

COMMUNICATION

Facile synthesis of a genuinely alkane-soluble but isolable lithium hydride transfer reagent

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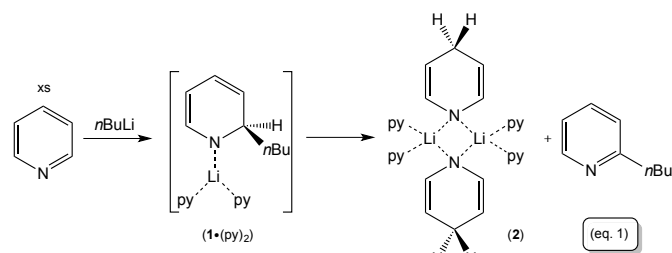
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1-lithio-2-butyl-1,2-dihydropyridines, typically formed as intermediates in the nucleophilic substitution (addition/elimination) of pyridine with (*n*- or *t*-) butyl lithium, have been isolated and comprehensively characterized. The linear substituted isomer is polymeric while the branched substituted isomer is a cyclotrimer. The lower oligomerization of the latter complex confers exceptional hexane solubility making it an excellent lithium hydride source in non-polar, aliphatic media. A Me₆TREN stabilized monomer of the *t*-butyl complex represents the first 1, 2-dihydropyridyllithium complex to be characterized crystallographically.

Binary s-block metal hydrides¹ represent theoretically ideal reagents for fundamentally important synthetic procedures such as metallation or reduction, as well as, in the case of lightweight metals, potential sources of hydrogen for energy storage purposes.² Unfortunately, while their lattice structures and associated high lattice energy generally confers stability on them, making them easy to handle, it also renders them highly insoluble and thus fairly unreactive in even the most polar of solvents. Recent focus has centred on preparing molecular cluster complexes which contain a metal hydride component within them, the presence of sterically bulky peripheral ligands bestowing increased solubility.³ This has proved to be a particularly effective strategy for the Group 2 hydrides principally due to the excellent recent contributions of Jones, Hill, and Harder amongst others.⁴ Much less progress has been made in Group 1. With respect to practical sources of LiH, Brandsma, Schleyer *et. al* prepared LiH *in situ* by hydrogenating *n*BuLi in hexane in the presence of TMEDA (*N,N,N',N'*-tetramethylethylenediamine)⁵ and noted its increased reactivity compared to commercial samples.⁶ More recently Stasch reported an arene soluble complex formulated as [(DippNPPH₂)Li]₄(LiH)₄ (Dipp = 2,6-diisopropylphenyl) which can reduce benzophenone to benzhydrol,⁷ although its stabilizing

phosphinoamine ligand has been shown not to be innocent in selected reactions.⁸ Its solubility in non-polar alkane solution was not addressed. Some very interesting heteroleptic lithium hydride containing clusters have also been reported and characterized crystallographically although their syntheses or isolation are often relatively difficult and their effectiveness as reducing agents are underdeveloped.⁹

The 1,2-addition of organolithium reagents to pyridine to yield 1-lithio-2-alkyl-1,2-dihydropyridines is a well known reaction first reported in 1930.¹⁰ This reaction has been studied primarily from a pyridine functionalization (nucleophilic substitution) standpoint,¹¹ although the lability of lithium hydride from such a complex was noted by Abramovitch and Vig in reducing ketones to alcohols with a PhLi/pyridine pairing.¹² Similar reactivity was also serendipitously spotted by Levine and Kadunce when they tried to metallate pyridine with *n*BuLi and then quench the metallo intermediate with benzophenone,¹³ making this reaction essentially an alkyl version of the Chichibabin reaction (α -amination of pyridine).¹⁴ Dihydropyridine systems also have an important role to play in biological reducing agents, for example NADP(H) (nicotinamide adenine dinucleotide phosphate) and Hantzsch esters.¹⁵ Despite this, the reactive intermediate 1-lithio-2-alkyl-1,2-dihydropyridines have not been well studied in their own right since they were generally prepared and used *in situ*¹¹ although there are some reports of ¹H NMR spectra of such complexes recorded in donor solvents.¹⁶ The closest literature report of such characterization was by Snaith and Mulvey who reported that 1,2-addition of *n*BuLi to excess pyridine results in an isolable product 2-*n*Bu(C₅H₅N)Li•(py)₂ [1•(py)₂] which was unstable towards air, moisture, heat and light in the solid state but which acted as a lithium hydride source, intramolecularly transferring LiH to a solvating pyridine molecule to yield 2-*n*butylpyridine and a mixture of 1, 2- and 1, 4-dihydropyridyllithium (2, equation 1).¹⁷ Here we report the isolation and characterization of *n*- and *t*-butyl congeners of the intermediate 1-lithio-2-alkyl-1,2-dihydropyridines; by altering the alkyl lithium:pyridine ratio to unity; and the use of the *t*-butyl complex as an easy to prepare aliphatic hydrocarbon



