

Vilsmeier–Haack reaction of tertiary alcohols: formation of functionalised pyridines and naphthyridines

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Vilsmeier–Haack reaction of 2-arylpropan-2-ols proceeds with multiple iminoalkylations leading to the formation of conjugated iminium salts which on ammonium acetate-induced cyclisation afford 4-arylnicotinaldehydes in good yields. Tertiary alcohols derived from aliphatic or alicyclic ketones by the addition of methyl Grignard are converted into substituted pyridines and naphthyridines by the action of Vilsmeier's reagent in *N,N*-dimethylformamide followed by nucleophile-assisted cyclisation in the presence of ammonium acetate.

Introduction

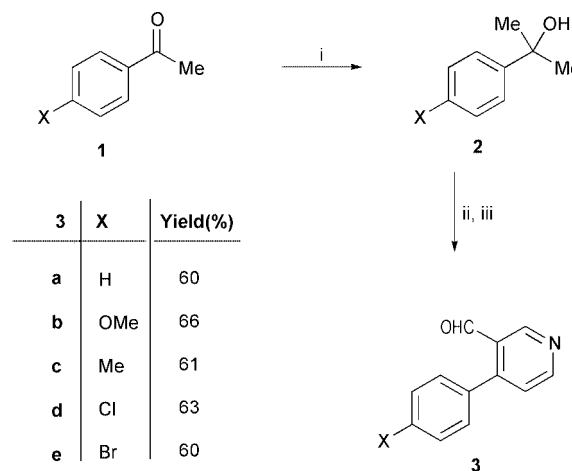
Pyridines are important among heterocyclic compounds and are present in several biological systems. They also find applications as agrochemicals and anticancer agents.¹ Extensive studies have been carried out on the synthesis of these valuable compounds owing to their importance as drugs and biologically active natural products.² The synthesis of pyridines with aldehyde functionality is particularly significant, considering the lack of reactivity of pyridines towards electrophilic substitution reactions.³ Moreover, the formyl group present on these molecules makes them promising precursors for further synthetic transformations. Surprisingly, the readily available tertiary alcohols have not been explored so far as starting materials for the synthesis of pyridines.

The Vilsmeier–Haack reaction is a convenient method for the formylation of activated aromatic and heteroaromatic compounds.⁴ Meth-Cohn and co-workers have extensively explored the usefulness of chloromethyleneiminium salts in the synthesis of heterocycles.⁵ Perumal and co-workers have reported some interesting cyclisation reactions under Vilsmeier conditions.⁶

Reactions of aliphatic alkenes with chloromethyleneiminium salts are often accompanied by multiple iminoalkylations leading to the formation of conjugated polyenaldehydes as end products. As early as 1966, Jutz *et al.* demonstrated that the intermediate iminium salts formed from 2-phenylpropene and isobutene can cyclise to substituted pyridine or naphthyridine, respectively, in the presence of ammonium acetate.⁷ We envisaged that the direct treatment of tertiary alcohols, readily available by the addition of methyl Grignard to ketones, with chloromethyleneiminium salts should lead to five-carbon units with terminal electrophilic centres. Treatment of such intermediates with ammonium acetate would provide an easy access to valuable functionalised pyridines. We have subjected the tertiary alcohols derived from alkyl aryl ketones such as substituted acetophenones to Vilsmeier conditions. The reactivity of tertiary alcohols derived from α,β -unsaturated ketones towards Vilsmeier reagents was also studied. In these cases, the corresponding 4-aryl- or -styryl-pyridinecarbaldehydes were obtained in good yields. Synthesis of functionalised 4-arylpyridines is of significant importance due to the prevalence of this moiety in alkaloids of biological importance such as streptonigrin and β -carboline.⁸ When the same reaction protocol was extended to tertiary alcohols derived from aliphatic ketones and alicyclic ketones, naphthyridine derivatives were obtained, though in relatively lower yields.

