Reaction of magnesiated bases on substituted pyridines: deprotonation or 1,4-addition?

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Received (in Cambridge, UK) 7th September 2000, Accepted 22nd September 2000
First published as an Advance Article on the web 20th November 2000

N-(*tert*-Butyl)pyridine-2-carboxamide (**1**), *N*-phenylpyridine-2-carboxamide (**7**) and 2,2-dimethyl-*N*-(2-pyridyl)-propanamide (**18**) are readily deprotonated at C3 with a stoichiometric amount of Pr^iMgCl or Bu_2Mg in THF under reflux. Subsequent trapping with various electrophiles (deuterated water, aldehydes, iodine and dimethyl disulfide) gives 2,3-disubstituted pyridines carrying a useful carboxylic acid- or amino-derived function at C2. When *N*-(*tert*-butyl)pyridine-3-carboxamide (**12**) and 2,2-dimethyl-*N*-(3-pyridyl)propanamide (**22**) are subjected to the same reaction conditions, 1,4-addition to the pyridine ring occurs, giving 4-alkyl derivatives. Starting from *N*-(*tert*-butyl)pyridine-4-carboxamide (**15**), 1,2-addition and deprotonation reactions occur simultaneously.

Introduction

The current abundant literature devoted to the lithiation of azines[1,2] shows that such a reaction plays an important role in the synthesis of natural products and pharmaceuticals, and in the elaboration of building blocks for material science and supramolecular chemistry. This methodology often requires low temperatures which are not easy to realize on an industrial scale. A survey of the literature revealed that some benzenes[3,4] and pi-electron rich aromatic rings[5,6] could be deprotonated at higher temperatures with alkylmagnesium halides, Hauser bases (R_2NMgX) or magnesium diamides. In the case of substrates more prone to nucleophilic addition, metallation has only been effected with Hauser bases. Indeed, deprotonation of pyridines containing useful carboxylic acid- and amino-derived functions was accomplished by Mulzer and co-workers with (2,2,6,6-tetramethylpiperidino)magnesium chloride;[7–9] because of its weaker reactivity when compared to alkylmagnesium halides, a large excess (6 to 8 equivalents) of expensive base, which is not available commercially, in general has to be used to ensure good yields.

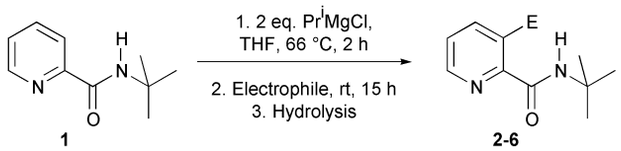
In this paper, we report to what extent a stoichiometric amount of commercial dibutylmagnesium, alkylmagnesium halide or phenylmagnesium halide can deprotonate such pyridine derivatives.

Results and discussion

N-Substituted pyridinecarboxamides

N-(*tert*-Butyl)pyridine-2-carboxamide (**1**) was exposed to various bases such as Bu_2Mg, Pr^iMgCl, BuMgCl, Bu^tMgCl and PhMgBr in THF. All these bases, when used in THF under reflux, were found to be effective in deprotonating **1** at C3 since deuteriolysis after two hours afforded 3-deuterated compound **2** in 92, 97 (run 1, Table 1), 78, 77 and 49% yield, respectively. Thus, a stoichiometric amount of Pr^iMgCl or Bu_2Mg is enough to obtain an almost complete deprotonation at C3. Note that no reaction was observed at rt. Quenching the pyridine Grignard derivative with aldehydes (runs 2–4, Table 1) and iodine (run 5, Table 1) respectively gave the alcohols **3**–**5** and the iodopyridine **6** in moderate to good yields. The yields obtained largely depend on the trapping step with the electrophiles, since starting material **1** is the only product recovered beside the desired compound (Table 1).

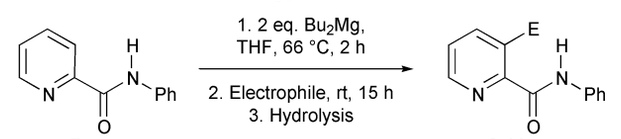
Table 1 Functionalization of pyridine **1**



Run	Electrophile, E	Product, yield[a] (%)
1	D_2O, D	**2**, 97[b]
2	PhCHO, CH(OH)Ph	**3**, 42
3	Pr^iCHO, $CH(OH)Pr^i$	**4**, 25
4	Bu^tCHO, $CH(OH)Bu^t$	**5**, 37
5	I_2, I	**6**, 69

[a] Isolated yields based on **1**. [b] 100% deuterium incorporation was observed from the ^1H NMR spectra integration values.

