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Stereoselective functionalisation of pinopyridine with anisidines and *o*-phenylenediamine

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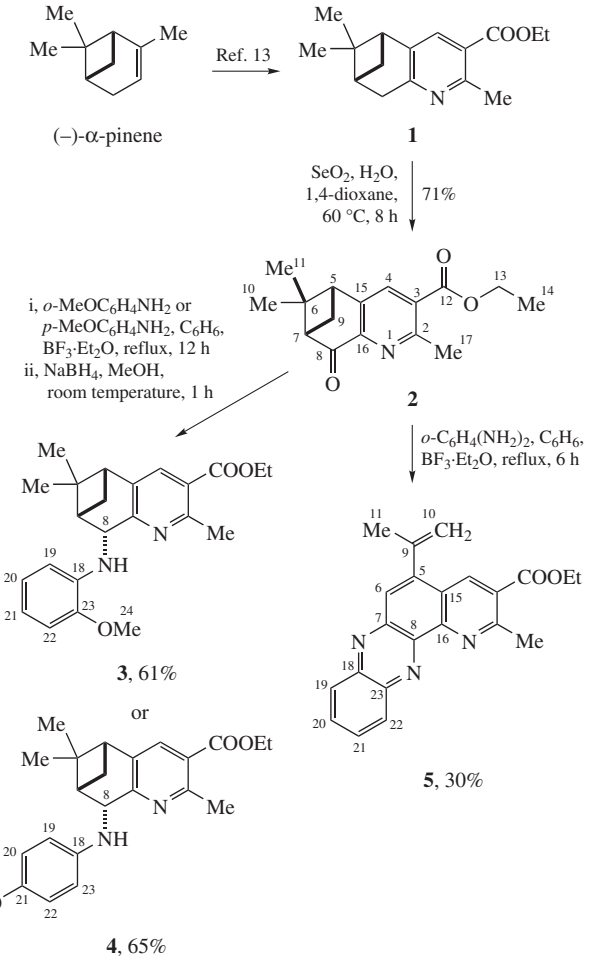
Benzylic oxidation of pinopyridine with SeO_2 affords the corresponding keto derivative (71% yield) whose reductive amination with *o*- and *p*-anisidines proceeds stereoselectively to give 8*R*-amino derivatives; the reaction with *o*-phenylenediamine results in achiral pyridophenazine derivative possessing intense blue fluorescence at 441 nm. Structures of *o*-anisidine derivative and substituted pyridophenazine have been characterized by X-ray crystallography.

Chiral pyridines are of special interest as ligands for synthesis of coordination compounds[1] used as chiral catalysts in many organic reactions,[2] *e.g.*, preparation of cyclopropanes *via* diaza compounds,[3] allylic oxidation or substitution,[4] the Heck reaction[5] and dialkylzinc addition.[6] Chiral pyridines are studied in supramolecular chemistry,[7] molecular recognition processes[8] and chemistry of three-dimensional structures prepared by bidirectional association;[9] and they are explored as components of self-assembled systems,[10] building blocks for chiral polymers,[11] as well as biologically active compounds.[12]

Pinopyridine **1** is available in optically active form as product of simple transformation of natural α-pinene.[13] Herein, we report on additional stereoselective functionalisation of the pinane moiety of pinopyridine and formation of unusual pyridophenazine derivative.

Pinopyridine **1** was prepared from (–)-α-pinene according to published procedure.[13] Benzylic oxidation of compound **1** with SeO_2 afforded keto derivative **2**.† Reductive amination of ketone **2** with *o*- and *p*-anisidines proceeds smoothly‡ to form stereoselectively secondary amines **3**§ and **4**¶ (Scheme 1) as a result of reduction of the primary Shiff bases. Analysis of high-field 2D ^{1}H–^{1}H and ^{13}C–^{1}H-correlation NMR spectra of products **3** and **4** showed both derivatives to belong to the same configuration series as concerns that of the C(8) atom. The stereochemistry of the compounds synthesized was determined by X-ray analysis of *o*-anisidine derivative **3** (Figure 1).†† Secondary amines **3** and **4** are formed in highly stereoselective manner: no C(8)-epimers



Scheme 1 (The numbering scheme is given for NMR interpretation only.)