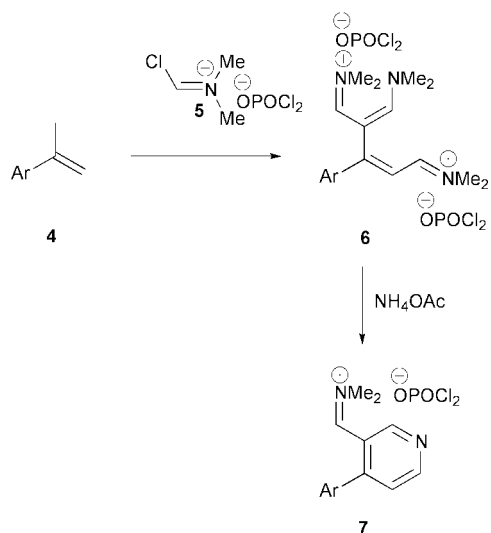
Results and discussion

2-Phenylpropan-2-ol **2a**, prepared by the addition of methyl Grignard to acetophenone **1a**, was treated with the chloromethyleneiminium salt derived from POCl₃ and DMF for two hours at 80 °C, using DMF as solvent. Excess of solid ammonium acetate (15 equiv.) was then added to the reaction mixture, which was again heated at 80 °C for two more hours. Subsequent treatment with saturated aq. potassium carbonate afforded 4-phenylnicotinaldehyde **3a**^{7,9} in 60% yield (Scheme 1). The reaction was extended to several 2-arylpropan-2-ols derived by the addition of methyl Grignard to substituted acetophenones **1b–e**. Thus the hitherto unreported 4-arylnicotinaldehydes **3b–e** were obtained in 60–66% overall yield. All 4-arylnicotinaldehydes **3** gave satisfactory spectral and analytical data.

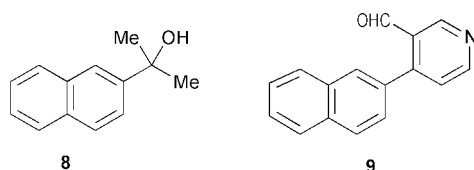


Scheme 1 Reagents and conditions: i, CH₃MgI, Et₂O; ii, POCl₃, DMF (4 equiv.), 80 °C, 2 h; iii, NH₄OAc, 80 °C, 2 h.

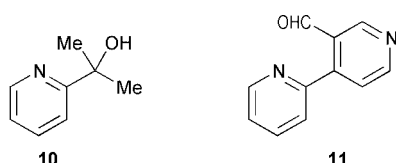
The mechanism for the formation of 4-arylpyridine-3-carbaldehydes⁷ from 2-arylpropan-2-ols can be rationalised as follows.⁷ Acid-catalysed dehydration of the alcohols **2** affords the intermediate 2-arylprop-2-ene **4** which adds sequentially to three moles of chloromethyleneiminium salt **5** to give the multiply iminoalkylated bis(iminium) salt **6**. This undergoes cyclisation in the presence of ammonium acetate to form the pyridyl iminium salt **7** which on subsequent hydrolysis affords 4-arylnicotinaldehyde **3** (Scheme 2).



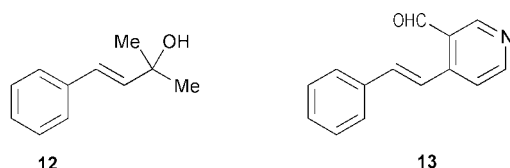
Similarly 2-(2-naphthyl)propan-2-ol **8** derived from 2-acetylnaphthalene reacts with chloromethyleneiminium salt followed by ammonium acetate to afford the corresponding 4-(2-naphthyl)nicotinaldehyde **9** in 43% yield.



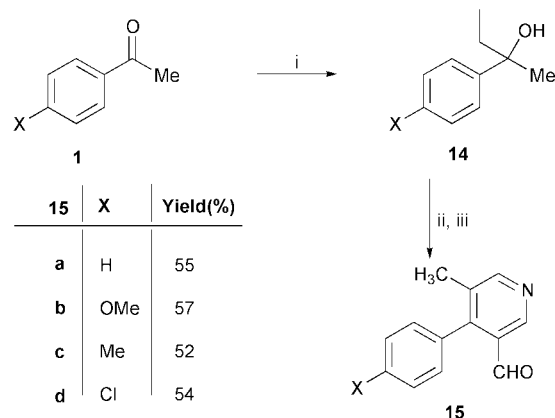
However, the reaction of 2-(2-pyridyl)propan-2-ol **10** with chloromethyleneiminium salt followed by treatment with ammonium acetate gave a rather complex product mixture under these conditions from which 4-(2-pyridyl)pyridine-3-carbaldehyde **11** could not be isolated.



