n-Butyl By-products in the Syntheses of 2-(1- and 2-Naphthyl)pyridines *via* Lithiation

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By-products in the syntheses of 2-(1- and 2-naphthyl)pyridines by successive treatments of 1- and 2-bromonaphthalenes with (a) *n*-butyllithium in ether and (b) pyridine are identified as 5-butyl-2-(1-naphthyl)pyridine and, tentatively, 5-butyl-2-(2-naphthyl)pyridine, respectively. It is proposed that these by-products result from reaction of intermediate compounds 1-lithio-2-naphthyl-1,2-dihydropyridines and 1-bromobutane.

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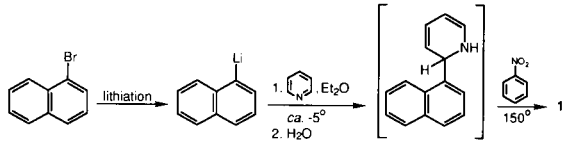
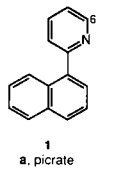
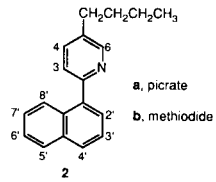
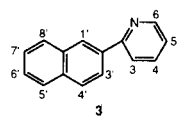
In 1956 Bradsher and Beavers reported the synthesis of 2-(1-naphthyl)pyridine (**1**) in 34% crude yield by the steps shown in Scheme 1 [3]. Compound **1**, a liquid, was obtained in analytically pure form only as its picrate. Unfortunately, no experimental details were presented on the reagent or the procedure used in the lithiation step. In 1975, as a project in synthesis, Daniel Purtzer in our laboratory attempted to reproduce the Bradsher synthesis of **1** (by use of *n*-butyllithium in the first step) and extended this procedure to the analogous conversion of 2-bromonaphthalene into 2-(2-naphthyl)pyridine (**3**). Recently, we have examined Purtzer's crude products by methods of spectrometry and picrate formation and have repeated his syntheses with similar results. As indicated in this paper our method gives butyl derivatives of **1** and **3**, as well as their parent compounds, and separation of product components can be tedious.

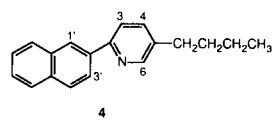
Scheme 1







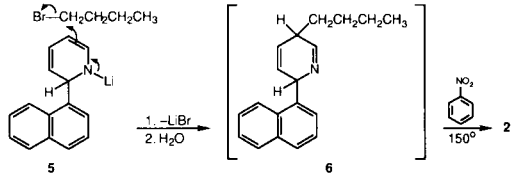




In our experiments ether solutions of the bromonaphthalenes were treated with 1.12 molar quantities of *n*-butyllithium in hexane at room temperature and subsequent steps followed those given by Bradsher except that the final reaction mixture was refluxed (at 38°) for one hour. The viscous, yellow distilled product mixture from Scheme 1 showed the presence of both **1** (m/z 204, 100%, 1^+-H) and butyl-**1** (260, 6%, M^+-H) by mass spectrometry. Quantitatively, the ^{1}H nmr spectrum indicated a molar ratio of **1**:butyl-**1** of 2.3:1, or yields of 16% and 7%, respectively. Pure samples of the picrates of **1** (*i.e.* **1a**), mp 196°, and butyl-**1** (*i.e.* **2a**), mp 145°, were obtained by fractional crystallization. Additionally, **2a** was transformed into the methiodide of **2** (*i.e.* **2b**), mp 136°. All of these compounds were characterized by ^{1}H nmr and mass spectrometry, as well as by elemental analysis for the derivatives of the new compound **2**.

The presence of the *n*-butyl group in **2a** and **2b** is readily observed from their nmr spectra and is corroborated by the presence of a prominent peak for loss of a propyl group on electron impact. Location of the *n*-butyl group at C-5 on the pyridine ring is established from the nmr spectra. Thus, both **2a** and **2b** exhibit a singlet for H-6 as the signal furthest downfield, plus a doublet of doublets for H-4 and H-3 at $\delta > 8$. It is, therefore, apparent that naphthyl substitution on the pyridine ring occurs *alpha* to the heterocyclic nitrogen atom, while butylation on the pyridine ring occurs *beta* to the nitrogen and not in the other *alpha* position [4]. Hence, it is unlikely that **2** results from addition of *n*-butyllithium to **1** as a reaction intermediate. Instead, it is proposed that adduct **5** from interaction of 1-naphthyllithium with pyridine gives nucleophilic attack on 1-bromobutane (formed *in situ* from metathesis of bromonaphthalene and *n*-butyllithium) as shown in Scheme 2 [4]. Subsequent treatment of the reaction mixture with water should produce dihydro compound **6**, which would be oxidized to **2** by heating with nitrobenzene [5].

