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Reaction Intermediates in the Alkylation of Pyridine with *tert*-Butyllithium[1]

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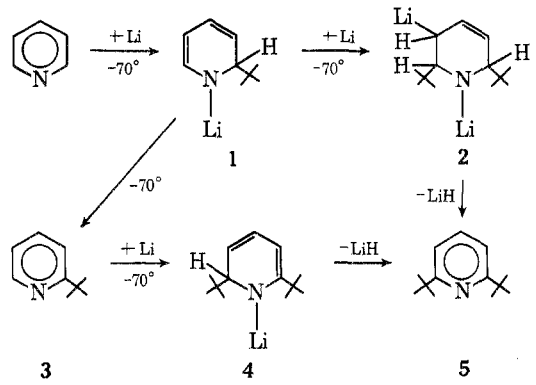
The complex 1,3-dilithio-2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**2**) is formed from pyridine and excess *tert*-butyllithium and decomposes on heating to 2,6-di-*tert*-butylpyridine (**5**). Complex **2** has been isolated as the protonated analog 2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**10**), which can be catalytically dehydrogenated to **5**. The precursor of 2-*tert*-butylpyridine (**3**), 1-lithio-2-*tert*-butyl-1,2-dihydropyridine (**1**), was isolated from a reaction of pyridine with *tert*-butyllithium at −70°. Treatment of **1** with methanol gives a mixture containing 2-*tert*-butyl-1,2-dihydropyridine (**6**) and 2-*tert*-butyl-2,5-dihydropyridine (**7**). When heated, dihydropyridines **6** and **7** form 2-*tert*-butylpyridine (**3**) and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**). Pyridine and excess *tert*-butyllithium above room temperature also give 2,4,6-tri-*tert*-butylpyridine (**9**) which is formed only by alkylation of **5**.

The reactions of pyridine with organolithium compounds have provided a variety of products resulting from monoalkylation or arylation of pyridine α to nitrogen.[2] We recently reported[3] isolation of 4-alkyl- and 2,4- and 2,6-dialkylpyridines in addition to the expected 2-alkylpyridine from reactions in which an excess of the appropriate alkyllithium compound was used. This investigation led to the direct synthesis in good yield of a variety of 2,6-dialkylpyridines.[3] The reaction of pyridine with excess *tert*-butyllithium is significant because it gives 2,4,6-tri-*tert*-butylpyridine (**9**)[3,4] in addition to other products. However, trialkylated products were not observed in reactions of pyridine with other alkyllithium compounds.

Intermediates which are precursors to dialkyl- and trialkylpyridines have not been reported previously. However, the recent conclusive evidence[5] for the existence of intermediate σ complexes in monoalkylation and arylation of pyridine with organolithium compounds suggested that isolation and characterization of similar complexes leading directly to *tert*-butylpyridines **5** and **9** might also be possible.

Two reaction schemes were considered as the most likely pathways to 2,6-di-*tert*-butylpyridine (**5**). Direct alkylation of intermediate **1** and alkylation of 2-*tert*-butylpyridine (**3**) formed by decomposition of **1** could give intermediates **2** and **4**, respectively. These intermediates could form dialkylpyridine **5** by loss of lithium hydride. Formation of **5** by decomposition of intermediate **1** followed by a second alkylation step corresponds to the previously utilized[2d] two-step synthesis of 2,6-dialkylpyridines. Intermediate **2** could result from direct alkylation of **1**, a reaction not unlike the known[6] addition of *tert*-butyllithium to 1,3-butadiene, or from alkylation of the isomeric 5-lithio-2-*tert*-butyl-2,5-dihydropyridine.



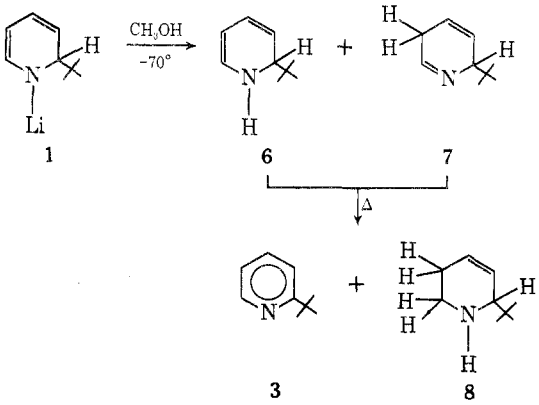
Results and Discussion

The results of a series of reactions of pyridine with excess *tert*-butyllithium conducted under varied conditions are summarized in Table I. A reaction in which reagents were mixed at −70° and stirred at room temperature for 5 days (reaction 1, Table I) afforded the best yield (58%) of 2,6-di-*tert*-butylpyridine (**5**). Thus, isolation and identification of an intermediate leading directly to **5** initially was attempted under similar conditions.

