Aggregative activation in heterocyclic chemistry. Part 5.† Lithiation of pyridine and quinoline with the complex base BuLi·$Me_2N(CH_2)_2OLi$ (BuLi·LiDMAE)

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It is shown that the complex base BuLi·LiDMAE reacts with pyridine to give metallated species which, after trapping by electrophiles, lead to 2-substituted pyridines in good to excellent yields. The same reactions have been less successfully performed with quinoline.

Introduction

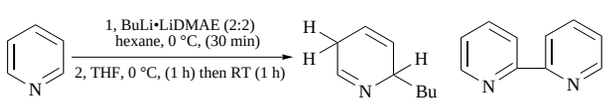
The current abundant literature[1] devoted to the metallation of π-deficient heteroaromatic rings shows that such a reaction plays an important role in the synthesis and chemistry of heterocycles. Examination of the work dealing with the important family of nitrogen-containing heterocycles[1] shows that proton abstraction with an appropriate base has been particularly well investigated in order to obtain the corresponding lithium derivatives. Of value would be the use of commercially available and easily handled basic reagents to perform such reactions; in this respect, use of BuLi would be particularly welcome. However, this reagent suffers from important drawbacks because of its strong nucleophilicity, abundant examples of which have been documented in the pyridine series.[2] Thus, the reaction of BuLi with pyridine itself or quinoline is particularly illustrative. Use either of BuLi by itself or with reagents such as tetramethylethylenediamine (TMEDA) which activate it leads essentially to a Chichibabin-type reaction.[3] In contrast the very powerful, but not easily handled LICKOR (BuLi·Bu^{t}OK) metallates pyridine unselectively to give a mixture of lithiated pyridines.[4] We have previously shown that the complex base (CB) BuLi·$LiO(CH_2)_2NMe_2$ (BuLi·LiDMAE), a unimetal superbase[5] easily obtained from BuLi and *N*,*N*-dimethylaminoethanol, easily metallated 2-methoxypyridine at the C-6 position.[6] This unusual effect was attributed to the aggregative activation[7] of BuLi with, as a consequence, a considerable increase of the basicity/nucleophilicity ratio ([B/N]R).

These results led us to believe that our new CB could furnish a solution to the simple metallation of pyridine and quinoline with BuLi. Here we report that, as expected, pyridine and less efficiently quinoline, may be easily functionalised by the use of the complex base BuLi·LiDMAE.

Results and discussion

Lithiation of pyridine with BuLi·LiDMAE

Taking into account the results previously obtained with 2-methoxypyridine, only a few preliminary experiments were necessary to fit the metallation conditions to the pyridine reactivity. From this short study using Me_3SiCl as a trapping agent, a number of observations were made. According to the literature[2] the main or only product formed with both BuLi and BuLi·TMEDA resulted from the nucleophilic addition of the lithium reagent whatever the ratio BuLi/pyridine or metallation temperature. With BuLi (1.5 equiv.)–LiDMAE (1.5 equiv.) (abbreviated to 1.5 equiv. CB) in hexane at −78 °C for 3 h, the only product formed by trapping with a THF solution of Me_3SiCl was 2-trimethylsilylpyridine (90%). A shorter metallation time (1 h) was necessary when 2 equiv. CB were used. The nature of the solvent played an important role. As with 2-methoxypyridine, the metallation step must be carried out in hexane and simultaneous addition of THF with the electrophile may favour the trapping of the metallated species.[6] The temperature was also an important factor. Thus, at 0 °C only 10% of electrophilic condensation took place. The main products formed were 2-butyl-2,5-dihydropyridine **3**[2c] (39%) and 2,2′-bipyridine **4** (43%). Related to the above observations, the metallation carried out at 0 °C without trapping by an electrophile led mainly to the formation of 2,2′-bipyridine **4** (Scheme 1).