Table 2 Functionalization of pyridine **7**



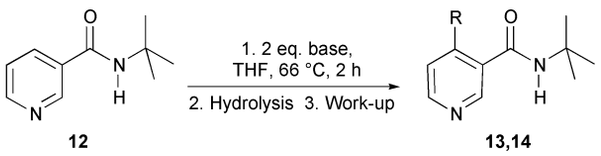
Run	Electrophile, E	Product, yield[a] (%)
1	D_2O, D	**8**, 60[b]
2	PhCHO, CH(OH)Ph	**9**, 58
3	Pr^iCHO, $CH(OH)Pr^i$	**10**, 15
4	MeSSMe, SMe	**11**, 22

[a] Isolated yields based on **7**. [b] 98% deuterium incorporation was observed from the ^1H NMR spectra integration values.

With *N*-phenylpyridine-2-carboxamide (**7**), Pr^iMgCl and Bu_2Mg were effectively tested under the same conditions. In the case of Bu_2Mg, quenching the intermediate with D_2O (run 1, Table 2), aldehydes (runs 2–3, Table 2) and dimethyl disulfide (run 4, Table 2) respectively afforded the deuterated compound **8**, the desired alcohols **9**–**10** and the sulfide **11**.

DOI: 10.1039/b007270m

Table 3 Functionalization of pyridine **12**

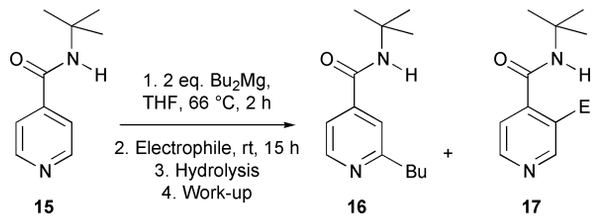


12 **13,14**

Run	Base, R	Product, yield[a](%)
1	Pr^iMgCl, Pr^i	**13**, 70
2	Bu_2Mg, Bu	**14**, 51

[a] Isolated yields based on **12**.

Table 4 Functionalization of pyridine **15**



15 **16** **17**

Run	Electrophile	Yield of **16**(%)	Product **17**, E, yield[a](%)
1	D_2O	60	**17a**, D, 23[b]
2	I_2	59	**17b**, I, 22

[a] Isolated yields based on **15**. [b] 83% deuterium incorporation was observed from the ^1H NMR spectra integration values.

With isobutyraldehyde as the electrophile (run 3, Table 2), the main limitation is the abstraction of its enolizable proton by the magnesiated pyridine formed (Table 2).

N-(*tert*-Butyl)pyridine-3- and -4-carboxamides (**12** and **15**) were exposed to Pr^iMgCl, Bu_2Mg and 2-mesitylmagnesium bromide under the same reaction conditions. No reaction was observed using 2-mesitylmagnesium bromide.

With pyridine-3-carboxamide **12**, 1,4-addition of the base to the substrate was the only reaction observed when Pr^iMgCl (run 1, Table 3) and Bu_2Mg (run 2, Table 3) were used. Dihydropyridines are present in the crude product mixture but oxidation rapidly occurs during the work-up procedure (Table 3).

The reaction proceeds analogously to the previously reported 1,4-addition reaction of magnesiated bases such as EtMgBr and PhMgBr to *N*,*N*-di-*tert*-butylpyridine-2,5-dicarboxamide.[10]

In the case of pyridine-4-carboxamide **15**, deprotonation reaction at C3 was observed together with the 1,2-addition reaction of the base to the substrate when Bu_2Mg was used in THF under reflux. Aromatization of the dihydropyridine intermediates is likewise observed during the work-up procedure (Table 4).

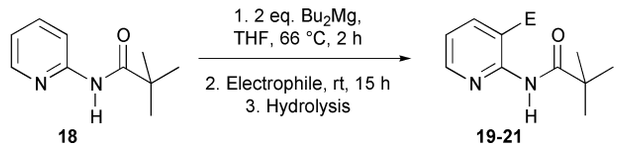
Our results can be compared to those observed by Epsztajn and co-workers during the reaction of *N*-phenylpyridinecarboxamides with BuLi.[11,12] When treated with BuLi, *N*-phenylpyridine-2- and -4-carboxamides are deprotonated at C3 while 1,4-addition was the only reaction observed in the case of *N*-phenylpyridine-3-carboxamide.

2,2-Dimethyl-*N*-pyridylpropanamides

Clean deprotonation of 2,2-dimethyl-*N*-(2-pyridyl)propanamide (**18**) at C3 has likewise been performed with Bu_2Mg (run 1, Table 5). Alcohol **20** and iodopyridine **21** were synthesized by trapping with benzaldehyde (run 2, Table 5) and iodine (run 3, Table 5) respectively.