We next examined the reactivity of 2-methyl-4-phenylbut-3-en-2-ol **12**, derived from benzalacetone, with Vilsmeier–Haack reagent. The carbinol was treated with four equivalents of Vilsmeier reagent and the product mixture was subjected to cyclisation under similar conditions to afford a pale yellow solid, having mp 66–67 °C, in 51% yield, which was identified as 4-styrylnicotinaldehyde **13**.

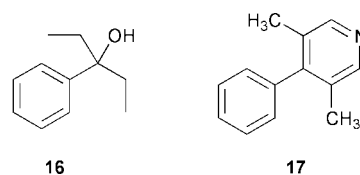


The reactivity of 2-arylbutan-2-ols with chloromethyleneiminium salt was also studied to further explore the generality of this procedure. When 2-phenylbutan-2-ol **14a** was treated with Vilsmeier reagent prepared from POCl₃ and DMF at 80 °C followed by treatment with NH₄OAc, 5-methyl-4-phenyl-nicotinaldehyde **15a** was obtained in 55% yield (Scheme 3). Similarly the other 2-arylbutan-2-ols **14b–d** afforded the substituted nicotinaldehydes **15b–d**.



Scheme 3 Reagents and conditions: i, C₂H₅MgI, Et₂O; ii, POCl₃, DMF (4 equiv.), 80 °C, 2 h; iii, NH₄OAc, 80 °C, 2 h.

However the reaction 3-phenylpentan-3-ol **16** with chloromethyleneiminium salt followed by subsequent reaction with Vilsmeier reagent and ammonium acetate did not give the expected 3,5-dimethyl-4-phenylpyridine **17** under our conditions.

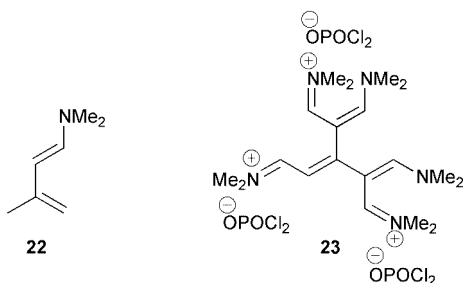


Jutz *et al.* have reported that the reaction of 2-methylpropene with excess of chloromethyleneiminium salt proceeds with multiple iminoalkylations and that cyclisation of the iminoalkylated intermediate induced by ammonium acetate leads to the formation of [2,7]naphthyridine-4-carbaldehyde.⁷ Isoolefins are known to undergo stepwise acetylations under Friedel–Crafts conditions followed by treatment with liquid ammonia to afford, *e.g.*, 1,3,6,8-tetramethyl[2,7]naphthyridine along with 2,4,6-trimethylpyridine.¹⁰ Nevertheless, these methodologies have not been further explored for the synthesis of naphthyridines. We have examined the reactions of aliphatic tertiary alcohols directly with chloromethyleneiminium salt and the subsequent cyclisation of the intermediates in the presence of ammonium acetate. Considering the prevalence of the [2,7]-naphthyridine moiety in biologically active marine natural alkaloids,¹¹ the transformation of simple tertiary alcohols into naphthyridine derivatives is valuable. Our survey of the literature revealed that the chemistry of [2,7]naphthyridine derivatives has been little explored, partly due to the difficult and multistep synthesis of these compounds.^{12,13} We envisaged that the reaction of tertiary alcohols with chloromethyleneiminium salts would lead to the formation of the corresponding alkene, which upon sequential multiple iminoalkylation followed by ammonium acetate-mediated cyclisation should afford substituted naphthyridines.

tert-Butyl alcohol **18** was treated with six equivalents of Vilsmeier reagent at room temperature for 15 hours, cooled to 0 °C, treated with solid ammonium acetate in excess (15 equiv.) and the mixture again stirred at 0 °C for 1 more hour. The reaction mixture after usual work-up and purification by chromatography afforded [2,7]naphthyridine-4-carbaldehyde **20**^{7,14} in 18% yield.

Formation of 2-methylpropene from *tert*-butyl alcohol by the elimination of water followed by iminoalkylation and loss of





HCl would afford the *N,N*-dimethylamino-substituted diene **22**. Further sequential iminoalkylations involving four equivalents of chloromethyleneiminium salt would finally lead to the tris(iminium) salt **23**, which on treatment with ammonium acetate followed by aqueous basic work-up would afford the [2,7]-naphthyridine-4-carbaldehyde **20**.⁷ Similarly, the reaction of 2-methylbutan-2-ol **19** with Vilsmeier reagent prepared from POCl₃ and DMF, followed by treatment with ammonium acetate, gave 5-methyl[2,7]naphthyridine-4-carbaldehyde **21** in 11% yield. 1-Methylcyclohexanol **24** under similar conditions gave 8,9-dihydro-7*H*-benzo[*de*][2,7]naphthyridine **25** in 8% yield.