1 **3** (12%) **4** (82%)

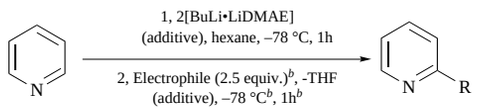
Scheme 1

According to our previous work,[6b] this result is attributable to the formation of a radicaloid intermediate between the substrate and the aggregates of the complex base. From these data we carried out the reactions whose results are gathered in Table 1 and merit some comment. Under the conditions used, no nucleophilic addition of BuLi was observed. This is in harmony with the expected[6b] notable increase in the [B/N]R of BuLi due to its activation by aggregate formation with LiDMAE. As mentioned in our previous publication,[6b] the presence of additives may be essential during the trapping step with a number of electrophiles (run 5). Thus, CuI was necessary to obtain acceptable yields with hexyl iodide. However, this additive did not suppress the competitive classical lithium halide exchange with benzyl bromide (run 6). This suggested that such a reaction could take place with more efficient halogenating agents. This expectation was verified (run 7) and 2-bromopyridine was obtained in good yield using CBr_4 as an electrophile.

With carbonyl derivatives (runs 8–12), the main limitation was the enolization of the substrate due to the basicity of the reaction medium evidenced by the formation of 2-ethylpyridine with MeI (run 4). However it is worth noting that hexanal gave the expected product in good yield (run 8) indicating a good nucleophilicity of the generated metallated species. With base-sensitive ketones less reactive than aldehydes against nucleophiles (runs 10, 11), LiBr electrophilic assistance had to be used to overcome the enolization which was the only reaction observed without an additive. Dialkyl carboxamides also

† For Part 4 in this series see *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3071.

Table 1 Metallation of pyridine with BuLi·LiDMAE and condensation with electrophiles[a]

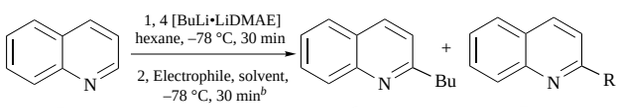


1 **2**

Run	Electrophile	Additive (equiv.)	R	Product	Yield (%)[c]
1	D_2O or MeOD[d]	—	D	**2a**	80
2	MeSSMe	—	SMe	**2b**	90 (80)
3	Me_3SiCl	—	$SiMe_3$	**2c**	90 (80)
4	MeI	—	Me	**2d**	74[e] (60)
5	HexI	CuI(0.2)[f]	Hex	**2e**	50 (45)
6	$PhCH_2Br$	CuI(0.2)[f]	CH_2Ph	**2f**	35[g] (25)
7	CBr_4	—	Br	**2g**	85 (72)
8	PentCHO	—	CH(OH)Pent	**2h**	60 (50)
9	PhCHO	—	CH(OH)Ph	**2i**	90 (80)
10	MeCOMe	LiBr(0.25)[h]	$C(OH)Me_2$	**2j**	45 (35)
11	MeCOEt	LiBr(0.25)[h]	C(OH)MeEt	**2k**	77 (67)
12	$(CH_2)_5CO$	—	$C(OH)(CH_2)_5$	**2l**	80 (70)
13	Me_2NCHO[i]	—	COH	**2m**	45 (40)
14	Me_2NCOPh	—	COPh	**2n**	80 (65)

[a] Reactions performed on 4 mmol of pyridine. [b] Unless otherwise specified. [c] GC yields, the numbers in parentheses are isolated yields after purification on a Chromatotron. [d] 10 equiv. used. [e] Accompanied by 16% of 2-ethylpyridine. [f] CuI was added with electrophile. [g] Accompanied by 45% of 2-bromopyridine. [h] LiBr was added to the base before metallation. [i] Condensation performed at −40 °C for 30 min with 1.5 equiv. of DMF.