2,2-Dimethyl-*N*-(3-pyridyl)propanamide **22** is much more prone to nucleophilic addition of the base leading to 4-alkylpyridines **23**, **24** (Table 6). Similar addition of BuLi to **22** has been previously reported by Turner.[13]

Table 5 Functionalization of pyridine **18**

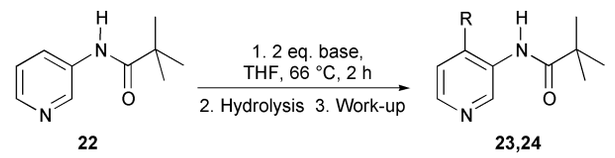


18 **19-21**

Run	Electrophile, E	Product, yield[a](%)
1	D_2O, D	**19**, 97[b]
2	PhCHO, CH(OH)Ph	**20**, 45
3	I_2, I	**21**, 66

[a] Isolated yields based on **18**. [b] 98% deuterium incorporation was observed from the ^1H NMR spectra integration values.

Table 6 Functionalization of pyridine **22**



22 **23,24**

Run	Base, R	Product, yield[a](%)
1	Pr^iMgCl, Pr^i	**23**, 68
2	Bu_2Mg, Bu	**24**, 50

[a] Isolated yields based on **22**.

Note that 2,2-dimethyl-*N*-(4-pyridyl)propanamide[13] did not react at all when treated with Pr^iMgCl or Bu_2Mg under the same reaction conditions.

During lithiation, deprotonation of 2,2-dimethyl-*N*-pyridylpropanamides is effected at higher temperatures than deprotonation of *N*-substituted pyridinecarboxamides, so nucleophilic addition of the base to the substrate occurs concurrently.[13,14] In our case, weaker reactivity of magnesiated bases compared to the lithiated bases did not allow deprotonation in the cases of **22** and 2,2-dimethyl-*N*-(4-pyridyl)propanamide.

Conclusion

This work describes the first pyridine deprotonation using an alkylmagnesium halide (Pr^iMgCl) and a dialkylmagnesium (Bu_2Mg). The method gives good results when the carboxylic acid- or amino-derived functional group is present at C2, allowing a range of groups to be introduced at C3. The effectiveness of these reagents in promoting deprotonation avoids the use of a large excess (in general 6 to 8 equivalents) of (2,2,6,6-tetramethylpiperidino)magnesium chloride, which is a rather expensive base which is not available commercially.

Compared to the lithiation reaction which often requires low to very low temperatures, this magnesiation method proceeds under reflux.

Interestingly, the magnesiated pyridines, which are more stable than their corresponding lithio derivatives, could also be involved in coupling reactions.

Experimental

General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded in $CDCl_3$ on a Bruker AM 300 spectrometer (^1H at 300 MHz and ^{13}C decoupled spectra at 75 MHz) with residual protic solvent as the internal reference. Chemical

shifts are quoted in ppm and coupling constants in Hz. IR spectra were taken on a Perkin-Elmer FT IR 205 spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

THF was distilled from benzophenone–Na. Reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. Pr^iMgCl (2 mol dm^{-3} in THF), BuMgCl (2 mol dm^{-3} in THF), PhMgBr (1 mol dm^{-3} in THF), Bu^tMgCl (1 mol dm^{-3} in THF), 2-mesitylmagnesium bromide (1 mol dm^{-3} in THF), and Bu_2Mg (1 mol dm^{-3} in heptane) were purchased from Aldrich in Sure/Seal™ bottles. Petrol refers to petroleum ether (bp 40–60 °C).

Note: unless otherwise specified 'work-up' refers to extraction with diethyl ether (20 cm^3) and DCM (2 × 20 cm^3), followed by drying ($MgSO_4$) and removal of the solvent *in vacuo*.

Starting materials

N-Substituted pyridinecarboxamides were prepared from the corresponding ethyl pyridinecarboxylates, using a procedure described in the literature.[9,15] To a solution of *tert*-butylamine (25 mmol, 1.8 g, 2.6 cm^3) or aniline (25 mmol, 2.3 g, 2.3 cm^3) in dry toluene (100 cm^3) was added dropwise BuMgCl (25 mmol) and the resulting mixture was heated under reflux for 10 min. The required ethyl pyridinecarboxylate (7.3 mmol, 1.1 g, 1.1 cm^3) in THF (30 cm^3) was added dropwise and the resulting mixture was refluxed for an additional 2 h. The solution was poured into cooled 10% aqueous NH_3.

***N*-(*tert*-Butyl)pyridine-2-carboxamide 1.**[7] Column chromatography on silica gel (DCM) afforded **1** (1.1 g, 87%) as a pale yellow oil (Found: C, 67.7; H, 8.0; N, 15.9. $C_{10}H_{14}N_2O$ requires: C, 67.4; H, 7.9; N, 15.7%); ν_{max}/cm^{-1} (neat) 3375, 2966, 2931, 1679, 1518, 1463, 1288; δ_H 8.21 (1 H, d, *J* 4.8, 6-H), 7.86 (1 H, d, *J* 8.0, 3-H), 7.72 (1 H, s, NH), 7.51 (1 H, m, 4-H), 7.05 (1 H, m, 5-H), 1.05 (9 H, s, Bu^t); δ_C 161.8 (CO), 149.3 (2-C), 146.7 (6-C), 136.0 (4-C), 125.3 (3-C), 120.4 (5-C), 50.7 (CMe_3), 28.9 (CMe_3).

