Synthesis of (±)-4-Substituted Pipecolinic Acids from 4-Alkylpyridines

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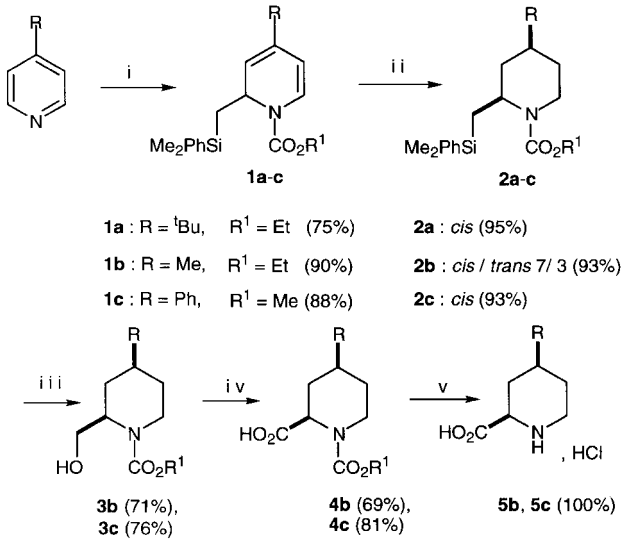
Abstract: Starting from various 4-alkylpyridines, the phenyldimethylsilyl group was introduced using their 1-acylpyridium salts and its oxidative unmasking afforded the corresponding pipecolinic acids.

Pipecolinic acid and derivatives have been widely used as cyclic homologues of proline in numerous peptidomimetics.[1] In this context several syntheses of 4-substituted pipecolinic acids have been performed.[2-11] In this letter, we report a new approach to pipecolinic acids starting from commercially available 4-alkylpyridines.

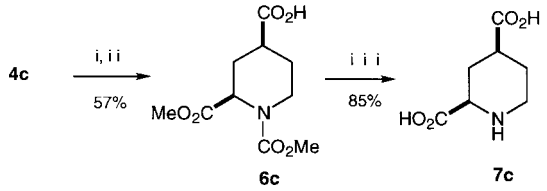


Scheme 1. (i) $Me_2PhSiCH_2MgCl$, $ClCO_2R^1$; (ii) H_2, PtO_2, AcOEt; (iii) $Hg(CF_3CO2)_2$ (1.2 eq), AcOOH/AcOH, RT; (iv) $RuCl_3/NaIO_4$, Ref.15; (v) HCl (6 N), reflux

As outlined in Scheme 1, our approach involved the nucleophilic addition of [(phenyldimethylsilyl)methyl]magnesium chloride to the 1-acyl-4-substituted pyridinium salts and subsequent reduction of the dihydropyridines (**1a-c**) which afforded the piperidines (**2a-c**). The interconversion of the phenyldimethylsilyl group into the primary alcohol yielded the piperidinols (**3b-c**) and subsequent oxidation, the N-protected pipecolinic acids (**4b-c**). A final hydrolytic cleavage afforded the pipecolinic acids (**5b-c**). This sequence needs some comments.

The addition of $Ph(Me)_2SiCH_2MgCl$ to 4-alkylpyridines, without precedent in the literature, was effective using the *in situ* generation of the corresponding N-acyliminium ion.[12] After acidic hydrolysis, and chromatographic purification, 1,2-dihydropyridines (**1a-c**) were obtained in good yields.[13] The hydrogenation of the 1,2-dihydropyridines afforded the piperidines (**2a-c**) : compounds **2a** and **2c** were isolated as the *cis* diastereomers. Whereas compound **2b** was obtained as a diastereomeric mixture (*cis* / *trans* : 7 / 3), as evidenced by the integration of the corresponding methyl peaks in the ^{1}H-NMR spectra; the *cis* isomer (**2b**-*cis*) could be obtained in pure form after chromatography.[13] Among the experimentated oxidative methods to transform the phenyldimethylsilyl into the hydroxymethylene group,[14] we found that the mixture : $(CF_3CO_2)_2Hg$ (1.2 eq), AcOOH (20 eq), AcOH was the best choice and represented an improvement of the already existing methods. Indeed, the reaction was completed within 1 h at room temperature and the N-protected piperidinols **3b**-*cis*[13] and **3c** were obtained in 71% and 76% yield, respectively. The oxidation of **3b**-*cis* and **3c** under Sharpless conditions[15] afforded the N-protected pipecolinic acids **4b** (69%) and **4c** (81%) which could be readily deprotected with HCl 6 N to (±)-(*cis*)-4-methyl- and (±)-(*cis*)-4-phenylpipecolinic acid respectively **5b**[5,13] and **5c**[13] in quantitive yields.