† *Ethyl (5*R*,7*S*)-8-oxo-2,6,6-trimethyl-5,6,7,8-tetrahydro-5,7-methanoquinoline-3-carboxylate* **2**. Selenium dioxide (1.03 g, 9.31 mmol) and water (0.33 g) were added to 1,4-dioxane (55 ml) and the mixture was stirred for 30 min at 60 °C, then pinopyridine **1** (2.0 g, 7.7 mmol) was added and the mixture was refluxed for 5 h. A new portion of SeO_2 (0.309 g, 2.78 mmol) was added and the mixture was refluxed for additional 3 h. The solvent was distilled off *in vacuo*, the residue was treated with EtOAc (50 ml), the resulting solution was washed subsequently with saturated aqueous $NaHCO_3$ (50 ml) and brine (90 ml). The combined aqueous washings were back-extracted with EtOAc (3×25 ml), the combined organic extract was dried over Na_2SO_4, filtered and concentrated at reduced pressure to leave the crude product which was then purified by column chromatography (SiO_2, hexane–EtOAc, 9:1→4:1) to afford ketone **2** as a pale pink solid (1.5 g, 71%), mp 149–151 °C, $[\alpha]_D^{23}$ –166 (*c* 2.1, $CHCl_3$). IR (*c* 0.75% in KBr, ν_{max}/cm^{-1}): 1724, 1705, 1255. ^{1}H NMR (500 MHz, CCl_4–$CDCl_3$) δ: 0.77 (s, 3H, H^{10}), 1.40 (t, 3H, H^{14}, *J* 7.2 Hz), 1.59 (s, 3H, H^{11}), 2.1 (m, 1H, H$^9_{pro\text{-}S}$), 2.87 (s, 3H, H^{17}), 3.17 (m, 3H, H$^9_{pro\text{-}R}$, H^5, H^7), 4.31 (q, 2H, H^{13}, *J* 7.2 Hz), 7.99 (s, 1H, H^4). ^{13}C NMR (125 MHz, CCl_4–$CDCl_3$) δ: 13.70 (C^{14}), 22.10 (C^{10}), 23.92 (C^{17}), 26.10 (C^{11}), 38.34 (C^9), 46.16 (C^5), 51.57 (C^6), 57.47 (C^7), 69.68 (C^{13}), 127.02 (C^3), 142.31 (C^{15}), 148.40 (C^2), 158.10 (C^{16}), 164.80 (C^{12}), 197.20 (C^8). MS, *m*/*z* (%): 272.1280 (12, [M – H]$^+$, calc. for $[C_{16}H_{18}O_3N_1]^+$: 272.1360), 258 (18), 246 (16), 245 (100), 244 (96), 230 (82), 228 (30), 217 (39), 216 (57), 204 (19), 202 (49), 83 (27).

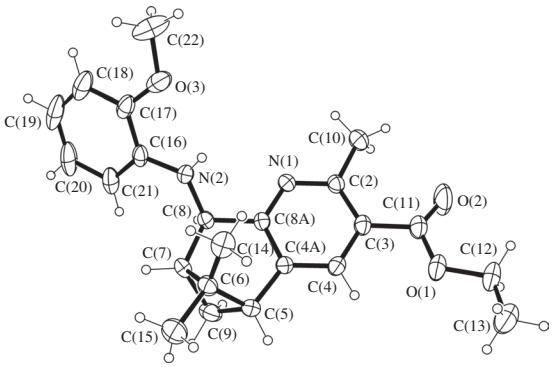


Figure 1 Crystal structure of compound **3**.

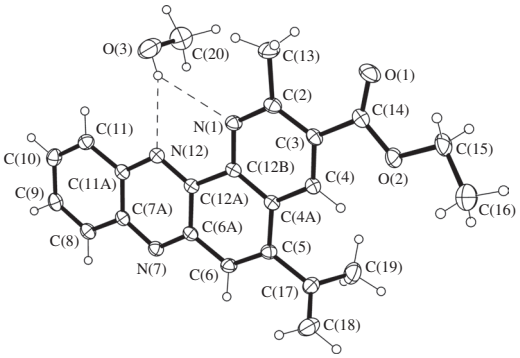


Figure 2 Crystal structure of compound **5**.

were detected. (*R*)-Configuration of the C(8) atom corresponds to attack of a reducing reagent from the less hindered side of the C=N bond in the intermediate Shiff bases.