***N*-(*tert*-Butyl)pyridine-3-carboxamide 12.** Washing with petrol (20 cm^3) afforded **12** (1.0 g, 78%) as a white powder; mp 88–90 °C (lit.,[16,17] 85–86 °C) (Found: C, 67.1; H, 7.9; N, 15.7. $C_{10}H_{14}N_2O$ requires: C, 67.4; H, 7.9; N, 15.7%); ν_{max}/cm^{-1} (KBr) 3358, 2981, 2961, 1639, 1545, 1313, 1220, 1022; δ_H 8.84 (1 H, s, 2-H), 8.63 (1 H, dd, *J* 4.9 and 0.9, 6-H), 7.99 (1 H, dd, *J* 7.9 and 0.9, 4-H), 7.29 (1 H, dd, *J* 7.9 and 4.9, 5-H), 5.93 (1 H, s, NH), 1.42 (9 H, s, Bu^t); δ_C 165.3 (CO), 153.4 (6-C), 148.5 (2-C), 136.4 (4-C), 131.9 (3-C), 124.3 (5-C), 52.4 (CMe_3), 29.7 (CMe_3).

***N*-(*tert*-Butyl)pyridine-4-carboxamide 15.**[18] Recrystallization from petrol afforded **15** (0.99 g, 76%) as a white powder; mp 117–118 °C (Found: C, 67.2; H, 7.9; N, 15.5. $C_{10}H_{14}N_2O$ requires: C, 67.4; H, 7.9; N, 15.7%); ν_{max}/cm^{-1} (KBr) 3283, 2979, 2963, 1638, 1546, 1320, 1215; δ_H 8.64 (2 H, dd, *J* 4.5 and 1.5, 2-H and 6-H), 7.49 (2 H, dd, *J* 4.5 and 1.5, 3-H and 5-H), 5.94 (1 H, s, NH), 1.41 (9 H, s, Bu^t); δ_C 162.8 (CO), 150.9 (2-C and 6-C), 143.3 (4-C), 121.1 (3-C and 5-C), 52.5 (CMe_3), 29.1 (CMe_3).

***N*-Phenylpyridine-2-carboxamide 7.** Recrystallization from petrol afforded **7** (1.1 g, 75%) as a white powder; mp 72–74 °C (lit.,[19] 76 °C); the spectroscopic data are in accordance with those of the literature.[20]

2,2-Dimethyl-*N*-pyridylpropanamides were prepared using the procedure described in the literature.[13] 2,2-Dimethyl-*N*-(2-pyridyl)propanamide (**18**) and 2,2-dimethyl-*N*-(3-pyridyl)-propanamide (**22**) were found to be identical to authentic samples.[13]

Action of the magnesiated bases and condensation with electrophiles

The magnesiated base (10 mmol) was added to the pyridine substrate (5 mmol) in THF (15 cm^3) at 0 °C. After 2 h under THF reflux, the mixture was cooled to rt and, when necessary, the electrophile (10 mmol, or 20 mmol when Bu_2Mg was used) was added. The mixture was stirred at rt for 15 h before hydrolysis with water (20 cm^3).

***N*-(*tert*-Butyl)-3-deuteriopyridine-2-carboxamide 2.** Compound **2** was obtained from **1** using Pr^iMgCl and after trapping with D_2O. Column chromatography on silica gel (DCM) afforded **2** (0.87 g, 97%, 100% *d*). The characteristics of this product were found to be identical to those described for **1** except for ^1H and ^{13}C NMR spectra where the 3-H and 3-C signals respectively had disappeared.

***N*-(*tert*-Butyl)-3-[hydroxy(phenyl)methyl]pyridine-2-carboxamide 3.** Compound **3** was obtained from **1** using Pr^iMgCl and then trapping with PhCHO. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **3** (0.60 g, 42%) as a white powder; mp 69–70 °C (Found: C, 72.0; H, 7.0; N, 9.8. $C_{17}H_{20}N_2O_2$ requires: C, 71.8; H, 7.1; N, 9.85%); ν_{max}/cm^{-1} (KBr) 3361, 2968, 1652, 1520, 1453, 1221, 1038; δ_H 8.34 (1 H, dd, *J* 4.7 and 0.8, 6-H), 7.89 (1 H, s, NH), 7.44 (1 H, dd, *J* 7.0 and 0.8, 4-H), 7.2 (5 H, m, Ph), 6.54 (1 H, dd, *J* 7.0 and 4.7, 5-H), 6.09 (1 H, d, *J* 7.0, OH), 4.53 (1 H, d, *J* 7.0, C*H*(OH)Ph), 1.29 (9 H, s, Bu^t); δ_C 165.0 (CO), 148.6 (2-C), 145.5 (6-C), 141.1 (1′-C), 139.7 (3-C), 137.6 (4-C), 127.4 (3′-C and 5′-C), 126.3 (4′-C), 125.6 (2′-C and 6′-C), 124.6 (5-C), 72.2 (*C*H(OH)Ph), 50.3 (CMe_3), 27.4 (CMe_3).

