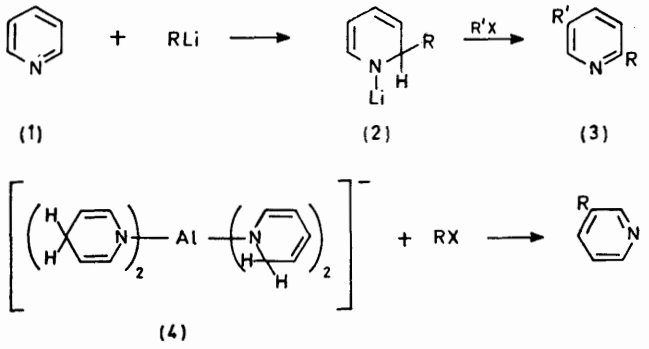
Interactions of 4-Isopropylpyridine with Organolithium Reagents and Lithium Aluminium Hydride: Unusual Electrophilic Substitutions

By **Choo-Seng Giam,* Thomas E. Goodwin, Kathryn F. Rion,** and **Scot D. Abbott,** Department of Chemistry, Texas A & M University, College Station, Texas 77843, U.S.A.

Products from the interaction of several organolithium reagents with 4-isopropylpyridine have been shown by ^{1}H n.m.r. to be σ-complexes and-or *N*-lithio-dihydropyridines. Treatment of the σ-complex from 4-isopropylpyridine and t-butyl-lithium with benzyl chloride affords new tri- and di-substituted pyridines. The reaction of lithium aluminium hydride with 4-isopropylpyridine, followed by treatment with electrophilic reagents, leads to side-chain rather than ring substitution. Spectral evidence is presented for the intermediacy of an *N*-lithio-species.

WE have reported [1] the isolation and characterization of crystalline σ-complexes from the interaction of organolithium reagents with pyridine and its derivatives [*e.g.* (1)→(2)], as well as the reactions of these complexes with electrophilic reagents to afford 2,5-disubstituted pyridines [(2) → (3)].[2] In addition a direct procedure for substitution at the β-position of a pyridine ring *via* the interaction of lithium tetrakis(dihydropyridyl)aluminate (4) (from pyridine and lithium aluminium hydride) with electrophilic reagents has been described.[3]



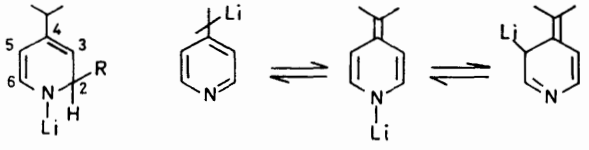
Pyridine derivatives possessing benzylic or other acidic hydrogen atoms on the substituent at the 2- or 4-position were excluded from our initial studies. In an extension of these procedures, we now detail the behaviour of such a compound, 4-isopropylpyridine, in the presence of several organolithium reagents as well as lithium aluminium hydride.

Reactions of 4-Isopropylpyridine with Organolithium Reagents.—A solution of 4-isopropylpyridine in tetrahydrofuran (THF) at −78 °C was treated with 1 mol. equiv. of n-butyl-lithium. After warming slowly to ambient temperature, ^{1}H n.m.r. analysis revealed the presence of only σ-complex (5a) and solvent. This intermediate was readily identified by reference to the spectra of analogous σ-complexes,[1,4] exhibiting a doublet (*J* 6 Hz) at δ 6.59 (H-6), a doublet of doublets (*J* 6 and 2 Hz) at δ 4.44 (H-5), and a broad doublet (*J* 5 Hz) at δ 4.16 (H-3).

In contrast, exposure of 4-isopropylpyridine to phenyl-lithium under identical conditions led to a *ca.* 1.8 : 1 mixture (by ^{1}H n.m.r.) of σ-complex (5b) and intermediate (7). The former showed a doublet (*J* 6 Hz) at δ 6.63, characteristic [1,4] of H-6 (signals for H-3 and -5 were obscured by solvent), and the latter a new pair of doublets (AB pattern; *J* 8 Hz) centred at δ 5.08 and 6.13 corresponding to the vinylic protons.

The σ-complex (5b) arises by nucleophilic attack of the phenyl-lithium at the pyridine 2-position; the metalloenamine (7) is produced by deprotonation at the isopropyl group followed by a 1,5-lithiotropic rearrangement from carbon to nitrogen [(6) → (7)]. Structure (7) is preferred to (6) because of the higher electronegativity of nitrogen *vis-à-vis* carbon, the high-field AB pattern in the ^{1}H n.m.r. spectrum (suggesting a non-aromatic ring), and the results of the lithium aluminium hydride experiment discussed below.