Our attempts to carry out the similar reductive amination of ketone **2** with *o*-phenylenediamine brought about another result.[‡‡] The primary Shiff base was unstable under the reaction conditions and underwent further transformations affording fused tetracyclic derivative **5** (Scheme 1).[§§] This compound possessed an intense blue fluorescence (λ_{max} 441 nm in $CHCl_3$). Chemical structure of the unusual heterocycle was proved by X-ray crystallography (Figure 2).[¶¶]

[‡] A solution of $BF_3{\cdot}Et_2O$ (14 mg, 0.1 mmol) in benzene (5 ml) was added to a solution of ketone **2** (300 mg, 1.1 mmol) and *o*- or *p*-anisidine (246 mg, 2 mmol) in benzene (50 ml), the reaction mixture was kept at reflux for 12 h. The mixture was concentrated at reduced pressure, the residue was dissolved in MeOH (50 ml), $NaBH_4$ (38 mg, 1 mmol) was added to the methanolic solution and the mixture was left at room temperature for 1 h. The solvent was distilled off, the residue was treated with EtOAc, the organic solution was washed with saturated aqueous NH_3 (10 ml) and extracted with EtOAc (3×25 ml). The combined organic extract was dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by column chromatography (SiO_2, hexane–EtOAc, 20:1 → 5:1) to give anisidine derivatives **3** or **4**.

[§] *Ethyl (5*R*,7*S*,8*R*)-8-(2-methoxyphenylamino)-2,6,6-trimethyl-5,6,7,8-tetrahydro-5,7-methanoquinoline-3-carboxylate* **3**: yield 61%, yellowish crystals, mp 124 °C (MeOH), $[\alpha]_D^{23}$ –4.5 (*c* 0.85, $CHCl_3$). IR (*c* 0.75% in KBr, ν_{max}/cm^{-1}): 3417, 1724, 1243. ^{1}H NMR (500 MHz, CCl_4–$CDCl_3$) δ: 0.78 (s, 1H, H^{10}), 1.40 (t, 3H, H^{14}, *J* 8 Hz), 1.42 (s, 3H, H^{11}), 1.50 (m, 1H, $H^9_{pro\text{-}S}$), 2.80 (s, 3H, H^{17}), 2.76–2.82 (m, 3H, H^5, H^7, $H^9_{pro\text{-}R}$), 3.83 (s, 3H, H^{24}), 4.36 (q, 2H, H^{13}), 4.71 (s, 1H, H^8), 4.95 (br. s, 1H, H^{25}), 6.64 (td, 1H, H^{21}, *J* 8 and 2 Hz), 6.75 (d, 2H, H^{22}, H^{19}, *J* 8 Hz), 6.83 (td, 1H, H^{20}, *J* 8 and 2 Hz), 7.74 (s, 1H, H^4). ^{13}C NMR (125 MHz, CCl_4–$CDCl_3$) δ: 14.24 (C^{14}), 22.78 (C^{10}), 24.46 (C^{17}), 26.57 (C^{11}), 33.46 (C^9), 39.87 (C^6), 44.16 (C^7), 46.46 (C^5), 55.38 (C^{24}), 60.02 (C^8), 60.67 (C^{13}), 109.71 (C^{22}), 109.94 (C^{19}), 116.49 (C^{21}), 121.13 (C^{20}), 123.23 (C^3), 134.61 (C^4), 138.09 (C^{18}), 138.19 (C^{15}), 147.05 (C^{23}), 157.79 (C^2), 159.61 (C^{16}), 166.33 (C^{12}). MS, *m*/*z* (%): 380.2093 (87, $[M]^+$, calc. for $[C_{23}H_{28}O_3N_2]^+$: 380.2094), 311 (100), 283 (33), 258 (43), 123 (88). UV [EtOH, λ_{max}/nm (ε)]: 207 (40 100), 245 (13200), 286 (7400).