The presence of the phenyl rest in **4c** gives us the opportunity to extend the scope of our procedure in preparing the (±)-*cis*-2,4-piperidinedicarboxylic acid, a selective NMDA agonist,[16] in the following way. Compound **4c** was traited with an ethereal solution of diazomethane at 0°C and submitted to the Sharpless conditions,[15] adapted for oxidative cleavage of an aromatic ring, to yield **6c** in moderate yields. Finally the rigid glutamic analogue **7c** was obtained as hydrochloride under hydrolytic conditions (Scheme 2).



Scheme 2 . (i) CH_2N_2, Et_2O; (ii) $RuCl_3/NaIO_4$, Ref.15; (iii) HCl (6 N) reflux

In summary, we have developed a general method for the synthesis of (±)-(*cis*)-4-substituted pipecolinic acids starting from 4-substituted pyridines. This method takes advantage of the nucleophilic addition of [(phenyldimethylsilyl)methyl]magnesium chloride to pyridinium salts and of oxidative removal of the phenyldimethylsilyl moiety. We are currently exploring the scope of this method for the synthesis of other heterocyclic compounds.

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(13) Experimental procedures and physical data:

1b [(Phenyldimethylsilyl)methyl-]magnesium chloride, prepared from chloromethyl-dimethylphenylsilane (3 ml, 16.63 mmol) and magnesium (424 mg, 17.46 mmol) in ether (17 ml), was added to a solution of 4-picoline (1.47 ml, 15.12 mmol) in THF (15 ml) at -20°C. Then a solution of ethyl choloroformate in THF (2 ml) was added and the mixture was left to reach 0°C. After quenching with 5% HCl, the mixture was extracted with ether (2x30 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (5% ether in hexane) to afford 4.31 g (90%) of dihydropyridine **1b** as a colorless oil.

^{1}H NMR [200 MHz, $CDCl_3$] : δ 7.55 - 7.35 (m, 5 H), 6.68 and 6.52 (2d, J = 7.5 Hz and 7.7 Hz, 1H), 5.20 - 5.00 (m, 2 H), 4.90 - 4.70 (m, 1 H), 4.16 (m, 2 H), 1.63 (s, 3H), 1.50 - 0.85 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.34 and 0.32 (2 s, 6 H).

2b-*cis* : A solution of dihydropyridine **1b** (3 g, 9.51 mmol) in ethyl acetate (95 ml), was hydrogenated in the presence of PtO_2. After stirring for 6 h, the mixture was filtred over celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (80% CH_2Cl_2 in hexane) to afford 2.83 g (93%) of **2b** as a mixture of diastereomers (*cis / trans* : 7/3). A second purification by chromatography yielded 1.55 g (53%) of pure **2b**-*cis*.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.55 - 7.33 (m, 5 H), 5.50 (m, 0.3 H), 4.07 (q, J = 7.1 Hz, 2 H), 4.13 -3.93 (m, 1 H), 3.69 (ddd, J = 2.8 Hz, 7 Hz, and 13.6 Hz, 0.7 H), 3.04 (ddd, J = 6 Hz, 10.1 Hz and 16.2 Hz, 0.7 H), 2.82 (dt, J = 6.3 Hz, 0.3 H), 1.9 - 1.48 (m, 2 H), 1.45 - 1.00 (m, 5 H), 1.22 and 1.21 (2 t, J = 7.1 Hz, 3 H), 0.91 and 0.79 (2 d, J = 6.7 Hz and 6.3 Hz, 3 H), 0.32, 0.31 and 0.29 (3 s, 6 H). Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66 %; H, 9.15 %; N, 4.38 %. Found : C, 67.55%; H, 9.33%; N, 4.35%.