In summary we have examined the reactions of a variety of tertiary alcohols with a chloromethyleneiminium salt. These studies reveal that the multiply iminoalkylated intermediates derived from them could be cyclised using ammonium acetate to afford substituted pyridines and naphthyridines having functional groups for further synthetic transformations.

Experimental

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were recorded in deuteriochloroform (internal standard TMS) on JEOL EX90, Bruker WM200 or Bruker WM300 spectrometers; ¹H spectra at 90, 200 or 300 MHz and ¹³C spectra at 22.4, 50.3 or 75.5 MHz, respectively, and coupling constants are given in Hz. Electron-impact mass spectra were obtained on a Finnigan-MAT 312 spectrometer. GCMS were obtained on a Hewlett Packard 5890 Series II GC connected to a 5890 mass-selective detector. Solvents were dried and distilled before use: *N,N*-dimethylformamide from P₂O₅; diethyl ether from Na. Organic extracts were dried over anhydrous Na₂SO₄.

Reactions of 2-arylpropan-2-ols **2**, **8** with Vilsmeier reagent followed by ammonium acetate: Synthesis of 4-arylnicotinaldehydes **3**, **9**

Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and POCl₃ (1.87 mL, 20 mmol). The mixture was then stirred for 15 minutes at room temperature. The 2-arylpropan-2-ol **2a–e** or **8** (5 mmol) obtained from the Grignard reaction was dissolved in dry DMF and added over about 15 minutes at 0–5 °C. The reaction mixture was stirred for 10 minutes at room temperature and heated to 80 °C for 2 hours with stirring. After the heating excess of solid ammonium acetate (15 equiv., 5.8 g) was added to the reaction mixture and heating was continued with stirring at 80 °C for two hours more. The mixture was then added to cold, saturated aq. K₂CO₃ (500 mL) and extracted with diethyl ether (3 × 50 mL). The organic layer was washed with water, dried over anhydrous Na₂SO₄, and evaporated to afford the crude product, which was chromatographed over

silica gel using hexane–ethyl acetate (8 : 2) as eluent to give the 4-arylnicotinaldehydes^{7,9} **3a–e**, **9**.

4-Phenylnicotinaldehyde 3a. Prepared by the reaction of 2-phenylpropan-2-ol **2a** (0.68 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a solid (0.54 g, 60%); mp 40–41 °C (lit.,⁹ 40–41 °C).

4-(4-Methoxyphenyl)nicotinaldehyde 3b. Prepared by the reaction of 2-(4-methoxyphenyl)propan-2-ol **2b** (0.83 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a pale brown solid (0.78 g, 66%); mp 82–83 °C (Found: C, 73.02; H, 5.06; N, 6.44. C₁₃H₁₁NO₂ requires C, 73.23; H, 5.20; N, 6.57%); ν_{\max} (KBr)/cm⁻¹ 2950, 2830, 1680, 1600, 1580, 1510, 1465 and 1380; δ_{H} (90 MHz) 3.90 (3H, s, OCH₃), 7.05 (2H, d, *J* 8, ArH), 7.30–7.50 (3H, m, ArH + Py 5-H), 8.75 (1H, d, *J* 6.5, 6-H), 9.10 (1H, s, 2-H), 10.10 (1H, s, CHO); δ_{C} (22.4 MHz) 54.71 (OCH₃), 113.81, 123.96, 126.46, 127.89, 130.46, 149.11, 150.99, 152.60, 160.15 (aromatic), 190.67 (C=O); *m/z* (GCMS) 213 (M⁺, 100%), 212 (22.4), 170 (37.8), 142 (19.4).