Table 2 Metallation of pyridine with BuLi·LiDMAE and condensation with electrophiles[a]



5 **6** **7**

Run	E^+ (equiv.), Solvent (ml/equiv.)	Yield of **6** (%)[c]	R	Product	Yield (%)[c]
1	Me_3SiCl (5), Hexane (5)	32	$SiMe_3$	**7a**	40
2	Me_3SiCl (5), THF (5)[d]	27	$SiMe_3$	**7a**	70
3	Me_3SiCl (5), Et_2O (5)	25	$SiMe_3$	**7a**	75 (65)
4	D_2O or MeOD (10–20), THF (2.5–1.25)	19	D	**7b**	40
5	D_2O or MeOD (10–20), Et_2O (2.5–1.25)	10	D	**7b**	65
6	MeI (10), THF (2.5)	4	Et	**7c**	40 (30)[e]
7	MeSSMe (5), Et_2O (5)	2	SMe	**7d**	63 (55)
8	Bu′CHO (10), THF (2.5)	25	$CH(OH)Bu^t$	**7e**	35 (25)
9	PhCHO (10), Et_2O (2.5)	1	CH(OH)Ph	**7f**	52 (45)
10	MeCOEt (10), THF (2.5)	17	C(OH)MeEt	**7g**	32 (25)
11	PhCOPh (10), Et_2O (2.5)	13	$C(OH)Ph_2$	**7h**	50 (40)

[a] Reactions performed on 2 mmol of quinoline. [b] Unless otherwise specified. [c] GC yields, the numbers in parentheses are isolated yields after purification on a Chromatotron. [d] Reaction time 60 min. [e] Only 2-ethylquinoline was obtained.

condensed to yield the corresponding carbonyl derivatives (runs 13, 14). Surprisingly with dimethylformamide, too large an excess of electrophile led to the formation of numerous by-products.

Lithiation of quinoline with BuLi·LiDMAE

Quinoline **5**, in agreement with the literature data,[8] was found to be less easily metallated than pyridine derivatives and much more prone to nucleophilic addition leading to 2-butylquinoline **6**.[9] From a preliminary study, the results of which are not presented here, the following observations were made. An excess of 4 equivalents of CB was necessary to metallate quinoline efficiently. The metallation and electrophilic quenching temperatures must not exceed −78 °C. We also found that a co-solvent was necessary to improve the trapping step yield. From the literature data,[10] THF and Et_2O appeared as the best candidates. The selection between them was done empirically as a function of the electrophile. The additives used during the trapping of metallated pyridines had no such beneficial effect with metallated quinoline. The best results obtained with a few electrophiles are gathered in Table 2.

Runs 1–5 illustrate the role played by the trapping co-solvent. On the other hand it appears that the metallated species obtained from quinoline and CB, reacted with the customary electrophiles although yields were lower than those obtained with metallated pyridines under comparable conditions. In fact, large amounts (30–50%) of unchanged quinoline were recovered during these reactions. So we attribute the moderate efficiency of the trapping to a lower reactivity of the metallated quinoline rather than to a lack of metallation.

Conclusion

We have shown that the complex base BuLi·LiDMAE furnishes an answer to the difficult problem of the metallation of pyridine and quinoline. The present results in conjunction with those obtained with 2-methoxypyridine[6] prove that unimetal superbases may be useful in the metallation of π-deficient

heterocycles and thus further extend the range of aggregative activation in organic synthesis.

Experimental

General methods

^{1}H NMR spectra were recorded on a JEOL PMX60 spectrometer at 60 MHz with $SiMe_4$ as internal standard and $CDCl_3$ as solvent. *J* Values are given in Hz. GC/MS analysis (EI and CI) were performed on HP5890 spectrometers using Macherey-Nagel OPTIMA-5 15 m columns and temperature programming.

Materials

BuLi (1.6 M solution in hexane) was purchased from Aldrich. *N*,*N*-Dimethylaminoethanol (DMAE) was distilled before use. Pyridine and quinoline were dried over KOH powder before use. Hexane, THF and Et_2O were distilled and stored over sodium wire before use. LiBr and CuI were dried at 100 °C under reduced pressure for 24 h and used immediately. Chlorotrimethylsilane, dimethyl disulfide, ketones, aldehydes, amides and alkyl halides were commercially available and distilled or recrystallized before use.

