dihydropyridine.

Water (0.347 ml., 0.0193 mole) was added dropwise with

stirring to a solution of **1** (2.76 g., 0.0193 mole) in 50 ml. of dry ether under a nitrogen atmosphere at 0°. The solution was allowed to stand at 0° for 15 minutes before returning to room temperature. A solution of cyanogen bromide (2.05 g., 0.0193 mole) in 10 ml. of dry ether was added and the reaction allowed to proceed for 1 hour after which water (20 ml.) was added. The reaction was completed and preparative tlc effected as described under (a) above to yield **6** (0.238 g., 7.2%) and **2** (0.896 g., 27.1%).

2-*n*-Butyl-5-bromopyridine (**8**).

(a) From Cyanogen Bromide.

A solution of **1** (2.86 g., 0.02 mole) in 50 ml. of dry ether was added slowly with stirring to a solution of cyanogen bromide (10.59 g., 0.10 mole) in 25 ml. of dry ether under a nitrogen atmosphere at -65°. The reaction was completed as described in the general procedure to afford a brown oil which was subjected to preparative tlc using six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, with benzene-ether (3:1 v/v) as the development solvent. Extraction of the band with R_f 0.67 using warm methanol (50 ml.) gave **8** (0.638 g., 14.9%); nmr: δ 0.9 (t (J = 7 Hz), 3, CH_3), 1.1-2.0 (m, 4, $-CH_2-CH_2-CH_2CH_3$), 2.71 (t (J = 7 Hz), 2, $-CH_2CH_2CH_2CH_3$), 6.98 (d ($J_{3,4}$ = 8 Hz), 1, C_3-H), 7.63 (d ($J_{3,4}$ = 8 Hz) of d ($J_{4,6}$ = 2.5 Hz), 1, C_4-H), 8.49 (d ($J_{4,6}$ = 2.5 Hz), 1, C_6-H). Extraction of the fraction having R_f 0.78 afforded **2** (0.638 g., 14.9%).

(b) From *N*-Bromosuccinimide.

A solution of **1** (2.86 g., 0.02 mole) in 50 ml. of dry ether was added dropwise with vigorous stirring to a suspension of *N*-bromosuccinimide (17.8 g., 0.1 mole) in 100 ml. of dry ether under an atmosphere of nitrogen at -65°. The reaction was allowed to proceed for 2 hours at -65° and then completed according to the general procedure to yield a reddish semi-solid which was purified by preparative tlc as under (a) above to give **8** (0.445 g., 10.5%) and **2** (0.223 g., 8.2%).

Reaction of 1-Lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) with *N*-Methanesulfonylpyridinium Chloride (**9**).

A solution of **9** (3.87 g., 0.02 mole) in 50 ml. of dry THF was added slowly with stirring to a solution of **1** (2.86 g., 0.02 mole) in 50 ml. of dry ether under a nitrogen atmosphere at -65°. The reaction was completed as described in the general procedure to afford an orange oil which was separated on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene-ether (1:9 v/v) as the development solvent. Extraction of the fractions having R_f's of 0.54 and 0.72 afforded **6** (0.369 g., 6.9%) and **2** (0.562 g., 20.8%), respectively.

2-*n*-Butyl-5-methanesulfonylpyridine (**10**).

A solution of **9** (3.87 g., 0.02 mole) in 50 ml. of dry THF was added slowly with stirring to a solution of 2-*n*-butyl-1,2-dihydropyridine (**7**) (2.74 g., 0.02 mole) in 50 ml. of dry ether under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 30 minutes and then completed according to the general procedure to afford a brown oil which was subjected to preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene-ethyl acetate (1:2 v/v) as the development solvent. Extraction of the band having R_f 0.54 gave **10** (0.233 g., 11.2%), m.p. 45-47°; ir: 1155 and 1295 cm^{-1} (SO_2); nmr: δ 0.98 (t (J = 7 Hz), 3, CH_3), 1.2-2.1 (m, 4, $-CH_2CH_2CH_2CH_3$), 2.92 (t (J = 7 Hz), 2, $-CH_2CH_2CH_2CH_3$), 3.12 (s, 3, SO_2CH_3), 7.35 (d ($J_{3,4}$ = 8 Hz), 1, C_3-H), 8.12 (d ($J_{3,4}$ = 8 Hz) of d ($J_{4,6}$ = 2 Hz), 1, C_4-H), 9.0 (d ($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{10}H_{15}NO_2{}^{32}S$, 213.0824; found, 213.0831. Extraction of fraction with R_f 0.75 gave **2** (0.793 g., 39.8%).

2-*n*-Butyl-5-phenylselenylpyridine (**11**).