4-(4-Methylphenyl)nicotinaldehyde 3c. Prepared by the reaction of 2-(4-methylphenyl)propan-2-ol **2c** (0.75 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a brown liquid (0.6 g, 61%) (Found: C, 78.94; H, 5.51; N, 6.87. C₁₃H₁₁NO requires C, 79.17; H, 5.62; N, 7.10%); ν_{\max} (film)/cm⁻¹ 3025, 2850, 1690, 1590, 1540, 1510, 1470 and 1390; δ_{H} (90 MHz) 2.40 (3H, s, CH₃), 7.30 (4H, s, ArH), 7.36 (1H, d, *J* 6.5, 5-H), 8.75 (1H, d, *J* 6.5, 6-H), 9.12 (1H, s, 2-H), 10.10 (1H, s, CHO); δ_{C} (22.4 MHz) 21.00 (CH₃), 125.00, 127.50, 128.00, 129.00, 132.00, 140.00, 150.00, 152.00, 153.00 (aromatic), 191.50 (C=O); *m/z* (GCMS) 197 (M⁺, 87.8%), 182 (100), 168 (32.7), 154 (19.4), 115 (18.4).

4-(4-Chlorophenyl)nicotinaldehyde 3d. Prepared by the reaction of 2-(4-chlorophenyl)propan-2-ol **2d** (0.85 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a pale yellow solid (0.68 g, 63%) mp 75–76 °C (Found: C, 65.93; H, 3.59; N, 6.36. C₁₂H₈ClNO requires C, 66.22; H, 3.70; N, 6.44%); ν_{\max} (KBr)/cm⁻¹ 3050, 2875, 1690, 1580, 1470 and 1390; δ_{H} (90 MHz) 7.20–7.70 (5H, m, ArH + Py 5-H), 8.80 (1H, d, *J* 6.5, 6-H), 9.12 (1H, s, 2-H), 10.10 (1H, s, CHO); δ_{C} (22.4 MHz) 124.17, 127.87, 128.59, 130.38, 133.15, 135.24, 149.53, 150.13, 153.08 (aromatic), 190.13 (C=O); *m/z* (GCMS) 217 (M⁺, 100%), 182 (73.5), 154 (21.4), 126 (23.5).

4-(4-Bromophenyl)nicotinaldehyde 3e. Prepared by the reaction of 2-(4-bromophenyl)propan-2-ol **2e** (1.08 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a brown solid (0.79 g, 60%); mp 80–82 °C (Found: C, 54.58; H, 2.91; N, 5.21. C₁₂H₈BrNO requires C, 54.99; H, 3.08; N, 5.34%); ν_{\max} (KBr)/cm⁻¹ 2849, 1696, 1593, 1471 and 1392; δ_{H} (300 MHz) 7.20 (2H, d, *J* 8.5, ArH), 7.28 (1H, d, *J* 5.1, 5-H), 7.57 (2H, d, *J* 8.5, ArH), 8.71 (1H, d, *J* 5.1, 6-H), 9.02 (1H, s, 2-H), 9.96 (1H, s, CHO); δ_{C} (75.5 MHz) 124.56, 124.99, 128.76, 131.42, 132.52, 134.39, 150.54, 151.23, 153.99 (aromatic), 191.09 (C=O); *m/z* (EI) 265 (M⁺ + 2, 61.9%), 264 (M⁺ + 1, 55.8), 263 (M⁺, 73.2), 184 (24), 183 (100), 155 (49.9), 154 (37.9), 127 (62.1), 106 (30.3), 77 (37.9), 64 (31.8), 50 (22.7).

4-(2-Naphthyl)nicotinaldehyde 9. Prepared by the reaction of 2-(2-naphthyl)propan-2-ol **8** (0.93 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a yellow solid (0.51 g, 43%); mp 103–104 °C (Found: C, 81.92; H, 4.61; N, 5.88. C₁₆H₁₁NO requires C, 82.38; H, 4.75; N, 6.00%); ν_{\max} (KBr)/cm⁻¹ 3050, 2825, 1680, 1580, 1480 and 1380; δ_{H} (200 MHz) 7.34–7.59 (4H, m, ArH + Py 5-H), 7.83–7.99 (4H, m, ArH), 8.82 (1H, d, *J* 5.1, 6-H), 9.18 (1H, s, 2-H), 10.10

(1H, s, CHO); δ_{C} (50.3 MHz) 124.57, 126.21, 126.85, 127.05, 127.48, 127.96, 128.37, 128.44, 129.16, 132.04, 132.52, 132.90, 149.54, 151.72, 153.07 (aromatic), 190.88 (C=O); m/z (EI) 233 (M^+ , 84.3%), 232 (60.6), 205 (70.1), 204 (61.9), 177 (22.4), 176 (34.8), 152 (18.3), 151 (26), 40 (100).