General procedure for metallation of pyridine with BuLi·LiDMAE

BuLi (16 mmol, 10 ml) was cooled to 0 °C under a nitrogen atmosphere and a solution of *N*,*N*-dimethylaminoethanol (8 mmol, 0.72 g) in anhydrous hexane (10 ml) was added dropwise to it over 15 min. The mixture was then cooled to −78 °C after which a solution of pyridine (0.32 g, 4 mmol) in hexane (5 ml) was also added dropwise to it. After 1 h an orange solution was obtained and an appropriate electrophile (10–40 mmol) as a solution in anhydrous THF (25 ml) was added rapidly to it. After 1 h at −78 °C, the reaction mixture was treated with 10% aqueous HCl (20 ml) to hydrolyse it. The aqueous layer was then separated and extracted twice with diethyl ether (20 ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the crude product was purified on a Chromatotron using AcOEt–hexane as eluents.

2-Methylpyridine **2d**, 2-benzylpyridine **2f**, pyridine-2-carbaldehyde **2m**, 2-benzoylpyridine **2n**, 2-bromopyridine **2g** and 2,2′-bipyridine **4** were identical in every respect with commercial samples.

[2-^{2}H]Pyridine 2a.[11] Obtained as a mixture with pyridine; δ_H 7.25–7.65 (m, 3 H, H-3 + H-5 + H-4) and 8.60 (d, 1 H, *J* 5, H-6); *m*/*z* (CI) 81 [(M + 1) + H$^+$] and 57.

2-Methylthiopyridine 2b.[12] δ_H 2.60 (s, 3 H, CH_3), 6.75–7.70 (m, 3 H, H-3 + H-5 + H-4) and 8.45 (d, 1 H, *J* 5, H-6); *m*/*z* (EI) 125 (M$^+$), 92, 79, 65 and 57.

2-Trimethylsilylpyridine 2c.[13] δ_H 0.25 (s, 9 H, CH_3Si), 7.25–7.75 (m, 3 H, H-3 + H-5 + H-4) and 8.70 (d, 1 H, *J* 5, H-6); *m*/*z* (EI) 151 (M$^+$), 136, 120, 106, 78, 73 and 57.

2-Hexylpyridine 2e.[14] δ_H 0.95 (t, 3 H, *J* 8, CH_3), 1.35–1.70 (m, 8 H, CH_2), 2.80 (t, 2 H, *J* 7.8, CH_2), 7.15–7.20 (m, 3 H, H-3 + H-5 + H-4) and 8.55 (d, 1 H, *J* 5, H-6); *m*/*z* (CI) 164, (M + H$^+$), 148, 121, 93, 80, 69 and 57.

1-(2-Pyridyl)hexan-1-ol 2h.[15] δ_H 0.89 (t, 3 H, *J* 7, CH_3), 1.50–1.55 (m, 6 H, CH_2), 1.95 (t, 2 H, *J* 7.5, CH_2), 3.95 (br s, 1 H, OH), 4.65 (t, 1 H, *J* 5.5, CHOH), 7.15–7.60 (m, 3 H, H-3 + H-5 + H-4) and 8.60 (d, 1 H, *J* 5, H-6); *m*/*z* (CI) 180 (M + H$^+$), 162, 146, 134, 108, 80, 69 and 57.

Phenyl(2-pyridyl)methanol 2i.[16] Mp 72–73 °C (lit.,[16] 72–74 °C); δ_H 5.50 (s, 1 H, OH), 5.70 (s, 1 H, CHOC), 7.25–7.70 (m, 8 H, H-Ar + Pyr-H-3 + Pyr-H-5 + Pyr-H-4) and 8.65 (d, 1 H, *J* 5, Pyr-H-6); *m*/*z* (CI) 186 (M + H$^+$), 168, 155, 108, 79 and 57.

2-(2-Pyridyl)propan-2-ol 2j.[17] δ_H 1.45 (s, 6 H, CH_3), 4.90 (br s, 1 H, OH), 7.70–7.80 (m, 3 H, H-3 + H-5 + H-4) and 8.30 (d, 1 H, *J* 5, H-6); *m*/*z* (EI) 134 (M$^+$), 120, 106, 93, 78 and 65.