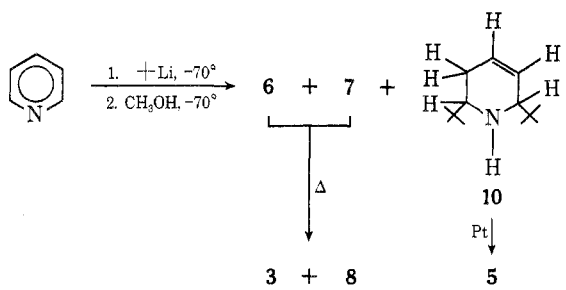
1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (**1**), the precursor of 2-*tert*-butylpyridine (**3**), was isolated as a crystalline solid from a mixture of *tert*-butyllithium and an equivalent amount of pyridine in ether or pentane at −70°. The assigned structure **1** follows from its nmr spectrum[5c] and from the properties of products resulting from protonation of **1**.

Addition of methanol to intermediate **1** at −70° resulted in formation of a yellow oil which gave two products by preparative glc identified as 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**) and 2-*tert*-butylpyridine (**3**). Assignment of **8** is based on a correct elemental analysis, nmr and ir spectra, and catalytic dehydrogenation (Pt–asbestos) of **8** to 2-*tert*-butylpyridine (**3**).

Tetrahydropyridine **8** and alkylpyridine **3** clearly were not present in a sample of the crude product which had not been subjected to glc analysis, as shown by the ir and nmr spectra of the mixture. These revealed the absence of aromatic hydrogens but showed absorptions not found in the spectra of either **3** or **8**, including those in the ir at 1580 and 1640 cm^{-1} characteristic of 1,2-dihydropyridines[7] and absorptions at 1675 cm^{-1} in the ir[8] and δ 7.92 (broad doublet) in the nmr assigned to the HC=N moiety of **7**. Compounds **3** and **8** are assumed to result, therefore, from decomposition of dihydropyridines **6** and **7** *via* hydride transfer from **6** to **7** and/or disproportionation of **6** and **7**. That decomposition had occurred was substantiated by observing that a mixture prepared from intermediate **1** and methanol at −70° contained only **3** and **8** after the sample had been heated on a steam bath for 1 hr. Formation of **7** by protonation of intermediate **1** at position 5 is analogous to a proposed[9] intermediate formed in the synthesis of 2,5-disubstituted pyridines from 1-lithio-2-phenyl-1,2-dihydropyridine. Although 1,2-dihydropyridines are common,[10] 2,5-dihydropyridines are virtually unknown,[8] presumably owing to the greater stability of 1,2- and 1,4-dihydropyridines. Nonisolable 2,5-dihydropyridines have been proposed,[11] however, as intermediates in the hydride reduction of pyridinium ions.



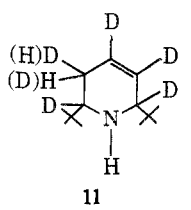
Evidence supporting intermediate **2** as a precursor of 2,6-di-*tert*-butylpyridine (**5**) was obtained initially from a reaction of pyridine with 10 equiv of *tert*-butyllithium at room temperature for 72 hr (reaction 2, Table I). After the reaction had been terminated at −70° with methanol, work-up gave a yellow oil which according to glc analysis contained several products, including alkylpyridines **3** and **5**. A third compound present in substantial amount was collected by preparative glc and identified as 2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**10**), which is logically derived from protonation of intermediate **2**. An analogous reaction conducted at −70° gave on work-up an oil from which only three alkylation products were obtained by preparative glc. These were identified as tetrahydropyridine **8** and 2-*tert*-butylpyridine (**3**) (derived from decomposition of dihydropyridines **6** and **7** as previously described) and tetrahydropyridine **10**.