soluble source of lithium hydride. Upon stirring an equimolar amount of *n*-butyl lithium and pyridine in hexane at room temperature, a yellow-orange powder immediately precipitated from the solution which was identified as 2-*n*Bu(C₅H₅N)Li (**1**) by its ¹H NMR spectrum, obtained in *d*₈-THF, which showed five distinct CH resonances (consistent with loss of symmetry), the chemical shifts of which (range 3.54 - 6.55 ppm, table 1) were consistent with loss of aromaticity (*cf* pyridine range 7.25 - 8.54 ppm¹⁸). Furthermore there were resonances representing the *n*Bu arm with no signal of a heavily shielded hydrogen atom since the α-CH₂ group is no longer bound to a metal, while the ⁷Li NMR spectrum showed a single resonance at 2.17 ppm. Repeating the reaction under high dilution did not yield single crystals but the same powdered product thus prompting the thought that in the absence of Lewis donors alkane insoluble **1** adopts either a polymeric chain [(-Li-N-)_∞] or infinite ladder structure in the solid state,²⁰ two common motifs for unsolvated lithium amide structures.

Table 1 Selected ¹H NMR data

	1 ^a	3 ^b	3 •Me ₆ TREN ^b
H2	3.54	3.12	3.62
H3	4.08	4.37	4.03
H4	5.72	6.12	5.88
H5	4.29	4.92	4.09
H6	6.55	6.85	6.53

^a *d*₈-THF solvent ^b C₆D₁₂ solvent

We then altered the alkyl substituent from linear *n*Bu to branched *t*Bu, stirring an equimolar amount of *t*BuLi and pyridine in hexane. In contrast to the previous reaction no solid precipitated from the resulting yellow solution showing that the product this time has much greater solubility in the non-donating low polarity solvent than **1**. Upon cooling the reaction mixture to -30°C for 48 hours, a crop of yellow (non x-ray quality) crystalline material was deposited (2-*t*Bu(C₅H₅N)Li, **3**) in excellent yield (83 %). The empirical formula of **3** was confirmed by NMR spectroscopy, this time in C₆D₁₂ solution due to the aforementioned solubility. The ¹H NMR spectrum again displayed five distinct resonances consistent with 1,2 addition of *t*BuLi to pyridine (range 3.12 - 6.85 ppm) and consequent loss of aromaticity plus a singlet at 0.82 ppm representing the *t*Bu group. Resonances were all broad and unresolved into their expected splitting patterns. The ¹³C NMR spectrum showed the quaternary carbon at 39.3 ppm consistent with it being metal free and the ⁷Li spectrum displayed a solitary broad singlet (-1.79 ppm). A DOSY NMR spectrum (see figure 1 and ESI) suggests **3** exists in C₆D₁₂ as a trimer at 0.2 mol/l, giving a calculated estimated molecular weight of 421 which is less than a 2 % error from the theoretical value [MW of (2-*t*Bu(C₅H₅N)Li)₃ = 429]. This lesser oligomerization compared to that suspected for **1** is almost certainly due to the steric bulk of the *t*Bu group and is what confers greater solubility upon **3**. The presence of a new chiral pyridyl N atom adjacent to a chiral C atom means there are a number of possible energetically similar cyclootrimeric enantiomers present in both the solid state and solution which perhaps explains why the solution NMR shows broad

resonances and why single crystals could not be grown from solution despite repeated attempts.

We note that solid **3** showed no obvious signs of decomposition when stored for months in an inert atmosphere glovebox; whereas the *n*Bu congener **1** appeared to degrade after about one month. A C₆D₁₂ solution of **3** also showed no degradation on heating at 60°C for 2 hours as evidenced by its ¹H NMR spectrum. Thermolysis of **1** (see SI for full details) shows that the evolution of volatile material occurs over a range spanning *ca.* 100°C, beginning near room temperature and reaching a maximum at 120°C (fig. 2).