The interaction of 4-isopropylpyridine with methyl-lithium or t-butyl-lithium gave only a trace of the *N*-lithio-species (7), the major products being σ-complexes, (5c) or (5d), as indicated by the ^{1}H n.m.r. signals of the C-6 protons (doublets at δ 6.50 and 6.58, respectively).† Treatment of the intermediate (5d) *in situ* with benzyl chloride resulted in the expected [2] production of 5-benzyl-



(5) a; R = Bu^n (6) b; R = Ph (7) c; R = Me (8) d; R = Bu^t

4-isopropyl-2-t-butylpyridine (10), as well as a small amount of 3-benzyl-4-isopropylpyridine (11).

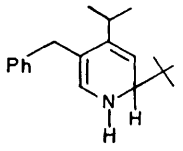
The dihydropyridine (9), produced by protic quenching of the intermediate σ-complex,‡ could, in principle, aromatize by either of two modes: loss of hydrogen to produce the t-butylated compound (10), or expulsion of isobutene to provide compound (11). Oxidative dealkylation of dihydropyridines has been observed previously.[7,§] Alternatively, though less likely, com-

† These results can be compared with those of Osuch and Levine,[5] who reported predominant addition of phenyl-lithium to the 2-position of 4-methylpyridine but predominant proton abstraction to yield 4-picolyl-lithium when methyl-lithium was employed.

‡ Dihydropyridines have been isolated recently from such reactions.[6]

§ When 4-t-butyl-3-(4,4-dimethyloxazolin-2-yl)-1,4-dihydropyridine is heated or oxidized, the 4-t-butyl moiety is eliminated to give 3-(4,4-dimethyloxazolin-2-yl)pyridine.[8]

pound (11) could arise by a simple β-alkylation of the metalloenamine (8), although (11) was not detected as a product of the lithium aluminium hydride reaction



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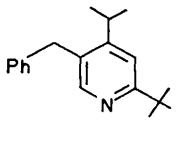

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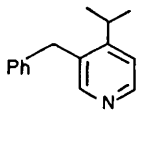
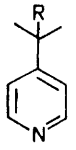


(11)

described below, which proceeds through the intermediate (7) and thus has the opportunity for alkylation through the mesomeric structure (8).

It is conceivable that modification of the reaction conditions could alter the product distribution in favour of the pyridine (11), thereby suggesting a new route to 3-substituted pyridines. We are investigating this reaction.

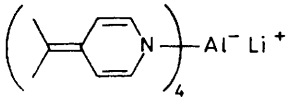
Reaction of 4-Isopropylpyridine with Lithium Aluminium Hydride.—The interaction of the aluminate (4) * with electrophilic reagents leads directly and conveniently to 3-substituted pyridines in high yield.[3] In contrast, when a solution of 4-isopropylpyridine in THF was exposed sequentially to lithium aluminium hydride and benzyl chloride, 2-benzyl-2-(4-pyridyl)propane (12a) was isolated as the major product, and none of the expected [3] 3-benzyl-4-isopropylpyridine (11) was detected. Similarly the reaction with allyl bromide leads to 2-allyl-2-(4-pyridyl)propane (12b). The intermediacy of the aluminate (13) or the *N*-lithio-enamine (7) is indicated and spectral evidence was sought to define the structure of the intermediate.



(12)

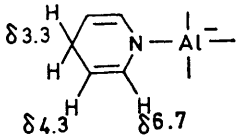
a ; R = $PhCH_2$

b ; R = $CH_2{=}CHCH_2$



(13)

Lansbury and Peterson [9] reported the ^1H n.m.r. spectrum (60 HMz) of the aluminate (4); their assignments are shown on partial structure (14). For comparison we subjected the 4-isopropylpyridine–lithium aluminium hydride mixture to ^1H n.m.r. analysis and observed a new pair of doublets (*J* 8 Hz) centred at δ 5.08 and 6.13, which exactly match the signals observed for the metalloenamine (7) from the organolithium reactions discussed above. These doublets are assigned to the vinylic protons of compound (7), which thus appears to be the probable intermediate of the lithium aluminium hydride reaction, unless the protons of the alternative structure (13) fortuitously exhibit identical shifts. Regardless of the structure of the intermediate complex, it seems likely that pyridine derivatives with acidic protons in the 4-position will not prove to be a good source of 3,4-disubstituted pyridines *via* lithium aluminium hydride-mediated alkylation procedures. Other compounds in this series are under investigation.