Scheme 2



The corresponding reaction in the 2-naphthyl series produced a mixture of crystals and amber liquid, from which 2-(2-naphthyl)pyridine (**3**), mp 72° (10% yield), was isolated by trituration. Compound **3** has been synthesized previously by different procedures [6,7], but we have characterized it further by tlc, ^{1}H nmr, and mass spectra. The triturate, also examined by these methods, was shown to contain both **3** and a by-product, tentatively identified as 5-butyl-2-(2-naphthyl)pyridine (**4**), estimated yield 3%. Arguments as to the location of the butyl group on the parent structure **3** and to the mechanism of the formation of **4** are analogous to those presented for **2** [4,5,8].

The syntheses of 2,5-disubstituted pyridines in two separate steps involving (a) the initial isolation of the adduct from RLi and pyridine (where R is phenyl or *n*-butyl) and (b) subsequent treatment of this intermediate with alkyl halide, aryl halide, or other electrophile was reported by Giam *et al.* [9,10], who recommended that *in situ* reactions not be used because they give lower yields and other side-products. Extensions of their two-step process have been made to prepare 3-substituted pyridines [11] and 2,5-disubstituted 2,5-dihydropyridines [12]. However, treatment of pyridine with excess *t*-butyllithium leads to 2-*t*-butyl,2,6-di-*t*-butyl, and/or 2,4,6-tri-*t*-butyl derivatives [13].

EXPERIMENTAL [14]

2-(1-Naphthyl)pyridine (**1**) and 5-Butyl-2-(1-naphthyl)pyridine (**2**).

All apparatus, solvent, and reagents used in the reaction proper were dried well [15]. To a stirred mixture of 51 ml (81.4 mmoles) of 1.6 *M* *n*-butyllithium in hexanes (Aldrich) and 500 ml of ether in an atmosphere of nitrogen gas at room temperature was added dropwise, over a period of 35 minutes, a solution of 15 g (72.5 mmoles) of 1-bromonaphthalene in 50 ml of ether. The mixture was cooled to −3 to −7° while a solution of 6.6 ml (81.4 mmoles) of pyridine in 19 ml of ether was added dropwise. This temperature was maintained for 15 minutes longer and then was allowed to increase to 25° over a period of 3 hours. Finally the mixture was refluxed for one hour and then treated with water carefully. The organic layer was extracted with 5% hydrochloric acid. The acidic extract plus precipitated gum were neutralized with sodium bicarbonate and extracted with ether. The residue from evaporation of the dried (sodium sulfate) ether layer was treated with 12 ml of nitrobenzene and heated, with stirring, at 150° for 1.5 hours. The cooled mixture was diluted with ether and extracted with excess 10% hydrochloric acid. The acidic extract was brought to *p*H 8 with concentrated aqueous ammonia. The dark organic layer which separated was extracted into ether, dried (potassium hydroxide pellets), and evaporatively distilled at 150-170° (0.07 mm) to yield 3.98 g of amber-yellow liquid, shown by ^{1}H nmr to contain about 70 mole % of **1** and 30 mole % of **2** [16], *i.e.* yields of 16% and 7%, respectively [5].

2-(1-Naphthyl)pyridine Picrate (**1a**).

A limited amount of anhydrous picric acid was dissolved in a solution of the preceding distillate in absolute ethanol. The precipitate (collected by filtration) was recrystallized from the same solvent to give **1a**, mp 193-196°, lit mp 197°, 199.5° [3,7], R_f's (silica gel/ethyl acetate) 0.41 (TNP) and 0.60 (**1**); ^{1}H nmr (DMSO-d_6): δ 8.96 (d, $J_{5,6}$ = 5.4 Hz, 1 H, H-6), 8.56 (s, 2 H, picrate ion), 7.95-8.2 (m, 4 H), 7.55-7.85 (m, 6 H); ms: m/z 229 (TNP$^+$, 14), 205 (M$^+$, 45), 204 (100), 203 (14), 102 ([M-H]$^{++}$, 13).