***N*-(*tert*-Butyl)-3-(α-hydroxy-β-methylpropyl)pyridine-2-carboxamide 4.** Compound **4** was obtained from **1** using Pr^iMgCl and then trapping with Pr^iCHO. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **4** (0.31 g, 25%) as a white powder; mp 78–79 °C (Found: C, 67.4; H, 8.8; N, 11.0. $C_{14}H_{22}N_2O_2$ requires: C, 67.2; H, 8.9; N, 11.2%); ν_{max}/cm^{-1} (KBr) 3402, 2966, 1658, 1520, 1374, 1364, 1222, 1035; δ_H 8.40 (1 H, dd, *J* 4.8 and 0.9, 6-H), 8.22 (1 H, s, NH), 7.66 (1 H, dd, *J* 7.0 and 0.9, 4-H), 7.26 (1 H, dd, *J* 7.0 and 4.8, 5-H), 6.18 (1 H, s, OH), 4.32 (1 H, m, C*H*(OH)Pr^i), 2.10 (1 H, m, C*H*Me_2), 1.38 (9 H, s, Bu^t), 1.02 (6 H, 2d, *J* 6.6, CHMe_2); δ_C 164.4 (CO), 146.8 (2-C), 145.2 (6-C), 139.8 (3-C), 138.5 (4-C), 124.4 (5-C), 79.9 (*C*H(OH)Pr^i), 52.4 (CMe_3), 32.5 (*C*HMe_2), 27.5 (CMe_3), 19.4 and 18.6 (CHMe_2).

***N*-(*tert*-Butyl)-3-(α-hydroxy-β,β-dimethylpropyl)pyridine-2-carboxamide 5.** Compound **5** was obtained from **1** using Pr^iMgCl and then trapping with Bu^tCHO. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **5** (0.49 g, 37%) as a pale yellow oil (Found: C, 68.2; H, 9.0; N, 10.4. $C_{15}H_{24}N_2O_2$ requires: C, 68.15; H, 9.15; N, 10.6%); ν_{max}/cm^{-1} (neat) 3459, 3321, 2961, 1661, 1520, 1364, 1223, 1044, 1011; δ_H 8.40 (1 H, dd, *J* 4.7 and 0.8, 6-H), 8.10 (1 H, s, NH), 7.80 (1 H, dd, *J* 6.9 and 0.8, 4-H), 7.32 (1 H, dd, *J* 6.9 and 4.7, 5-H), 6.12 (1 H, s, OH), 5.00 (1 H, s, C*H*(OH)Bu^t), 1.36 (9 H, s, NHBu^t), 0.79 (9 H, s, CH(OH)Bu^t); δ_C 166.8 (CO), 149.3 (2-C), 146.3 (6-C), 140.7 (4-C), 139.4 (3-C), 125.1 (5-C), 80.9 (*C*H(OH)Bu^t), 51.5 (NHCMe_3), 38.0 (CH(OH)CMe_3), 28.9 (NHCMe_3), 26.7 (CH(OH)CMe_3).

***N*-(*tert*-Butyl)-3-iodopyridine-2-carboxamide 6.** Compound **6** was obtained from **1** using Pr^iMgCl and then trapping with I_2. Column chromatography on silica gel (9:1 DCM–Et_2O) afforded **6** (1.0 g, 69%) as a yellow powder; mp 93–94 °C (Found: C, 39.3; H, 4.6; N, 9.2. $C_{10}H_{13}IN_2O$ requires: C, 39.5; H, 4.3; N, 9.2%); ν_{max}/cm^{-1} (KBr) 3372, 3054, 2966, 1681, 1519, 1222, 1014; δ_H 8.39 (1 H, dd, *J* 4.4 and 1.5, 6-H), 8.23 (1 H, dd,

J 7.7 and 1.5, 4-H), 7.40 (1 H, s, NH), 6.97 (1 H, dd, *J* 7.7 and 4.4, 5-H), 1.39 (9 H, s, Bu^t); δ_C 162.5 (CO), 150.9 (6-C), 149.2 (2-C), 147.3 (4-C), 126.3 (5-C), 87.5 (3-C), 51.6 (*C*Me$_3$), 29.1 (C*Me*$_3$).