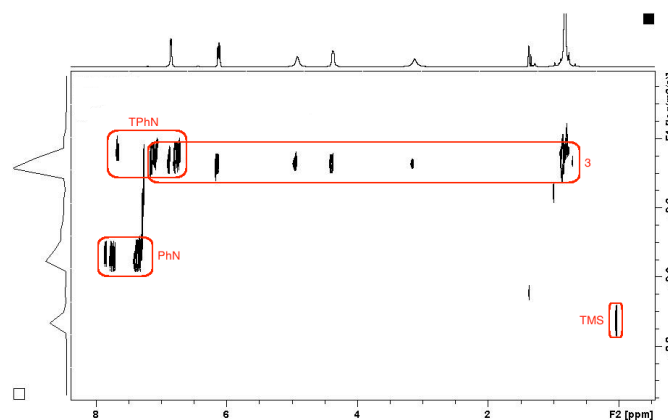


Figure 1 ¹H DOSY NMR spectrum of **3** in C₆D₁₂ at 300 K and inert standards 1,2,3,4-tetraphenyl-naphthalene (TPhN), 1-phenyl-naphthalene (PhN) and tetramethylsilane (TMS).

The absence of a signal for non-condensable products indicates that all evolved material has been collected in the liquid-N₂ cooled trap. Apart from a small amount of material evolving after 20 minutes (possibly residual solvent), the sub-ambient distillation curve for the condensed volatile product is indicative of a single high-boiling product (fig. S1). **3** behaved in a near identical manner to **1** under the same experimental conditions. In both cases the high boiling point product was analyzed by ¹H NMR and FTIR spectroscopy which confirmed them as being the 2-alkyl substituted pyridines (see SI for full characterization details). These results show that both lithiodihydropyridines are converted to lithium hydride and 2-alkylpyridine under relatively mild conditions.

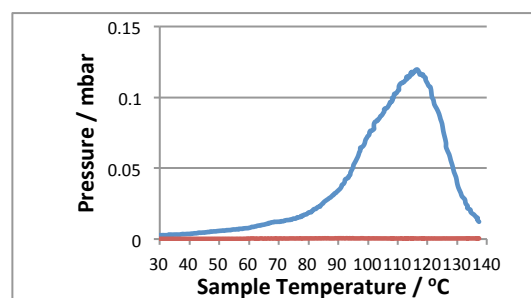


Figure 2 Thermal Volatility Analysis thermogram for **1**. The blue line represents total volatile products and the red line non-condensable volatile products.

Next we attempted to prepare a Lewis donor stabilized monomeric modification of **3**. For this task we re-dissolved **3** in hexane by gentle warming and introduced a molar equivalent of the polydentate amine Me₆TREN [tris(*N,N*-dimethyl-2-aminoethyl)amine], chosen due to its record of stabilizing sensitive *s*-block metal species as monomers.²¹ Surprisingly on adding Me₆TREN a yellow precipitate formed although this re-dissolved easily on introducing a few drops

of THF. Cooling the homogeneous solution to -30°C formed a crop of yellow/orange crystals identified empirically as 2-*t*BuC₅H₅NLi•Me₆TREN (**3**•Me₆TREN, isolated yield 53 %). The crystals were amenable to a X-ray diffraction study (see figure 3 for details).

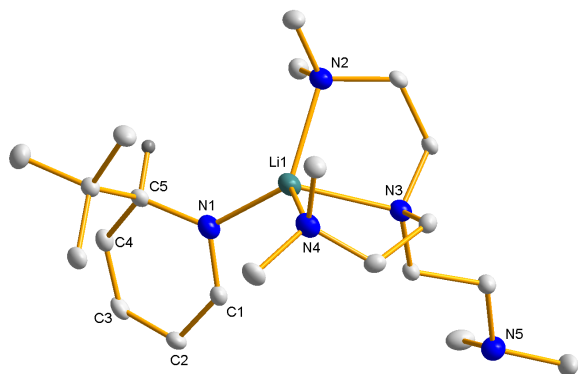


Figure 3 Molecular structure of 2-*t*BuC₅H₅NLi•Me₆TREN (**3**•Me₆TREN). Ellipsoids are displayed at 50% probability and all hydrogen atoms except that on saturated C5 are omitted for clarity. Selected bond lengths (Å) and angles (°): Li1-N1, 1.971(2); Li1-N2, 2.137(2); Li1-N3, 2.197(3); Li1-N4, 2.178(3); N1-C1, 1.336(2); C1-C2, 1.378(2); C2-C3, 1.424(2); C3-C4, 1.341(2); C4-C5, 1.510(2); C5-N1, 1.479(2); N1-Li1-N2, 120.6(1); N1-Li1-N3, 125.4(1); N1-Li1-N4, 114.9(1); N2-Li1-N3, 84.9(1); N2-Li1-N4, 117.8(1); N3-Li1-N4, 85.0(1).