[¶] *Ethyl (5*R*,7*S*,8*R*)-8-(4-methoxyphenylamino)-2,6,6-trimethyl-5,6,7,8-tetrahydro-5,7-methanoquinoline-3-carboxylate* **4**: yield 66%, yellowish oil, $[\alpha]_D^{23}$ –1.9 (*c* 0.323, $CHCl_3$). IR (*c* 0.75% in KBr, ν_{max}/cm^{-1}): 3370, 1721, 1242. ^{1}H NMR (500 MHz, CCl_4–$CDCl_3$) δ: 0.72 (s, 1H, H^{10}), 1.40 (t, 3H, H^{14}, *J* 8 Hz), 1.42 (s, 3H, H^{11}), 1.48 (m, 1H, $H^9_{pro\text{-}S}$), 2.79 (s, 3H, H^{17}), 2.73–2.81 (m, 3H, H^5, H^7, $H^9_{pro\text{-}R}$), 3.74 (s, 3H, H^4), 4.36 (q, 2H, H^3), 4.59 (d, 1H, H^8, *J* 2 Hz), 6.71 (d, 2H, H^{19}, H^{23}, *J* 8 Hz), 6.76 (dt, 2H, H^{22}, H^{20}, *J* 8 and 3 Hz), 7.74 (s, 1H, H^4). ^{13}C NMR (125 MHz, CCl_4–$CDCl_3$) δ: 14.37 (C^{14}), 22.90 (C^{10}), 24.59 (C^{17}), 26.73 (C^{11}), 33.40 (C^9), 40.07 (C^6), 44.04 (C^7), 46.57 (C^5), 55.65 (C^{24}), 60.86 (C^{13}), 61.48 (C^8), 114.80 (C^{19}, C^{23}), 155.31 (C^{20}, C^{22}), 123.36 (C^3), 134.88 (C^4), 138.18 (C^{15}), 142.33 (C^{18}), 152.70 (C^{21}), 157.82 (C^2), 159.65 (C^{16}), 166.37 (C^{12}). MS, *m*/*z* (%): 380.2093 (100, $[M]^+$, calc. for $[C_{23}H_{28}O_3N_2]^+$: 380.2094), 312 (21), 311 (82), 283 (34), 258 (22), 188 (23), 164 (18), 123 (75). UV [EtOH, λ_{max}/nm (ε)]: 203 (22 300), 242 (8900), 285 (3700).

[††] *Crystal data for compound* **3**: $C_{23}H_{28}N_2O_3$, *M* = 380.47, monoclinic, space group $P2_1$, at 296 K: *a* = 7.5040(8), *b* = 8.1816(11) and *c* = 17.2951(19) Å, β = 90.281(5)°, *V* = 1061.8(2) Å^3, *Z* = 2, d_{calc} = 1.190 g cm^{-3}, μ(MoKα) = = 0.79 cm^{-1}, *F*(000) = 408. The intensities of 5462 reflections were measured with a Bruker APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, φ and ω-scans, $2\theta < 56°$] and 3514 independent reflections (R_{int} = 0.0693) were used in the further refinement. Final *R* values are R_1 = 0.0522 for 3011 observed reflections with $I > 2\sigma(I)$, and R_1 = 0.0597, wR_2 = 0.1493, GOF = 1.026 for all independent reflections.

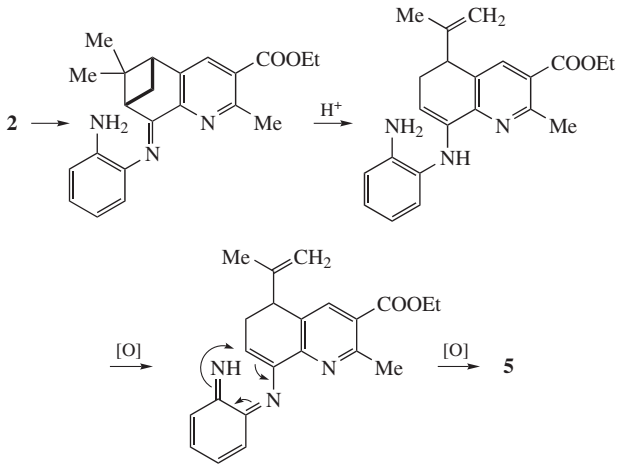
[‡‡] A solution of $BF_3{\cdot}Et_2O$ (21 mg, 0.15 mmol) in benzene (5 ml) was added to a solution of ketone **2** (300 mg, 1.1 mmol) and *o*-phenylenediamine (238 mg, 2.2 mmol) in benzene (50 ml), and the reaction mixture was refluxed for 6 h. The mixture was cooled to room temperature and poured into saturated aqueous NH_3 (10 ml), the reaction products were extracted with EtOAc (3×25 ml). The combined organic extract was dried over Na_2SO_4, filtered and concentrated at reduced pressure to leave the crude product which was then purified by column chromatography (SiO_2, hexane–EtOAc, 40:1 → 10:1) and subsequent crystallization from MeOH to give pyridophenazine **5** (117 mg, 30%).