***N*-Phenyl-3-deuteriopyridine-2-carboxamide 8.**[11,12] Compound **8** was obtained from **7** using Bu_2Mg and then trapping with D_2O. Column chromatography on silica gel (4:1 DCM–Et_2O) afforded **8** (0.60 g, 60%, 98% *d*). The characteristics of this product were found to be identical to those described for **7** except for ^{1}H and ^{13}C NMR spectra where the 3-H and 3-C signals respectively had disappeared.

***N*-Phenyl-3-[hydroxy(phenyl)methyl]pyridine-2-carboxamide 9.** Compound **9** was obtained from **7** using Bu_2Mg and then trapping with PhCHO. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **9** (0.88 g, 58%) as a white powder; mp 96–97 °C (Found: C, 75.2; H, 5.2; N, 9.4. $C_{19}H_{16}N_2O_2$ requires: C, 75.0; H, 5.3; N, 9.2%); ν_{max}/cm^{-1} (KBr) 3335, 2956, 2924, 2853, 1671, 1458, 1260; δ_H 10.3 (1 H, s, NH), 8.49 (1 H, m, 6-H), 7.68 (5 H, m, Ph), 7.56 (1 H, m, 4-H), 7.32 (5 H, m, Ph), 7.11 (1 H, m, 5-H), 6.45 (1 H, s, OH), 5.73 (1 H, s, C*H*(OH)Ph); δ_C 164.4 (CO), 147.4 (2-C), 147.0 (6-C), 142.2 (3-C), 142.1 (1″-C), 139.2 (4-C), 137.6 (1′-C), 129.4 (3′-C and 5′-C), 128.7 (3″-C and 5″-C), 127.7 (4″-C), 127.2 (2″-C and 6″-C), 125.1 (5-C), 120.5 (4′-C), 120.6 (2′-C and 6′-C), 72.9 (*C*H(OH)Ph).

***N*-Phenyl-3-(α-hydroxy-β-methylpropyl)pyridine-2-carboxamide 10.** Compound **10** was obtained from **7** using Bu_2Mg and then trapping with Pr^{i}CHO. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **10** (0.20 g, 15%) as a yellow powder; mp 78–79 °C (Found: C, 70.9; H, 6.6; N, 10.7. $C_{16}H_{18}N_2O_2$ requires: C, 71.1; H, 6.7; N, 10.4%); ν_{max}/cm^{-1} (KBr) 3448, 2966, 1729, 1469, 1387, 1262, 1160; δ_H 9.00 (1 H, s, NH), 8.41 (1 H, m, 6-H), 7.64 (1 H, m, 4-H), 7.37 (5 H, m, Ph), 7.15 (1 H, m, 5-H), 5.90 (1 H, s, OH), 4.32 (1 H, m, C*H*(OH)Pr^i), 1.86 (1 H, m, C*H*Me$_2$), 1.14 (6 H, d, *J* 6.5, CH*Me*$_2$); δ_C 165.1 (CO), 147.0 (2-C), 146.0 (6-C), 141.1 (3-C), 138.9 (4-C), 134.5 (1′-C), 128.5 (3′-C and 5′-C), 126.3 (5-C), 124.3 (4′-C), 120.5 (2′-C and 6′-C), 72.0 (*C*H(OH)Pr^i), 32.0 (*C*HMe$_2$), 15.2 (CH*Me*$_2$).

***N*-Phenyl-3-(methylthio)pyridine-2-carboxamide 11.** Compound **11** was obtained from **7** using Bu_2Mg and then trapping with dimethyl disulfide. Column chromatography on silica gel (9:1 petrol-Et_2O) afforded **11** (0.27 g, 22%) as a yellow powder; mp 96–98 °C (Found: C, 63.8; H, 4.9; N, 11.4; S, 13.0. $C_{13}H_{12}N_2OS$ requires: C, 63.9; H, 4.95; N, 11.5; S, 13.1%); ν_{max}/cm^{-1} (KBr) 3328, 3046, 2916, 1681, 1679, 1529, 1441; δ_H 10.1 (1 H, s, NH), 8.30 (1 H, d, *J* 4.7, 6-H), 7.4 (7 H, m, 4-H, 5-H and Ph), 2.36 (3 H, s, Me); δ_C 165.7 (CO), 147.2 (2-C), 142.6 (6-C), 135.0 (3-C), 133.2 (4-C), 132.9 (1′-C), 129.3 (3′-C and 5′-C), 126.3 (4′-C), 124.7 (5-C), 119.9 (2′-C and 6′-C), 15.3 (Me).