The assigned structure **10** is based on a correct elemental analysis, the dehydrogenation (Pt-asbestos) of **10** to 2,6-di-*tert*-butylpyridine (**5**), and the ir and nmr spectra of **10** and a deuterated analog.

The nmr spectrum of **10** showed two singlets (18 H) at δ 0.93 and 0.96 assigned to the two nonequivalent *tert*-butyl groups and a multiplet at δ 5.85 (2 H) attributed to the CH=CH moiety. The single hydrogen at position 6 adjacent to diastereotopic hydrogens at position 5 appeared as a doublet of doublets centered at δ 2.57.

Treatment of pyridine-d_5 with 10 equiv of *tert*-butyllithium at −70° followed by the appropriate work-up gave tetrahydropyridine **11**. The nmr spectrum of this compound revealed two broad absorptions at δ 1.70 and 1.90 for the diastereotopic hydrogens at position 5 which integrated for one hydrogen relative to the 18 hydrogens of the two *tert*-butyl groups. An absorption at δ 1.42 was assigned to NH. This was confirmed by observing that a decrease in the area of this peak relative to the *tert*-butyl absorptions occurred and a new absorption at δ 4.58 due to DOH appeared when a drop of D_2O was added to the nmr sample tube.



Tetrahydropyridine **10** and 2,6-di-*tert*-butylpyridine (**5**) were shown to originate from the same intermediate by the following experiments. Analysis (glc) of one half of a mixture of pyridine and 10 equiv of *tert*-butyllithium (−70°, 48 hr) which was quenched with methanol at −70° revealed the presence of tetrahydropyridine **10** (ir and nmr of a glc-collected sample) but showed no evidence of 2,6-di-*tert*-butylpyridine (**5**). A similar analysis of the remainder of the solution which had been refluxed (35°) for 24 hr revealed the presence of **5** but not tetrahydropyridine **10**.

Although 2-*tert*-butylpyridine (**3**) is readily converted by *tert*-butyllithium to 2,6-di-*tert*-butylpyridine (**5**) at room temperature (90% after 24 hr), no detectable conversion to **5** occurred at −70° after 24 hr. This result precludes formation of **5** at −70°. This conclusion is supported by reactions of pyridine with *tert*-butyllithium below room temperature (Table II) which did not give 2,6-di-*tert*-butylpyridine (**5**). That the sequence **1** → **3** → **4** was not a major source of **5** even at room temperature was suggested by an experiment which demonstrated the stability of intermediate **1** in solution at room temperature even after several days.

In order to optimize the yield of intermediate **2**, pyridine was treated with excess *tert*-butyllithium in a series of reactions (Table II) conducted below room temperature. However, the yield of **2** seldom exceeded 50% based on the yields of tetrahydropyridine **10**. Similar results were obtained from a reaction of intermediate **1** with excess *tert*-butyllithium, which gave 50% of **10**. Intermediate **2** could not be characterized by nmr from these solutions because of the presence of substantial quantities of **1**. Efforts to isolate **2** from **1** by crystallization were also unsuccessful.

In reactions in which intermediate **2** was converted by protonation to tetrahydropyridine **10** before decomposition of **2** occurred, 2,4,6-tri-*tert*-butylpyridine (**9**) was not formed. However, **9** was formed in reactions conducted above room temperature and became the major alkylpyridine formed (80%) in refluxing heptane at 80° (Table I). Thus, the only source of **9** is from the reactions of 2,6-di-*tert*-butylpyridine (**5**) with *tert*-butyllithium. This was confirmed by reactions of **5** with *tert*-butyllithium, which did not give **9** after 24 hr at room temperature but gave **9** in 50% yield after 24 hr in refluxing hexane at 60°. In an attempt to isolate the protonated analog of an intermediate leading to **9**, reactions in which **5** was only partially converted to **9** were cooled to −70° and quenched with methanol, and the temperature was not allowed to exceed 10° during work-up. Only aromatic species could be detected in an nmr spectrum of the residue. This result suggests that the temperature required to effect conversion of **5** to **9** is sufficient to cause immediate decomposition of the precursor of **9**.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained from Varian T-60 and HA-100 instruments using $DCCl_3$ and CCl_4 as solvents and TMS as the internal standard. Infrared spectra were taken as thin films from a Perkin-Elmer 257 instrument. Chemical analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Actual yields or relative percentages of products as specified in Tables I and II were determined by glc analysis utilizing standardized 20 ft × 0.25 in. 30% SE-30 on Chromosorb W and 20 ft × 0.25 in. 20% Versamid 900 on Chromosorb W columns on Hewlett-Packard F & M 5750 and Aerograph 90-P3 chromatographs.

