Electronic Supplementary Information

First C-3 Lithiation of 4-DMAP : A New Entry into Chemical Tuning of Acylation Catalysts

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General considerations.

All solvents were distilled and stored over sodium wire before use. 2-Dimethylaminoethanol was distilled over KOH under nitrogen and stored over molecular sieves. $TMSCH_2Li$ (FMC Lithium) was used as a 0.92 M solution in hexanes. All reagents were commercially available and used as such or purified if needed. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (TMS as internal standard) on a Bruker AC400 instrument at 200 and 50 MHz respectively. GC experiments were performed on a Shimadzu chromatograph (FID detection) through a 15m capillary HP1 column. EI mass spectra were recorded on a Trio1000 spectrometer.

General procedure for C-3 functionalisation of 1.

$TMSCH_2Li$ (6 mL of a 0.92M solution in hexane, 5.52 mmoles) was added dropwise to a solution of 2-dimethylaminoethanol (164 mg, 1.84 mmol) in hexane (6 mL) at 0 °C. After 30 min of stirring, a solution of **1** (225 mg, 1.84 mmol) in THF (12 mL) was then added dropwise. The solution was then stirred for 4 h at the same temperature and treated at –78 °C with a solution of the appropriate electrophile (2.02 mmoles) in THF (1 mL). The temperature was maintained at –78 °C for 1 hour and at 0 °C for 30 min. Hydrolysis was then performed at this temperature with water (10 mL). The reaction medium was then extracted twice with diethylether (25 mL), the organic layer was dried over $MgSO_4$ and evaporated under vacuum.

The crude product was first subjected to GC analysis and purified by chromatography on silica gel or distilled when necessary.

Products

Dimethyl-(3-methylsulfanyl-pyridin-4-yl)-amine (1a). Obtained by the general procedure using dimethyldisulfide as electrophile. Purification by column chromatography (AcOEt) gave **1a** (79%) as a colorless oil. δ_H 2.46 (s, 3H), 2.98 (s, 6H), 6.75 (d, *J* = 5.5 Hz, 1H), 8.23 (d, *J*=5.5 Hz, 1H), 8.32 (s, 1H). δ_C 16.6, 42.5, 111.9, 125.3, 147.5, 149.8, 157.8. EI m/z (%) 168 (M^+, 100), 153 (59), 138 (35), 137 (82), 119 (73), 92 (32), 82 (20), 51 (25).

(3-Bromo-pyridin-4-yl)-dimethyl-amine (1b).[1] Obtained by the general procedure using carbon tetrabromide as electrophile. Purification by column chromatography (AcOEt/hexane 90/10) gave **1b** (70%) as a pale yellow oil. δ_H 2.97 (s, 6H), 6.78 (d, *J* = 5.7 Hz, 1H), 8.26 (d, *J*=5.7 Hz, 1H), 8.50 (s, 1H). δ_C 42.6, 113.5, 113.8, 148.8, 153.4, 157.1.

(3-Iodo-pyridin-4-yl)-dimethyl-amine (1c). Obtained by the general procedure using iodine as electrophile. Purification by column chromatography (AcOEt) gave **1c** (65%) as an orange oil. δ_H 2.96 (s, 6H), 6.80 (d, *J* = 5.7 Hz, 1H), 8.31 (d, *J*=5.7 Hz, 1H), 8.76 (s, 1H). δ_C 43.3, 89.4, 114.5, 149.7, 159.2, 160.7. EI m/z (%) 248 (M^+, 85), 127 (11%), 121 (M^+-127, 100), 106 (22), 95 (19), 79 (24), 51 (10).

Dimethyl-(3-tributylstannyl-pyridin-4-yl)-amine (1d). Obtained by the general procedure using tributyltin chloride as electrophile. Kügelrhor distillation (140-150°C/ 8 mTorr) gave **1d** (74%) as a colorless oil. δ_H 0.91-1.72 (m, 27H), 2.83 (s, 6H), 6.71 (d, *J* = 5.7 Hz, 1H), 8.27 (d, *J*=5.7 Hz, 1H), 8.31 (s, 1H). δ_C 11.4, 14.2, 27.4, 29.3, 43.1, 111.5, 126.7, 150.11, 157.2, 165.4.

(4-Dimethylamino-pyridin-3-yl)-phenyl-methanol (1e). Obtained by the general procedure using benzaldehyde as electrophile. Purification by column chromatography (from AcOEt to Et_3N/AcOEt 1/99) gave **1e** as a white solid (68%). Mp = 139 °C. δ_H 2.74 (s, 6H), 5.38 (brs, 1H), 6.11 (s, 1H), 6.88 (d, *J* = 5.4 Hz, 1H), 7.25-7.39 (m, 5H), 8.20 (s, 1H), 8.25 (d, *J*=5.4 Hz, 1H). δ_C 44.4, 71.7, 114.1, 127.1, 127.8, 128.8, 131.9, 143.6, 149.5, 151.2, 158.9. EI m/z (%) 228 (M^+, 15), 213 (30), 195 (36), 135 (48), 107 (18), 79 (46), 77 (100), 51 (43).

[1] M.P. Groziak, L. M. Melcher, *Heterocycles*, 1987, **26**, 2905-2910.

4-Dimethylamino-pyridine-3-carbaldehyde (1f).[2] Obtained by the general procedure using piperidinecarboxaldehyde as electrophile. Purification by column chromatography (from AcOEt to Et_3N/AcOEt 10/90) gave **1f** (83%) as a yellow solid. Mp = 69-70 °C (lit.[2] 69 °C). δ_H 3.07 (s, 6H), 6.72 (d, *J* =6.0 Hz, 1H), 8.32 (d, *J*=6.0 Hz, 1H), 8.67 (s, 1H), 9.96 (s, 1H). δ_C 44.5, 109.7, 119.6, 152.6, 156.1, 157.2, 189.1.

(4-Dimethylamino-pyridin-3-yl)-phenyl-methanone (1g). Obtained by the general procedure using N,N-dimethylbenzamide as electrophile. Purification by column chromatography (from AcOEt to Et_3N/AcOEt 1/99) gave **1g** (70%) as a yellow solid. Mp = 101 °C. δ_H 2.89 (s, 6H), 6.73 (d, *J* = 5.9 Hz, 1H), 7.45-7.62 (m, 3H), 7.90 (d, *J* = 7.2 Hz , 2H), 8.30 (m, 2H). δ_C 42.2, 108.9, 120.7, 128.6, 130.1, 133.3, 137.5, 150.9, 151.7, 154.9, 195.8. EI m/z (%) 226 (M^+, 57), 209 (M^+-17, 100), 149 (48), 119 (35), 91 (43), 77 (49), 51 (29).

[2] F. Marsais, F. Trécourt, P. Bréant, G. Quéguiner, *J. Heterocycl. Chem.*, 1988, **25**, 81-87.