Reaction of 2-methyl-4-phenylbut-3-en-2-ol 12 with Vilsmeier reagent followed by ammonium acetate: Synthesis of 4-(phenylvinyl)nicotinaldehyde 13

Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and POCl_3 (1.87 mL, 20 mmol). The mixture was then stirred for 15 minutes at room temperature. 2-Methyl-4-phenylbut-3-en-2-ol **12** (5 mmol) obtained from the Grignard reaction was dissolved in dry DMF and was added during about 15 minutes at 0–5 °C. The reaction mixture was stirred for 10 minutes at room temperature and heated to 80 °C for 2 hours with stirring. After the heating, excess of solid ammonium acetate (15 equiv., 5.8 g) was added to the reaction mixture and heating at 80 °C with stirring was continued for two hours more. The mixture was then added to cold, saturated aq. K_2CO_3 (500 mL) and extracted with diethyl ether (3 \times 50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 , and evaporated to afford the crude product, which was chromatographed over silica gel, using hexane–ethyl acetate (8 : 2) as eluent, to give 4-(phenylvinyl)nicotinaldehyde **13** as a pale yellow solid (0.52 g, 51%); mp 66–67 °C (Found: C, 80.03; H, 5.19; N, 6.57. $\text{C}_{14}\text{H}_{11}\text{NO}$ requires C, 80.36; H, 5.30; N, 6.69%); ν_{max} (KBr)/ cm^{-1} 1680, 1620, 1590, 1490, 1440, 1410, 1310, 1230 and 1190; δ_{H} (90 MHz) 7.20–7.80 (7H, m, ArH + Py 5-H + vinylic H), 8.15 (1H, d, J 16, vinylic H), 8.75 (1H, d, J 5.1, 6-H), 8.95 (1H, s, 2-H), 10.30 (1H, s, CHO); δ_{C} (22.4 MHz) 119.87, 122.05, 127.12, 127.30, 128.67, 129.12, 135.66, 137.03, 145.98, 153.14, 154.89 (aromatic and vinylic), 191.59 (C=O); m/z (EI) 208 (M^+ , 100%), 207 (45.4), 180 (19.4), 179 (84), 152 (21.1), 151 (39.6), 105 (18.2).

Reactions of 2-arylbutan-2-ols 14 with Vilsmeier reagent followed by ammonium acetate: Synthesis of 4-aryl-5-methylnicotinaldehydes 15

Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and POCl_3 (1.87 mL, 20 mmol). The mixture was then stirred for 15 minutes at room temperature. A carbinol **14a–d** (5 mmol) obtained from the Grignard reaction was dissolved in dry DMF and added during about 15 minutes at 0–5 °C. The reaction mixture was stirred for 10 minutes at room temperature and heated to 80 °C for 2 hours with stirring. Solid ammonium acetate was added to the reaction mixture in excess (15 equiv., 5.8 g) and the mixture was further heated at 80 °C for 2 more hours before being added to cold, saturated aq. K_2CO_3 (300 mL) and extracted with diethyl ether (3 \times 50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 , and evaporated to give the crude product, which was chromatographed using hexane–ethyl acetate (8 : 2) as eluent to give the corresponding 4-aryl-5-methylnicotinaldehyde **15a–d**.

5-Methyl-4-phenylnicotinaldehyde 15a. Prepared by the reaction of 2-phenylbutan-2-ol **14a** (0.76 g, 5 mmol), with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a pale brown solid (0.54 g, 55%); mp 65–66 °C (Found: C, 78.84; H, 5.51; N, 6.87. $\text{C}_{13}\text{H}_{11}\text{NO}$ requires C, 79.17; H, 5.62; N, 7.10%); ν_{max} (KBr)/ cm^{-1} 3050, 2850, 1680, 1575, 1435, 1380 and 1260; δ_{H} (200 MHz) 2.17 (3H, s, CH_3), 7.22–7.31 (2H, m, ArH), 7.45–7.60 (3H, m, ArH), 8.68 (1H, s, 6-H), 8.98 (1H, s, 2-H), 9.79 (1H, s, CHO); δ_{C} (50.3 MHz) 17.08 (CH_3), 129.09, 129.36, 132.38, 134.21, 147.30, 152.06, 155.08 (aromatic), 191.85 (C=O); m/z (EI) 197 (M^+ , 100%), 196 (98.9), 168 (50.5), 167 (45), 139 (27.3), 115 (59.6).