(14)

EXPERIMENTAL

I.r. spectra of neat liquids were recorded on a Perkin-Elmer 237B spectrophotometer and mass spectra on a Hewlett–Packard 5982A spectrometer. ^1H and ^{13}C n.m.r. spectra were run on $CDCl_3$ solutions, with Me_4Si as internal standard, on a Varian T-60 and a JEOL JNM-PS-100 spectrometer operating at 25.034 MHz in the Fourier-transform mode, respectively. G.l.c. analyses were performed on a 6-ft by ¼-in 3% OV-1 on 100—120 mesh GasChrom Q column in a Varian Aerograph Series 1520 chromatograph; for preparative t.l.c. Merck silica gel 60 PF-254 was used as adsorbent. Tetrahydrofuran was freshly distilled from lithium aluminium hydride before each reaction. Solutions were dried over anhydrous sodium sulphate.

4-Isopropylpyridine showed δ_C 23.1 (Me_2), 33.6 (CH of Pr^i), 121.9 (C-3), 149.8 (C-2), and 157.4 (C-4).

5-Benzyl-4-isopropyl-2-t-butylpyridine (10) *and 3-Benzyl-4-isopropylpyridine* (11).†—A solution of t-butyl-lithium (0.046 mol) in n-pentane (20 ml) was added over 10 min to a stirred mixture of 4-isopropyl pyridine (4.56 g, 0.037 7 mol) in dry THF (40 ml) under nitrogen at −78 °C. After 0.5 h the mixture was allowed to warm to room temperature (over 1.5 h). A solution of benzyl chloride (4.73 g, 0.037 mol) in THF (5 ml) was added over 10 min and stirring was continued for 1 h. The reaction was quenched by addition of water (10 ml) and THF was removed under reduced pressure. The residue was diluted with dichloromethane (100 ml), washed with water, and dried. Evaporation left a yellow oil (10.8 g). The yields of (10) and (11) were estimated by g.l.c. analysis (column temp. 125—250 °C, 20 °C min^{-1}; isoquinoline internal standard) to be 34 and 7%, respectively.‡

Analytical samples were prepared by several fractional, vacuum distillations (b.p. 119—125 °C, 0.35—0.5 Torr), followed by sublimation (56—60 °C, 0.5 Torr) to provide a mixture of pyridines (10) and (11) as an amorphous white solid, m.p. 43—68 °C. Preparative t.l.c. provided the *pyridine* (10) as a light yellow oil (R_F 0.22—0.44) [$\nu_{max.}$ (neat) 1 600, 1 500, 1 480, and 1 460 cm^{-1}; δ_H 1.15 (6 H, d, *J* 7 Hz, CMe_2), 1.40 (9 H, s, Bu^t), 3.00 (1 H, sept, *J* 7 Hz, CH of Pr^i), 4.02 (2 H, s, CH_2), 7.20 (6 H, m, Ph and C-3-H), and 8.35 (1 H, s, C-6-H); δ_C 23.0 (Me_2 of Pr^i), 29.1 (CH of

* Compound (4) is believed [9] to contain a mixture of 1,2- and 1,4-dihydropyridyl moieties depending upon the temperature of isolation; thus structure (4) is only an approximation of the reactive species.

† Reactions of n-butyl-, phenyl-, and methyl-lithium with 4-isopropylpyridine were carried out by similar procedures.

‡ (a) No 2-benzyl-2-(4-pyridyl)propane (12a), which would be indicative of significant side-chain metallation, was detected by g.l.c. analysis of the product mixture from this reaction. (b) Optimum conditions for purification and separation of compounds (10) and (11) have not yet been achieved; thus yields of isolated material are not reported.