The bonding in the formerly aromatic ring is now clearly a conjugated double bond system with C1-C2 and C3-C4 the shorter bonds [1.378(2) and 1.341(2) Å respectively] and C2-C3 and C4-C5 the longer bonds [1.424(2) and 1.510(2) Å respectively]. Loss of aromaticity is further confirmed by the loss of planarity in the C₅N ring with C5 now representing a chiral, distorted tetrahedral (sp³) centre which lies 0.336(1) Å outside the mean plane of the four sp² hybridised carbons (C1-C4). The lithium cation lies in a heavily distorted tetrahedral environment as a consequence of the chelating nature of the neutral Lewis donor (which binds in a hypodentate fashion) which enforces tighter than ideal N-Li-N angles [84.9(1) and 85.0(1)°]. The N_{anion}-Li bond distance [1.971(2) Å] is understandably shorter than the N_{donor}-Li distances [mean 2.171 Å] and is only marginally shorter than that in a PMDETA solvated 2-picolyl-lithium complex [2.002(4) Å].^{21d} This N_{donor}-Li bond distance is elongated with respect to the picolyl complex [mean 2.142 Å], possibly due to the increased steric bulk in the adjacent position (*t*Bu vs =CH₂).

Comparing the solution NMR data of **3**•Me₆TREN with those of unsolvated **3**, the ring H resonances are shifted upfield with the exception of H2 (on the chiral carbon) which is shifted downfield by more than 0.4 ppm. Resonances are considerably sharper in the solvated derivatives, presumably due to the monomerization, since the trimer has multiple configurational possibilities which give similar yet not totally identical chemical shifts (*vide supra*). Likewise, the ⁷Li spectrum displays a much sharper singlet (0.82 ppm, line width at half height = 6.09 Hz; *cf* **3**, 64.42 Hz). The hypodentate nature of Me₆TREN was not clear in the spectrum of **3**•Me₆TREN (that is the chemical inequivalence of the bound and free arms was not noticed) as only one set of resonances for the CH₂CH₂NMe₂ arms was present.

The effectiveness of hexane soluble **3** as a lithium hydride transfer reagent was tested by studying the hydrolithiation of benzophenone (Ph₂C=O) following the method utilized by Stasch for [(DippNPPH₂)Li]₄(LiH)₄. Benzophenone was added to an *in situ* prepared solution of **3** in hexane. Over the course of two hours this changed from yellow to a colourless solution with precipitate via a

pale green solution. The precipitate was analysed by ¹H and ⁷Li NMR which confirmed that it was the alkoxide Ph₂CHOLi (isolated yield 83 %). The ¹H NMR spectrum showed a resonance at 5.89 ppm in *d*₈-THF representing the transferred hydrogen atom (*cf* literature value of 6.03 ppm),²² while the ⁷Li NMR spectrum showed a single sharp resonance at 1.12 ppm. There did not appear to be any interaction between Lewis basic 2-*t*-butylpyridine and Lewis acidic lithium suggesting the bulk of the alkyl group might confer innocence on to the potential donor.

Conclusions

By holding the alkyl lithium:pyridine ratio to unity in the absence of reducible functional groups, the intermediate 1-lithio-2-alkyl-1,2-dihydropyridines can be isolated in excellent yield. While the *n*-butyl isomer is a hexane insoluble polymer, the *t*-butyl isomer represents an excellent hexane soluble source of lithium hydride as shown by the hydrolithiation of benzophenone in hexane solution. A key advantage of this reducing agent is that it can be easily prepared and ready to use in only minutes using commercially available starting materials as received at room temperature.

Notes and references

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Electronic Supplementary Information (ESI) available: Full experimental details including DOSY NMR spectroscopy, TVA and X-ray crystallography. See DOI: 10.1039/c000000x/

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