4-(4-Methoxyphenyl)-5-methylnicotinaldehyde 15b. Prepared by the reaction of 2-(4-methoxyphenyl)butan-2-ol **14b** (0.9 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a brown liquid (0.65 g, 56.5%) (Found: C, 73.61; H, 5.63; N, 5.93. $\text{C}_{14}\text{H}_{13}\text{NO}_2$ requires C, 73.99; H, 5.77; N, 6.16%); ν_{max} (film)/ cm^{-1} 2950, 2850, 1690, 1600, 1570, 1510, 1460 and 1390; δ_{H} (90 MHz) 2.30 (3H, s, PyCH_3), 4.00 (3H, s, OCH_3), 7.10–7.40 (4H, m, ArH), 8.85 (1H, s, 6-H), 9.15 (1H, s, 2-H), 10.50 (1H, s, CHO); δ_{C} (75.5 MHz) 16.20 (CH_3), 55.32 (OCH_3), 115.63, 131.94, 131.96, 139.73, 140.18, 144.67, 148.53, 154.06, 156.74 (aromatic), 195.16 (C=O); m/z (EI) 227 (M^+ , 100), 212 (18.3), 184 (58.1), 168 (19.8), 156 (25.1), 154 (19.5), 128 (26).

5-Methyl-4-(4-methylphenyl)nicotinaldehyde 15c. Prepared by the reaction of 2-(4-methylphenyl)butan-2-ol **14c** (0.82 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a brown liquid (0.55 g, 52%) (Found: C, 79.17; H, 5.93; N, 6.52. $\text{C}_{14}\text{H}_{13}\text{NO}$ requires C, 79.59; H, 6.20; N, 6.63%); ν_{max} (film)/ cm^{-1} 1692, 1581, 1463, 1387, 1268 and 1157; δ_{H} (300 MHz) 2.05 (3H, s, $\text{C}_6\text{H}_4\text{CH}_3$), 2.32 (3H, s, PyCH_3), 7.01 (2H, d, J 7.7, ArH), 7.20 (2H, d, J 7.7, ArH), 8.53 (1H, s, 6-H), 8.83 (1H, s, 2-H), 9.67 (1H, s, CHO); δ_{C} (75.5 MHz) 15.74 (PyCH_3), 20.23 (CH_3), 127.84, 127.95, 128.38, 129.66, 131.25, 137.71, 145.77, 151.02, 153.43 (aromatic), 190.67 (C=O); m/z (EI) 211 (M^+ , 100%), 210 (68.5), 196 (77.5), 182 (24.6), 168 (46.1), 167 (39.1), 139 (18).

4-(4-Chlorophenyl)-5-methylnicotinaldehyde 15d. Prepared by the reaction of 2-(4-chlorophenyl)butan-2-ol **14d** (0.92 g, 5 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a pale brown solid (0.62 g, 54%); mp 78–79 °C (Found: C, 67.03; H, 4.26; N, 5.84. $\text{C}_{13}\text{H}_{10}\text{ClNO}$ requires C, 67.40; H, 4.35; N, 6.05%); ν_{max} (KBr)/ cm^{-1} 1690, 1494, 1391, 1265 and 1092; δ_{H} (300 MHz) 2.31 (3H, s, PyCH_3), 7.01 (2H, d, J 7.9, ArH), 7.11 (2H, d, J 7.9, ArH), 8.53 (1H, s, 6-H), 8.83 (1H, s, 2-H), 9.58 (1H, s, CHO); δ_{C} (75.5 MHz) 17.15 (PyCH_3), 129.03, 129.51, 130.69, 132.55, 132.68, 135.49, 147.71, 150.89, 155.15 (aromatic), 191.45 (C=O); m/z (EI) 233 (M^+ + 2, 32%), 232 (M^+ + 1, 33.4), 231 (M^+ , 100), 230 (56.4), 196 (70.9), 192 (24.6), 168 (33.2), 167 (47), 140 (17.7), 139 (33.3), 119 (42.4).