2-(2-Pyridyl)butan-2-ol 2k.[18] δ_H 0.70 (t, 3 H, *J* 7.5, CH_3), 1.45 (s, 3 H, CH_3C), 1.85 (q, 2 H, *J* 7.5, CH_2), 4.50 (s, 1 H, OH), 6.90 (m, 1 H, H-5), 7.35–7.40 (m, 2 H, H-3 + H-4) and 8.40 (d, 1 H, *J* 4.8, H-6); *m*/*z* (CI) 152 (M + H$^+$), 134, 120, 108, 79, 73 and 57.

1-(2-Pyridyl)cyclohexanol 2l.[1b] δ_H 1.50–2.00 (m, 10 H, CH_2), 4.50 (s, 1 H, OH), 7.15–7.50 (m, 3 H, H-3 + H-5 + H-4) and 8.55 (d, 1 H, *J* 5, H-6); *m*/*z* (CI) 178 (M + H$^+$), 160, 149, 134, 106, 99 and 57.

General procedure for metallation of quinoline with BuLi·LiDMAE

The above prepared BuLi·LiDMAE cooled to −78 °C was treated dropwise with a solution of quinoline (0.26 g, 2 mmol) in hexane (5 ml). After 30 min, the deep red solution was treated with an appropriate electrophile (20–40 mmol) added as a solution in anhydrous diethyl ether (25 ml). After 1 h at −78 °C, the reaction mixture was treated with 10% aqueous HCl (20 ml) to hydrolyse it. After work-up, the crude product was purified on a Chromatotron using AcOEt–hexane as eluents.

2-Trimethylsilylquinoline 7a.[13] δ_H 0.32 (s, 9 H, CH_3Si) and 7.44–8.05 (m, 6 H, H-Ar); *m*/*z* (CI) 202 (M + H$^+$), 186, 130, 73 and 57.

[2-^{2}H]Quinoline 7b.[19] As a mixture with quinoline: δ_H 7.20–8.10 (m, 6 H, H-Ar); *m*/*z* (CI) 131 [(M + 1) + H$^+$] and 57.

2-Ethylquinoline 7c.[20] δ_H 1.25 (t, 3 H, *J* 7.5, CH_3), 2.80 (q, 2 H, *J* 7.5, CH_2) and 7.40–7.85 (m, 6 H, H-Ar); *m*/*z* (CI) 158 (M + H$^+$), 143, 130 and 57.

2-Methylthioquinoline 7d.[21] δ_H 2.70 (s, 3 H, CH_3S) and 7.25–8.10 (m, 6 H, H-Ar); *m*/*z* (CI) 176 (M + H$^+$), 143, 130 and 57.

Phenyl(2-quinolyl)methanol 7f.[22] Mp 68–72 °C (lit.,[22] 69–71 °C); δ_H 5.80 (s, 1 H, CH), 6.20 (s, 1 H, OH) and 7.25–7.80 (m, 6 H, H-Ar); *m*/*z* (CI) 236 (M + H$^+$), 218, 158, 130, 107, 79, 69 and 57.

2-(2-Quinolyl)butan-2-ol 7g.[23] δ_H 0.70 (t, 3 H, *J* 7.5, CH_3), 1.45 (s, 3 H, CH_3), 1.85 (q, 2 H, *J* 7.5, CH_2), 4.25 (s, 1 H, OH) and 7.40–7.80 (m, 6 H, H-Ar); *m*/*z* (CI) 202 (M + H$^+$), 184, 172, 130, 73 and 57.

Diphenyl(2-quinolyl)methanol 7h.[24] Mp 190–192 °C (lit.,[24] 193–195 °C); δ_H 5.90 (s, 1 H, OH) and 7.20–8.15 (m, 16 H, H-Ar); *m*/*z* (CI) 312 (M + H$^+$), 294, 234, 206, 183 and 128.

Acknowledgements

We thank the editor for useful corrections.

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Paper 7/05027E
Received 14*th July* 1997
Accepted 19*th September* 1997