Samples of products for chemical and spectral analyses and for preparation of derivatives were obtained by preparative glc using an Aerograph 90-P3 instrument equipped with a 20 ft × 0.375 in. column of 20% SE-30 on Chromosorb W.

Alkyllithium compounds were obtained from Lithium Corp. of America.

Synthesis of *tert*-Butylpyridines. A solution of pyridine and solvent (60 ml of solvent per 0.01 mol of pyridine) under a nitrogen atmosphere was cooled to −70° using a Dry Ice–acetone mixture. The pyridine–solvent mixture was mechanically stirred as a solution of *tert*-butyllithium in pentane was added at a rate necessary to maintain the temperature within a few degrees of −70° (2–4 hr required). The mixture was stirred for an additional period at a higher temperature. When a reflux temperature higher than that afforded by pentane (36°) was desired, pyridine and a higher boiling solvent were used and pentane from the addition of *tert*-butyllithium solution was removed by distillation.

The mixture was cooled in an ice–water or a Dry Ice–acetone mixture and treated with cold water or methanol, respectively, to destroy unchanged *tert*-butyllithium. The mixture was subjected to continuous liquid–liquid extraction with ether for 48 hr. The extract was dried (K_2CO_3), concentrated by rotary evaporation, and analyzed by glc. Specific conditions and results are summarized in Table I.

1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1). A 25 × 200 mm test tube containing 10 ml of dry ether or pentane and 3.2 g (0.04 mol) of pyridine was flushed with nitrogen, fitted with a serum cap, and cooled in a Dry Ice–acetone mixture (−70°). Subsequent addition and removal of liquids was accomplished using a syringe. Ten milliliters of 0.40 *M* *tert*-butyllithium in pentane was added slowly to the mixture. Pale yellow crystals of **1** formed in 15–20 min. After standing for an additional 2–3 hr, the remaining liquid was removed and the solid was washed with two 5-ml portions of dry ether or pentane. Additional solvent was removed by pulling a vacuum on the crystals. The nmr spectrum of **1** was obtained from a solution of the solid (approximately 40%) in tetramethylethylenediamine: δ 0.85 (s, 9, *tert*-butyl), 3.40 (d, 1, C-2), 4.13 (m, 1, C-3), 4.45 (t, 1, C-5), 5.98 (m, 1, C-4), 6.72 (d, 1, C-6).

A mixture containing **1** in ether prepared as described above was allowed to stand at room temperature for 8 days. During this period nmr spectra of the solution showed that no decomposition of intermediate **1** had occurred.

Hydrolysis of 1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1). A crystalline sample of **1** was prepared as described above, and the crystals were dissolved in anhydrous ether at room temperature. The solution was cooled to −70°, quenched with methanol, and warmed to room temperature. The ethereal solution was dried (K_2CO_3), and ether was removed by rotary evaporation. Analysis (glc) of the residue revealed the presence of two major products which were collected by preparative glc and identified as 2-*tert*-butylpyridine (nmr, ir) and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**).

Tetrahydropyridine **8** was characterized by ir and nmr spectra: ir 1655 cm^{-1}; nmr δ 0.93 (s, 9, *tert*-butyl), 1.63 (s, 1, NH), 2.00 (m, 2, C-6), 3.03 (m, 3 C-2, C-5), 5.77 (m, 2, CH=CH).

Anal. Calcd for $C_9H_{17}N$ (**8**): C, 77.61; H, 12.33; N, 10.06. Found: C, 77.40; H, 12.43; N, 9.71.

A second sample of **1** in ether was hydrolyzed (CH_3OH) at −70°. The major components of the residue obtained on work-up at room temperature were assigned as 2-*tert*-butyl-1,2-dihydropyridine (**6**) and 2-*tert*-butyl-2,5-dihydropyrieine (**7**) based on the ir and nmr spectra of the residue and the products (**3** and **8**) obtained on heating the mixture. The spectra showed ir 1580, 1640 (conjugated diene), 16.75 cm^{-1} (C=N); nmr δ 0.85 and 0.95 (*tert*-butyl), 2.00, 2.65, 3.08, 3.85, 4.45, 5.02, 5.96 (complex multiplets, allylic and vinylic hydrogens), 7.92 (broad doublet, N=CH).