Reactions of aliphatic and alicyclic tertiary alcohols 18, 19 and 24 with Vilsmeier reagent followed by ammonium acetate: Synthesis of substituted [2,7]naphthyridines 20, 21 and 25

Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and POCl_3 (11.2 mL, 120 mmol). The mixture was then stirred for 15 minutes at room temperature. The tertiary alcohol (20 mmol) was dissolved in dry DMF and added during about 15 minutes at 0–5 °C. The reaction mixture was stirred for 15 hours at room temperature and cooled in ice, solid ammonium acetate was added to the reaction mixture in excess (15 equiv., 23 g), and the mixture was again stirred for 2 hours more before being added to cold, saturated aq. K_2CO_3 (500 mL) and extracted with diethyl ether (3 \times 50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 , and evaporated to give the crude product, which was chromatographed using hexane–ethyl acetate (4 : 6) as eluent to give the substituted [2,7]naphthyridine.

[2,7]Naphthyridine-4-carbaldehyde 20. Prepared by the reaction of *tert*-butyl alcohol **18** (1.47 g, 20 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a white crystalline solid (0.57 g, 18%); mp 215–216 °C (lit.¹⁴ 215–216 °C); ν_{max} (KBr)/ cm^{-1} 3356, 2850, 1695, 1626, 1585, 1555, 1497, 1433, 1381, 1355, 1309, 1253, 1215, 1192, 1115, 1082, 1033, 943, 900, 840, 711, 789, 740 and 676 (ref. 7); δ_{H} (300 MHz) 7.28 (1H, d, J 5.6, 5-H), 8.96 (1H, d, J 5.6, 6-H), 9.17 (1H, s, 8-H), 9.54 (1H, s, 1-H), 9.60 (1H, s, 3-H), 10.42 (1H, s,

CHO); δ_{C} (75.5 MHz) 117.22, 123.34, 123.93, 135.61, 150.32, 153.23, 155.56, 158.51 (aromatic), 191.81 (C=O); m/z (EI) 158 (M^+ , 100%), 157 (45.5), 129 (73.7), 103 (25.3), 75 (22.2).

5-Methyl[2,7]naphthyridine-4-carbaldehyde 21. Prepared by the reaction of 2-methylbutan-2-ol **19** (1.76 g, 20 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a pale yellow solid (0.376 g, 11%); mp 181–182 °C (Found: C, 69.42; H, 4.57; N, 16.21. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}$ requires C, 69.76; H, 4.68; N, 16.27%); ν_{max} (KBr)/ cm^{-1} 2962, 1683, 1601, 1261, 1097 and 1023; δ_{H} (300 MHz) 2.72 (3H, s, CH_3), 8.65 (1H, s, 6-H), 9.05 (1H, s, 8-H), 9.28 (1H, s, 1-H), 9.46 (1H, s, 3-H), 10.86 (1H, s, CHO); δ_{C} (75.5 MHz) 21.69 (CH_3), 118.90, 123.38, 126.07, 127.66, 150.02, 150.46, 152.12, 158.28 (aromatic), 191.29 (C=O); m/z (EI) 172 (M^+ , 100%), 171 (56), 155 (72.9), 149 (30), 144 (61.4), 143 (44.8).

8,9-Dihydro-7H-benzo[de][2,7]naphthyridine 25. Prepared by the reaction of 1-methylcyclohexanol **24** (2.28 g, 20 mmol) with Vilsmeier reagent, and subsequent treatment with ammonium acetate, as a reddish brown semi-solid (0.268 g, 8%) (Found: C, 77.16; H, 5.81; N, 16.33. $\text{C}_{11}\text{H}_{10}\text{N}_2$ requires C, 77.62; H, 5.92; N, 16.46%); ν_{max} (film)/ cm^{-1} 2932, 1612, 1545, 1432, 1382, 1270 and 1119; δ_{H} (300 MHz) 2.05 (2H, quintet, J 6.2, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.99 (4H, t, J 6.2, $\text{CH}_2\text{CH}_2\text{CH}_2$), 8.44 (2H, s, 3-H and 6-H), 9.17 (2H, s, 1-H and 8-H); δ_{C} (75.5 MHz) 21.28 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 25.59 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 121.63 (C-8a), 127.59 (C-4 and C-5), 134.75 (C-4a), 142.89 (C-3 and C-6), 149.09 (C-1 and C-8); m/z (EI) 171 ($\text{M}^+ + 1$, 91.3%), 170 (M^+ , 100), 169 (25.5), 84 (22.4), 73 (49.3).

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