5-Butyl-2-(1-naphthyl)pyridine Picrate (**2a**).

The filtrate from the preceding crude precipitated **1a** was treated with additional picric acid to give a second adduct, mp 98-105°, converted to yellow needles of **2a**, mp 144-145.5° after recrystallations from absolute ethanol; R_f's (silica gel/absolute ethanol-ethyl acetate, 19:1) 0.43 (TNP) and 0.88 (**2**); ^{1}H nmr (DMSO-d_6): δ 8.90 (s, 1 H, H-6), 8.56 (s, 2 H, picrate ion), 8.51 (d, $J_{3,4}$ = 7.8 Hz, 1 H, H-4), 8.19 (d, 1 H, H-3), 8.07-8.17 (2 overlapping d, J $\cong$ 7.9 Hz, 2 aromatic H), 7.55-7.85 (m, 5 aromatic H), 2.86 (t, J = 7.5 Hz, 2 H, PyCH_2), 1.69 (pentet, J = 7.5 Hz, 2 H, PyCH$_2$CH_2), 1.38 (sextet, J = 7.5 Hz, 2 H, CH_2CH$_3$), 0.94 (t, 3 H, methyl group); ms: m/z 261 (M$^+$, 68), 260 (M$^+$-H, 100), 229 (TNP$^+$, 11), 218 (26), 217 (M$^+$-CH$_2$CH$_2$CH$_3$, 58), 216 (33), 189 (217$^+$-H$_2$CN, 24).

Anal. Calcd. for $C_{25}H_{22}N_4O_7$: C, 61.22; H, 4.52; N, 11.42. Found: C, 61.22; H, 4.45; N, 11.54.

5-Butyl-2-(1-naphthyl)pyridine Methiodide (**2b**).

A sample of preceding **2a** was dissociated by means of column chromatography with chloroform and silica gel. An ether solution of the eluted **2** was treated with excess iodomethane and the resultant precipitate was recrystallized from acetone-ether (1:1) to give cream-colored needles of **2b**, mp 134-136°; ^{1}H nmr (deuteriochloroform): δ 9.77 (s, 1 H, H-6), 8.37 (d, $J_{3,4}$ = 6.9 Hz, 1 H, H-4), 8.12 (d, $J_{7',8'}$ = 8.1 Hz, 1 H, H-8'), 8.01 (d, 1 H, H-3), 7.86 (d, J = 8.1 Hz, 1 H, H-2'), 7.74 and 7.67 (2d, J = 7.2, 7.8 Hz, 1 H each, H-4' and H-5'), 7.55-7.65 (m, 2 aromatic H), 7.27 (d, 1 aromatic H), 4.21 (s, 3 H, *N*-methyl group), 3.05 (t, J = 7.8 Hz, 2 H, PyCH_2), 1.87 (pentet, J = 7.8 Hz, 2 H, PyCH$_2$CH_2), 1.50 (sextet, J = 7.5 Hz, 2 H, CH_2CH$_3$), 0.99 (t, J_{Et} = 7.2 Hz, 3 H, CH$_2$CH_3); ms: m/z 261 (M$^+$, 53), 260 (100), 217 (M$^+$-CH$_2$CH$_2$CH$_3$, 22), 142 (CH$_3$I$^+$, 19), 127 (I$^+$,5).

Anal. Calcd. for $C_{20}H_{22}NI$: C, 59.56; H, 5.50; N, 3.47. Found: C, 59.31; H, 5.44; N, 3.21.

2-(2-Naphthyl)pyridine (**3**).