A solution of phenylselenyl chloride (1.82 g., 0.01 mole) in 5 ml. of dry ether was added dropwise with stirring to a solution of **1** (1.43 g., 0.01 mole) in 50 ml. of dry ether under a nitrogen atmosphere at -65°. The reaction was allowed to stir for 30 minutes; triethylamine (0.01 mole) was added followed by further stirring at -65° for 30 minutes. The reaction was completed *via* the general procedure to yield an orange oil. Quantitative vpc analysis on a 1/8 x 20 inch column packed with 10% UCW-98 on WAW-DMCS (80-100 mesh) with a helium flow rate of 25 ml./minute and a column temperature of 125° gave **2** (0.157 g., 12.2%), retention time of 1.2 minutes; and at 200° afforded **11** (0.449 g., 16.3%), retention time of 5.8 minutes; nmr: δ 0.9 (t (J = 7 Hz), 3, CH_3), 1.0-2.0 (m, 4, $-CH_2CH_2CH_2CH_3$), 2.7 (t (J = 7 Hz), 2, $-CH_2CH_2CH_2CH_3$), 6.8-7.5 (m, 7, C_6H_5, C_3-H, C_4-H), 8.53 (d ($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{15}H_{17}N^{80}Se$, 291.0526; found, 291.0525.

Reaction of 2-*n*-butyl-1,2-dihydropyridine (**7**) (1.37 g., 0.01 mole) with phenylselenyl chloride (1.82 g., 0.01 mole) at 25° and completion of the reaction as described above afforded **2** (0.171 g., 13.4%) and **11** (0.493 g., 17.8%).

2-*n*-Butyl-5-methylpyridine (**12**).

(a) From 1-Lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) and Methyl *p*-Toluenesulfonate.

Methyl *p*-toluenesulfonate (1.86 g., 0.01 mole) was added dropwise with stirring to a solution of **1** (1.43 g., 0.01 mole) in 50 ml. of dry ether under a nitrogen atmosphere at -65°. The reaction was completed according to the general procedure to give a brown oil. Quantitative vpc analysis on a 1/8 inch x 20 inch column packed with 10% UCW-98 on WAW-DMCS (80-100 mesh) with a flow rate of 25 ml./minute and a column temperature of 125° afforded **2** (0.076 g., 5.9%), retention time 1.2 minutes; and **12** (0.774 g., 54.7%) retention time 2.0 minutes; nmr: δ 0.9 (t (J = 7 Hz), 3, $-CH_2CH_2CH_2CH_3$), 1.0-2.0 (m, 4, $-CH_2CH_2CH_2CH_3$), 2.24 (s, 3, $-CH_3$), 2.74 (t (J = 7 Hz), 2, $-CH_2CH_2CH_2CH_3$), 6.95 (d ($J_{3,4}$ = 8 Hz), 1, C_3-H), 7.33 (d ($J_{3,4}$ = 8 Hz) of d ($J_{4,6}$ = 2 Hz), 1, C_4-H), 8.28 (d ($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{10}H_{15}N$, 149.1205; found, 149.1181.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.5; H, 10.1. Found: C, 80.9; H, 10.4.

(b) From 2-*n*-Butyl-1,2-dihydropyridine (**7**) and Methyl *p*-Toluenesulfonate.

Methyl *p*-toluenesulfonate (1.86 g., 0.01 mole) was added to a solution of **7** (1.37 g., 0.01 mole) in 50 ml. of dry ether under a nitrogen atmosphere at 25° and the reaction was completed and subjected to quantitative vpc analysis as described under (a) above to afford **2** (0.19 g., 14.8%) and **12** (0.23 g., 16.1%).

(c) From 1-Lithio-2-*n*-butyl-1,2-dihydropyridine (**1**) and Methyl Trifluoromethanesulfonate.

Methyl trifluoromethanesulfonate (1.56 g., 0.01 mole) was added to a solution of **1** (1.43 g., 0.01 mole) in 50 ml. of dry ether at -65° and the reaction was completed and subjected to quantitative vpc analysis as described under (a) above to give **2** (0.068 g., 5.3%) and **12** (0.605 g., 42.7%).

(d) From 2-*n*-Butyl-1,2-dihydropyridine (**7**) and Methyl Trifluoromethanesulfonate.

Methyl trifluoromethanesulfonate (1.56 g., 0.01 mole) was added to a solution of **7** (1.37 g., 0.01 mole) at 25°. The reaction

was completed and subjected to quantitative vpc analysis as described under (a) above to yield **2** (0.21 g., 16.4%) and **12** (0.28 g., 19.7%).

Acknowledgment.

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