Pr^i), 30.4 (Me_3 of Bu^t), 35.9 (CH_2), 36.1 (quaternary C), 115.5 (C-3), 126.1 (*para*-C of Ph), 128.4 (*ortho*- and *meta*-C of Ph), 129.7 (*ipso*-C of Ph), 140.4 (C-5), 150.1 (C-6), 155.9 (C-4), and 167.9 (C-2); *m/e* 267 (M^+), 266, 252 (base), and 225 (Found: *m/e*, 267.197 785. $C_{19}H_{25}N$ requires *M*, 267.198 695); picrate, m.p. 134.5—135 °C (from aqueous ethanol)]; and the *pyridine* (11) as a pale yellow liquid (R_F 0.03—0.22) [$\nu_{max.}$ (neat) 1 590, 1 495, 1 490, 1 455, and 1 410 cm^{-1}; δ_H 1.13 (6 H, d, *J* 7 Hz, Me_2), 2.33 (1 H, sept, *J* 7 Hz, CH of Pr^i), 4.08 (2 H, s, CH_2), and 6.83—7.48 (3 H, m, sp^2 CH); δ_C 22.9 (Me_2 of Pr^i), 28.9 (CH of Pr^i), 36.2 (CH_2), 120.7 (C-5), 126.3 (*para*-C of Ph), 128.4 (*ortho*- and *meta*-C of Ph), 131.1 (*ipso*-C of Ph), 140.0 (C-3), 148.4 (C-6), 151.2 (C-2), and 156.3 (C-4); *m/e* 211 (M^+ and base), 196, 168, 134, and 91 (Found: *m/e* 211.135 389. $C_{15}H_{17}N$ requires *M*, 211.136 095); picrate, m.p. 140 °C (from aqueous ethanol)].

2-Benzyl-2-(4-pyridyl)propane (12a).—A mixture of 4-isopropylpyridine 4.24 g (0.036 mol) and lithium aluminium hydride (334 mg, 0.009 mol) in dry THF (25 ml) was stirred at room temperature for 24 h under nitrogen. A solution of benzyl chloride (1.11 g, 0.009 mol) in THF (5 ml) was added and stirring was continued for 1 h. The mixture was quenched by cautious addition of water (10 ml), filtered over Celite, and concentrated. The residue was taken up in chloroform (100 ml), washed with water and saturated brine, and dried. Evaporation left a golden liquid (1.88 g), 1.82 g of which was fractionally distilled to give compound (12a) (573 mg, 31%) as a colourless liquid, b.p. 99—102 °C (0.38—0.40 Torr); $\nu_{max.}$ (neat), 1 600, 1 500, 1 465, and 1 420 cm^{-1}; δ_H 1.30 (6 H, s, Me_2), 2.80 (2 H, s, CH_2), 6.80 (2 H, m, C-3-H and C-5-H), 7.20 (5 H, m, Ph), and 8.43 (2 H, dd, *J* 5 and 2 Hz, C-2-H and C-6-H); δ_C 27.5 (Me_2), 34.3 (quaternary C), 50.4 (CH_2), 121.5 (C-3), 126.2 (*para*-C of Ph), 127.6 (*meta*-C of Ph), 130.2 (*ortho*-C of Ph), 137.7 (*ipso*-C of Ph), 149.5 (C-2), and 157.8 (C-4); *m/e* 211 (M^+), 196, 172, 120, 92, and 91 (base); *picrate*, m.p. 113—114 °C (from aqueous ethanol) (Found: C, 57.7; H, 4.65; N, 13.0. $C_{21}H_{20}N_4O_7$ requires C, 57.25; H, 4.6; N, 12.7%).

2-Allyl-2-(4-pyridyl)propane (12b).—A mixture of 4-isopropylpyridine (4.28 g, 0.035 mol) and lithium aluminium hydride (338 mg, 0.009 mol) in dry THF (25 ml) was stirred at room temperature for 23.5 h. A solution of allyl bromide (1.10 g, 0.009 mol) in THF (5 ml) was added and stirring was continued for 1 h. The mixture was worked up as described above to provide a yellow oil (2.72 g), fractional distillation of which gave compound (12b) as a colourless oil (357 mg, 24%), b.p. 40—41 °C (0.15 Torr); $\nu_{max.}$ (neat) 1 602 and 1 420 cm^{-1}; δ 1.30 (6 H, s, Me_2), 2.32 (2 H, d, *J* 6 Hz, CH_2), 4.70—4.99 (1 H, m, olefinic), 5.00—5.15 (1 H, m, olefinic), 5.15—5.90 (1 H, m, olefinic H), 7.19 (2 H, dd, *J* 5 and 2 Hz, C-3-H), and 8.50 (dd, *J* 5 and 2 Hz, C-2-H); δ_C 27.7 (Me_2), 36.3 (sp^3 C), 48.1 (CH_2), 117.7 (terminal olefinic C), 121.2 (C-3), 134.3 (non-terminal olefinic C), 149.7 (C-2), and 158.1 (C-4); *m/e* 161 (M^+), 122, 120 (base), and 93; *picrate*, m.p. 113 °C (from aqueous ethanol) (Found: C, 52.5; H, 4.6; N, 14.3. $C_{17}H_{18}N_4O_7$ requires C, 52.3; H, 4.65; N, 14.35%).

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