The same general procedure as for the synthesis of **1** was followed, except that 2-bromonaphthalene (Aldrich, recrystallized) was used instead of 1-bromonaphthalene. Evaporative distillation of the crude, dark product up to 180° (0.1 mm) gave 2.92 g of a mixture of faintly yellow crystals and an amber liquid. Trituration of the mixture with 35-60° petroleum ether gave 1.5 g (10%) of **3**, mp 66-68°, converted to colorless needles, mp 70-72°, lit 71-72° [6,7], on recrystallization from 35-60° petroleum ether; blue fluorescence in 254 nm light; ^{1}H nmr (DMSO-d_6): 9.70 (d, $J_{5,6}$ = 4.5 Hz, 1 H, H-6), 8.65 (s, 1 H, H-1'), 8.24 (d, J = 8.7 Hz, 1 H) and 8.12 (d, J = 8.1 Hz, 1 H, H-3 and H-3'), 7.87-8.07 (m, 4 H, H-4, H-4', H-5', H-8'), 7.5-7.6 (m, 2 H, H-6' and H-7'), 7.34-7.42 (2 overlapping d, 1 H, H-5); ms: m/z 206 (24), 205 (M$^+$, 100), 204 (77), 203 (17), 176 (M$^+$-H$_2$CN, 18), 102 (26).

5-Butyl-2-(2-naphthyl)pyridine (**4**).

The triturate from isolation of crystalline **3** was warmed to 80° at 0.1 mm to remove volatile components and leave 1.34 g of amber, viscous liquid; R_f's (silica gel/methylene chloride): <0.1, impurities; 0.50, **3**; 0.64, **4** (blue fluorescence); 40 mole % of **4** as ad-

judged by proton nmr [17]; ^{1}H nmr (deuteriochloroform) for **4**: δ 7-9 (obscured, or uncertain assignments), 2.73 (t, J = 7.5 Hz, 2 H, PyCH_2), 1.72 (pentet, 2 H, PyCH$_2$CH_2), 1.47 (sextet), J = 7.4 Hz, 2 H, CH_2CH$_3$), 1.03 (t, J_{Et} = 7.4 Hz, 3 H, CH$_2$CH_3); ms: m/z 262 (15), 261 (**4**$^+$, 58), 219 (15), 218 (**4**$^+$-C_3H_7, 59), 206 (24), 205 (**3**$^+$, 100), 204 (64).

Anal. Calcd. for $C_{19}H_{19}N$: exact mass, 261.1521. Found: exact mass, 261.1519.

Efforts to isolate pure **4** or its picrate were unsuccessful.

REFERENCES AND NOTES

[1] Undergraduate research student, 1990-1991.

[2] Undergraduate student, 1974-1975.

[3] C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

[4] One can estimate the expected chemical shift for the PyCH_2 protons in the various *n*-butylpyridines from the data reported for the isomeric picolines, as measured in carbon tetrachloride (assumed approximately the same when measured in deuteriochloroform). See T. J. Batterham, NMR Spectra of Simple Heterocycles, John Wiley and Sons, Inc., New York, NY, 1973, Table 2.4, p 16. By adding 0.4 ppm to the chemical shift for the methyl groups one predicts values of δ 2.94 for the α-PyCH_2 protons and δ 2.72-2.75 for the β- and γ-PyCH_2 protons. The signal for **2** (in crude admixture with **1**) falls at δ 2.74, consistent with the structure shown and not with interchanged naphthyl and butyl groups. Likewise the corresponding signal for **4** occurs at 2.73.

[5] The main product in the reaction is tar. It is believed that tar formation occurs largely during the treatment with nitrobenzene. Although we did not try alternative reagents for dehydrogenation, it seems likely that much better methods for this step could be found. See U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

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[13] R. F. Franscis, W. Davis and J. T. Wisener, *J. Org. Chem.*, **39**, 59 (1974).

[14] ^{1}H Nmr spectra were obtained by James Dorsey and Dr. Gerald O'Bannon by means of a General Electric QE-300 instrument; and mass spectra, by Dr. Richard Wielesek at 70 eV with a CEC 21-110 double-focusing instrument. Elemental analyses were conducted by Desert Analytics Labs., Tucson, Arizona.

[15] Glassware was dried in an oven at 250° for several days. Drying agents for chemicals were sodium wire for ether, potassium hydroxide pellets for pyridine, and anhydrous calcium chloride for 1-bromonaphthalene.

[16] This molar ratio is based on integrations of the combined signals for H-6 of **1** and **2** as compared to integration of the PyCH_2 signal for **2** at δ 2.74 in deuteriochloroform.

[17] This molar ratio is based on a comparison of the integration for the PyCH_2 signal for **4** at δ 2.73 with total integrations for aliphatic protons and for aromatic protons in the sample.