***N*-(*tert*-Butyl)-4-isopropylpyridine-3-carboxamide 13.** Compound **13** was obtained from **12** using Pr^{i}MgCl. Column chromatography on silica gel (7:3 DCM–Et_2O) afforded **13** (0.77 g, 70%) as a white powder; mp 112–113 °C (Found: C, 70.6; H, 9.4; N, 12.8. $C_{13}H_{20}N_2O$ requires: C, 70.9; H, 9.15; N, 12.7%); ν_{max}/cm^{-1} (KBr) 3264, 2972, 1633, 1364, 1328, 1224; δ_H 8.41 (1 H, d, *J* 4.7, 6-H), 8.36 (1 H, s, 2-H), 7.15 (1 H, d, *J* 4.7, 5-H), 5.79 (1 H, s, NH), 3.30 (1 H, m, C*H*Me$_2$), 1.40 (9 H, s, Bu^t), 1.18 (6 H, d, *J* 6.6, CH*Me*$_2$); δ_C 165.3 (CO), 156.1 (4-C), 151.0 (6-C), 149.0 (2-C), 130.2 (3-C), 121.4 (5-C), 52.6 (*C*Me$_3$), 29.9 (*C*HMe$_2$), 29.2 (C*Me*$_3$), 23.6 (CH*Me*$_2$).

***N*-(*tert*-Butyl)-4-butylpyridine-3-carboxamide 14.** Compound **14** was obtained from **12** using Bu_2Mg. Column chromatography on silica gel (7:3 DCM–Et_2O) afforded **14** (0.60 g, 51%) as a pale yellow oil (Found: C, 71.5; H, 9.8; N, 11.7. $C_{14}H_{22}N_2O$ requires: C, 71.8; H, 9.5; N, 11.95%); ν_{max}/cm^{-1} (KBr) 3358, 2982, 2962, 1639, 1462, 1313; δ_H 8.48 (1 H, s, 2-H), 8.46 (1 H, d, *J* 4.8, 6-H), 7.20 (1 H, d, *J* 4.8, 5-H), 5.69 (1 H, s, NH), 3.08 (2 H, m, C*H*$_2$CH$_2$CH$_2$Me), 1.6 (4 H, m, CH$_2$C*H*$_2$-C*H*$_2$Me), 1.45 (9 H, s, Bu^t), 1.21 (3 H, t, *J* 7.8, CH$_2$CH$_2$-CH$_2$*Me*); δ_C 166.3 (CO), 154.3 (6-C), 148.6 (2-C), 145.6 (4-C), 132.9 (3-C), 123.8 (5-C), 51.5 (*C*Me$_3$), 35.6 (*C*H$_2$CH$_2$CH$_2$Me), 30.5 (CH$_2$*C*H$_2$CH$_2$Me), 27.9 (C*Me*$_3$), 20.7 (CH$_2$CH$_2$*C*H$_2$Me), 12.8 (CH$_2$CH$_2$CH$_2$*Me*).

***N*-(*tert*-Butyl)-2-butylpyridine-4-carboxamide 16.** Compound **16** was obtained from **15** using Bu_2Mg. Column chromatography on silica gel (1:1 DCM–Et_2O) afforded **16** (0.70 g, 60%) as a colorless viscous oil (Found: C, 72.1; H, 9.3; N, 11.6. $C_{14}H_{22}N_2O$ requires: C, 71.8; H, 9.5; N, 11.95%); ν_{max}/cm^{-1} (KBr) 3284, 2978, 2962, 1639, 1546, 1461, 1319; δ_H 8.51 (1 H, d, *J* 4.5, 6-H), 7.38 (1 H, d, *J* 0.6, 3-H), 6.11 (1 H, s, NH), 7.26 (1 H, dd, *J* 4.5 and 0.6, 5-H), 2.66 (2 H, m, C*H*$_2$CH$_2$CH$_2$Me), 1.5 (4 H, m, CH$_2$C*H*$_2$C*H*$_2$Me), 1.26 (9 H, s, Bu^t), 0.88 (3 H, t, *J* 7.5, CH$_2$CH$_2$CH$_2$*Me*); *m*/*z* (CI) 235 (100%, M + H$^+$).

***N*-(*tert*-Butyl)-3-deuteriopyridine-4-carboxamide 17a.** Compound **17a** was obtained from **15** using Bu_2Mg and then trapping with D_2O. Column chromatography on silica gel (4:1 DCM–Et_2O) afforded **17a** (0.20 g, 23%, 83% *d*). The characteristics of this product were found to be identical to those described for **15** except for ^{1}H and ^{13}C NMR spectra where the 3-H and 3-C signals respectively had disappeared.

***N*-(*tert*-Butyl)-3-iodopyridine-4-carboxamide 17b.** Compound **17b** was obtained from **15** using Bu_2Mg and then trapping with I_2. Column chromatography on silica gel (7:3 DCM–Et_2O) afforded **17b** (0.33 g, 22%) as a white powder; mp 161–162 °C (Found: C, 39.5; H, 4.0; N, 9.3. $C_{10}H_{13}IN_2O$ requires: C, 39.5; H, 4.3; N, 9.2%); ν_{max}/cm^{-1} (KBr) 3224, 2966, 2930, 1649, 1458, 1365, 1341, 1227; δ_H 8.86 (1 H, s, 2-H), 8.48 (1 H, d, *J* 4.9, 6-H), 7.23 (1 H, d, *J* 4.9, 5-H), 5.63 (1 H, s, NH), 1.42 (9 H, s, Bu^t); δ_C 166.7 (CO), 159.5 (2-C), 150.8 (6-C), 149.5 (4-C), 123.2 (5-C), 99.7 (3-C), 52.6 (*C*Me$_3$), 29.1 (C*Me*$_3$).