An nmr spectrum obtained from a sample of the reaction residue which had been heated (steam bath) for 1 hr was clearly that of a mixture of tetrahydropyridine **8** and 2-*tert*-butylpyridine (**3**).

Catalytic Dehydrogenation[12] of Tetrahydropyridine 8. A 0.66-g (0.0034 mol) sample of **8** was placed in a 100-ml flask connected by an L-shaped adapter to a catalyst chamber consisting of a 20-cm section of 12-mm glass tubing loosely packed with 30% platinized asbestos. The catalyst chamber was connected to a cold trap followed by a mineral oil bubbler. The system was flushed with nitrogen, the catalyst chamber was heated to 300° with a Lindberg Hevi-duty tube furnace, and hydrogen was allowed to pass slowly through the system (about 3 hr). The sample of tetrahydropyridine **8** was evaporated into the catalyst chamber by heating it at 150° in an oil bath. The reaction afforded as the only product 0.24 g (37%) of 2-*tert*-butylpyridine (**3**) identified by the ir and nmr spectra of a glc-collected sample.

2,6-Di-*tert*-butyl-1,2,3,6-tetrahydropyridine (10). The gener-

Table I
Synthesis of *tert*-Butylpyridines[a]

Reaction no.	Solvent, temp,[b] °C	Time, hr	*tert*-Butylpyridines,[c] %[d] 2-	4-	2,4-	2,6-	2,4,6-
1	*n*-Hexane, ambient	120	9	7	22	58	
2[e]	*n*-Hexane, ambient	72	49			13	
3	*n*-Hexane, 60	48	3	3	3	16	38
4[a]	*n*-Hexane, 60	48			6	22	33
5	*n*-Heptane, 80	48			1	5	76

[a] A 10:1 mole ratio of *tert*-butyllithium to pyridine was used in all reactions except 3, which employed a 3:1 ratio. [b] Following addition of *tert*-butyllithium at −70°. [c] Except for 2,4,6-tri-*tert*-butylpyridine, nmr and ir spectra of glc-collected samples were compared with those of authentic samples. Derivatives were 2-picrate, mp 104–105° [lit. mp 104.6–105.2°: H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951)]; 4-picrate, mp 129–130° (lit. mp 130.9–131.4°: Brown and Murphey); 2,4-chloroplatinate, mp 201.5–202.0°; 2,6-chloroaurate, mp 183.5–184.0° (lit.[3d] mp 184.2–184.5°); 2,4,6-tri-*tert*-butylpyridine, mp 68.0° [lit. mp 69.0°: K. Dimroth and W. Mack, *Angew. Chem., Int. Ed. Engl.*, **7**, 460 (1968)]. [d] Glc analyses of weighed residues obtained after work-up. [e] This reaction also provided 38% of tetrahydropyridine **10**. Yields given are relative percentages of the three major products. Small quantities of other products were not identified.

Table II
Some Reactions of Pyridine with *tert*-Butyllithium[a] below Ambient Temperature

Reaction no.	Temp, °C	Time, hr	Products, relative %[b] 3	8	5	10
1	−70	48	9	9		52
2	−70	48	22	16		55
3[c]	−70	48	23	13		45
4[d]	0	24	35	13		
5	−40	48	25	25		48
6	−90	24	29	33		24
7	−70	24	27	22		41
8	−90	96	39	9		44

[a] *tert*-Butyllithium was added to pyridine in *n*-hexane (reaction 1) or ethyl ether (other reactions). A 10:1 mole ratio of *tert*-butyllithium to pyridine was used in all reactions except reaction 1, which employed a 5:1 ratio. [b] The material balance consisted of small quantities of 4-*tert*-butylpyridine, bipyridyl, and unchanged pyridine. [c] Pyridine in ethyl ether was added to *tert*-butyllithium at −70°. [d] The major product was bipyridyl.

al procedure described previously for synthesis of alkylpyridines was used with the following modification. After addition of *tert*-butyllithium, the reaction period and termination with methanol were completed below room temperature. Specific reaction conditions and relative percentages of **10** are summarized in Table II. Tetrahydropyridine **10** was characterized from a glc-collected sample: ir 1648 cm^{-1}; nmr δ 0.93 and 0.96 (two singlets, 18, *tert*-butyl), 1.37 (s, 1, NH), 1.52 and 1.84 (two multiplets, 2, C-5), 2.57 (doublet of doublets, 1, C-6), 2.93 (m, 1 C-2), 5.82 (m, 2, C-3 and C-4).