[§§] *Ethyl 2-methyl-5-(prop-1-en-2-yl)pyrido[2,3-*a*]phenazine-3-carboxylate* **5**: yield 30%, yellowish crystals, mp 183–185 °C (MeOH). IR (*c* 0.75% in KBr, ν_{max}/cm^{-1}): 1721, 1239. ^{1}H NMR (500 MHz, CCl_4–$CDCl_3$) δ: 1.46 (t, 3H, H^{14}, *J* 7.5 Hz), 2.31 (s, 3H, H^{11}), 3.20 (s, 3H, H^{17}), 4.47 (q, 2H, H^{13}, *J* 7.5 Hz), 5.27 (s, 1H, H^{10}_{α}), 5.59 (t, 1H, H^{10}_{β}, *J* 2 Hz), 7.87 (dd, 1H, H^{21}, *J* 2 and 3 Hz), 7.88 (dd, 1H, H^{20}, *J* 2 and 3 Hz), 7.90 (s, 1H, H^6), 8.23–8.25 (m, 1H, H^{22}), 8.56–8.58 (m, 1H, H^{19}), 8.90 (s, 1H, H^4). ^{13}C NMR (125 MHz, CCl_4–$CDCl_3$) δ: 14.35 (C^{14}), 24.60 (C^{11}), 25.93 (C^{17}), 60.48 (C^{13}), 118.44 (C^{10}), 125.34 (C^3), 125.87 (C^6), 126.06 (C^{15}), 129.19 (C^{22}), 130.07 (C^{21}), 131.08 (C^{19}), 131.18 (C^{20}), 137.33 (C^4), 140.87 (C^{23}), 141.90 (C^7), 142.69 (C^{18}), 143.80 (C^{16}), 144.71 (C^9), 145.04 (C^8), 147.56 (C^5), 159.50 (C^2), 166.13 (C^{12}). MS, *m*/*z* (%): 357.1471 (29, $[M]^+$, calc. for $[C_{22}H_{19}N_3]^+$: 357.1472), 284 (76), 149 (28), 97 (41), 83 (54), 71 (60), 69 (82), 57 (100), 55 (74). UV [EtOH, λ_{max}/nm (ε)]: 192 (24 800), 200 (44 600), 229 (33 700), 270 (35 900), 308 (51 600).

[¶¶] *Crystal data for compound* **5**: $C_{22}H_{19}N_3O_2$+MeOH, *M* = 389.44, triclinic, space group $P\bar{1}$, at 150 K: *a* = 8.6823(4), *b* = 10.7126(5) and *c* = 11.6696(6) Å, α = 99.017(2)°, β = 93.122(2)°, γ = 112.283(2)°, *V* = = 984.19(8) Å^3, *Z* = 2, d_{calc} = 1.314 g cm^{-3}, μ(MoKα) = 0.88 cm^{-1}, *F*(000) = 412. The intensities of 16 554 reflections were measured on a Bruker APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, φ and ω-scans, $2\theta < 56°$] and 4695 independent reflections (R_{int} = 0.0372) were used in the further refinement. Final *R* values are R_1 = 0.0426 for 3857 observed reflections with $I > 2\sigma(I)$, and R_1 = 0.0530, wR_2 = 0.1265, GOF = 1.046 for all independent reflections.

The structures of **3** and **5** were solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of ethanol molecule for compound **5** were located from the Fourier density synthesis and refined isotropically, the positions of all the rest hydrogen atoms were calculated geometrically and refined in riding model. All calculations were performed using SHELXTL PLUS 6.14.

CCDC 813734 and 813735 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2011.



Scheme 2

Formation of unexpected pyridophenazine derivative **5** seems to be a multistep process including cyclobutane ring opening, isomerisation and oxidation of the intermediate species. The key steps could be as follows: (1) formation of the ordinary Shiff base, (2) electrophilic fragmentation and isomerisation, (3) oxidation followed by aza-Claisen rearrangement leading to additional hydrophenazine nucleus, and (4) final oxidation resulting in pyrido[2,3-*a*]phenazine ring system (Scheme 2).

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