2,2-Dimethyl-*N*-(3-deuterio-2-pyridyl)propanamide 19.[13] Compound **19** was obtained from **18** using Bu_2Mg and then trapping with D_2O. Column chromatography on silica gel (3:2 AcOEt–petrol) afforded **19** (0.87 g, 97%, 98% *d*). The characteristics of this product were found to be identical to those described for **18** except for ^{1}H and ^{13}C NMR spectra where the 3-H and 3-C signals respectively had disappeared.

2,2-Dimethyl-*N*-(3-(hydroxy(phenyl)methyl)-2-pyridyl)propanamide 20. Compound **20** was obtained from **18** using Bu_2Mg and then trapping with PhCHO. Column chromatography on silica gel (AcOEt) afforded **20** (0.64 g, 45%) as a white powder; mp 115–117 °C (lit.,[13] 114–117 °C); δ_C 167.3 (CO), 150.9 (2-C), 148.1 (6-C), 139.2 (1′-C), 137.7 (4-C), 133.1 (5-C), 132.2 (3-C), 127.7 (3′-C and 5′-C), 126.4 (2′-C and 6′-C), 125.6 (4′-C), 71.8 (*C*H(OH)Ph), 51.2 (*C*Me$_3$), 29.3 (C*Me*$_3$).

2,2-Dimethyl-*N*-(3-iodo-2-pyridyl)propanamide 21. Compound **21** was obtained from **18** using Bu_2Mg and then trapping with I_2. Column chromatography on silica gel (1:1 AcOEt–petrol) afforded **21** (1.0 g, 66%) as a white powder; mp 148–149 °C (lit.,[21] 148 °C); δ_C 177.0 (CO), 152.4 (2-C), 148.7 (6-C), 148.3 (4-C), 122.1 (5-C), 88.2 (3-C), 50.2 (*C*Me$_3$), 27.9 (C*Me*$_3$).

2,2-Dimethyl-*N*-(4-isopropyl-3-pyridyl)propanamide 23. Compound **23** was obtained from **22** using Pr^{i}MgCl. Column chromatography on silica gel (4:1 AcOEt–petrol) afforded **23** (0.75 g, 68%) as a white powder; mp 104–105 °C (Found: C, 70.6; H, 9.4; N, 12.4. $C_{13}H_{20}N_2O$ requires: C, 70.9; H, 9.15;

N, 12.7%); ν_{max}/cm^{-1} (KBr) 3318, 2965, 2871, 1649, 1510, 1408; δ_H 8.58 (1 H, s, 2-H), 8.27 (1 H, d, *J* 4.7, 6-H), 7.86 (1 H, s, NH), 7.15 (1 H, d, *J* 4.7, 5-H), 2.97 (1 H, m, C*H*Me$_2$), 1.22 (9 H, s, Bu^t), 1.10 (6 H, d, *J* 6.6, CH*Me*$_2$); δ_C 176.9 (CO), 144.9 (6-C), 142.7 (2-C), 136.8 (4-C), 127.9 (3-C), 123.1 (5-C), 39.6 (*C*Me$_3$), 31.3 (*C*HMe$_2$), 28.4 (C*Me*$_3$), 26.2 (CH*Me*$_2$).

2,2-Dimethyl-*N*-(4-butyl-3-pyridyl)propanamide 24. Compound **24** was obtained from **22** using Bu_2Mg. Column chromatography on silica gel (1 : 1 AcOEt–petrol) afforded **24** (0.59 g, 50%) as a colorless oil (Found: C, 71.5; H, 9.8; N, 11.9. $C_{14}H_{22}N_2O$ requires: C, 71.8; H, 9.5; N, 11.95%); ν_{max}/cm^{-1} (KBr) 3172, 3046, 2896, 1680, 1476, 1365, 1164; δ_H 7.95 (1 H, s, 2-H), 7.89 (1 H, d, *J* 4.9, 6-H), 7.53 (1 H, s, NH), 6.88 (1 H, d, *J* 4.9, 5-H), 2.55 (2 H, m, C*H*$_2$CH$_2$CH$_2$Me), 2.44 (2 H, m, CH$_2$C*H*$_2$CH$_2$Me), 1.48 (2 H, m, CH$_2$CH$_2$C*H*$_2$Me), 1.18 (9 H, s, Bu^t), 1.04 (3 H, t, *J* 8.2, CH$_2$CH$_2$CH$_2$*Me*); *m*/*z* (CI) 235 (100%, M + H$^+$).

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