Anal. Calcd for $C_{13}H_{25}N$ (**10**): C, 79.93; H, 12.90; N, 7.17. Found: C, 80.19; H, 12.61; N, 7.13.

2,6-Di-*tert*-butyl-1,2,3,6-tetrahydropyridine-*2,3,4,5,6-d*$_5$ (11). The procedure described for the synthesis of tetrahydropyridine **10** was followed, treating pyridine-d_5 with 10 equiv of *tert*-butyllithium for 48 hr at −70°. Termination of the reaction at this temperature by addition of methanol followed by work-up afforded **11** collected as a colorless oil by preparative glc: nmr δ 0.90 and 0.94 (two singlets, 18, *tert*-butyl), 1.70 and 1.90 (two broad singlets, 1, C-5), 1.42 (s, 1, NH). The δ 1.70 and 1.90 absorptions integrated for one proton relative to the *tert*-butyl absorption. The NH assignment was confirmed by a simple exchange experiment by adding a drop of deuterium oxide to the nmr sample tube. A decrease in the area of the NH absorption relative to the *tert*-butyl absorption was observed and was accompanied by the appearance of an absorption due to DOH (δ 4.58).

Catalytic Dehydrogenation of Tetrahydropyridine 10. The procedure described previously for dehydrogenation of tetrahydropyridine **8** was followed. A 0.40-g (0.0020 mol) sample of **10** gave as the only product 0.26 g (60%) of 2,6-di-*tert*-butylpyridine (**5**) identified by ir and nmr spectra of a glc-collected sample.

Reaction of 1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1) with Excess *tert*-Butyllithium. A crystalline sample of **1** was prepared from 10 ml of 2 *M* *tert*-butyllithium added to 1.6 g (0.02 mol) of pyridine in 10 ml of anhydrous ether at −70° in a 250-ml flask. The solvent was removed with a syringe, the crystals were washed with ether, and additional ether (50 ml) was added. To the stirred mixture 90 ml of 2 *M* *tert*-butyllithium was added from an addition funnel over a 1-hr period. The mixture was stirred for 48 hr at −70° and worked up as previously described in the preparation of tetrahydropyridine **8**. Analysis (glc) of the reaction residue gave **10** (50%), which was identified by ir and nmr spectra of a glc-collected sample.

Reaction of 2-*tert*-Butylpyridine (3) with *tert*-Butyllithium. A 4.0-g (0.03 mol) sample of **3** in 200 ml of ether was treated with 150 ml of 2 *M* *tert*-butyllithium at −70° using the procedure previously described for the synthesis of *tert*-butylpyridines.

A sample of the mixture was removed after 24 hr at −70°, terminated with methanol at −70°, and worked up as described in the synthesis of alkylpyridines. Analysis (glc) of the residue showed only unchanged **3**.

The remainder of the mixture was stirred at room temperature for 24 hr and terminated with methanol at −70°. Analysis (glc) of the residue after work-up showed 2,6-di-*tert*-butylpyridine (90%).

2,4,6-Tri-*tert*-butylpyridine (9). A 115-ml sample of 1.24 *M* *tert*-butyllithium in pentane was added to 2.5 g (0.013 mol) of 2,6-di-*tert*-butylpyridine (**5**) in 100 ml of pentane at −70° using the general procedure described in the synthesis of *tert*-butylpyridines. The solution was warmed to room temperature, 100 ml of hexane was added, and the pentane was removed by distillation. The mixture was refluxed at 60° overnight, terminated at 0° with water, and worked up in the usual manner. Analysis (glc) showed a 50% conversion to **9**.

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Registry No. **1**, 42540-75-0; **6**, 42540-76-1; **7**, 42540-77-2; **8**, 42540-78-3; **10**, 42540-79-4; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4.

References and Notes

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