3b-*cis* : Mercuric trifluoroacetate (294 mg, 0.69 mmol) was added to a solution of **2b**-*cis* (200 mg, 0.63 mmol) in peracetic acid (2.65 ml, 12.6 mmol) and acetic acid (2.6 ml). After 1 h of stirring at room temperature, ether (50 ml) was added and the ether solution washed with $Na_2S_2O_3$ (20%), water, $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (25% AcOEt in Hexane) to afford 89 mg (71%) of piperidinol **3b**-*cis* as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.12 (q, J = 7.1 Hz, 2 H), 3.86 - 3.74 (m, 3 H), 3.45 (m, 3 H), 3.08 (m, 1 H), 1.76 - 1.55 (m, 3 H), 1.26 (t, 3 H, J = 7.1 Hz), 1.35 - 1.0 (m, 2 H), 0.95 (d, 3 H, J = 6.2 Hz).

4b-*cis* : $RuCl_3$,$3H_2O$ (4 mg) was added to a solution of piperidinol **3b**-*cis* (80 mg, 0.40 mmol) and $NaIO_4$ (350 mg, 1.64 mmol) in H_2O (2.4 ml), CCl_4 (1.6 ml) and CH_3CN (1.6 ml). After stirring at room temperature for 4 h, ether (40 ml) and H_2O (10 ml) was added, the organic layer were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (10% MeOH in CH_2Cl_2) to afford 59 mg (69%) of compound **4b**-*cis* as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.91 (brs, 1H), 4.48 (t, 1 H, 5.9 Hz), 4.1 (q, 2 H, J = 7.1 Hz), 3.8 - 3.55 (m, 1 H), 3.5 - 3.25 (m, 1 H), 2.15 - 1.6 (m, 4 H), 1.45 - 1.15 (m, 1 H), 1.24 (t, 3 H, J = 7.1 Hz), 1.02 (d, 3 H, J = 6.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) : δ 178, 157, 62, 54, 39, 33, 31, 26, 19, 15.

5b-*cis* : A solution of **4b**-*cis* (44 mg, 0.2 mmol) in 6 N HCl (2 ml) was refluxed for 4h. The mixture was then cooled and concentrated in vacuo. The resulting solid product was collected and washed with ether to afford 36 mg (100%) of **5b**-*cis* without further purification.

F = 257 - 259°C. ^{1}H NMR (200 MHz, D_2O) : δ 3.71 (dd, J = 12.7 Hz and 3.2 Hz, 1 H), 3.32 (dq, J = 12.8 Hz and 2.3 Hz, 1 H), 2.87 (td, J = 13.0 Hz and 2.8 Hz, 1 H), 2.15 (dq, J = 13.8 Hz and 2.4 Hz, 1H), 1.85 - 1.5 (m, 2 H), 1.3 - 1.0 (m, 2 H), 0.85 (d, J = 6.4 Hz, 3 H).

Compound **5c** : F = 252-254°C. ^{1}H NMR (200 MHz, D_2O) δ 7.28-7.10 (m, 5 H), 3.85 (dd, J = 12.7 Hz and 3.2 Hz, 1H), 3.43 (dq, J = 13.0 Hz and 2.3 Hz, 1H), 3.01 (td, 13.0 Hz and 3.2Hz, 1 H), 2.85 (tt, J = 12.3 Hz, 3.7 Hz, 1 H), 2.32 (dq, 14.1 Hz and 1.9 Hz) 1H), 1.92 (m, 1 H), 1.81-1.58 (m, 2 H). ^{13}C NMR (50 MHz, D_2O) δ 171, 142.7, 128.1, 126.3, 125.9, 56.9, 42.9, 38.6, 32.0, 27.7. MS (FAB) ($C_{12}H_{15}NO_2$) : 206 (MH^+).

7c-*cis :* ^{1}H NMR (200 MHz, D_2O) : δ 3.75 (dd, J = 3.2 Hz and 12.7 Hz, 1 H), 3.36 (dq, J = 2.3 Hz and 13.2 Hz, 1 H), 2.86 (dt, J = 3.2 Hz and 13.2 Hz, 1 H), 2.58 (td, J = 3.5 Hz and 12.3 Hz, 1H), 2.40 (m, 1 H), 2.02 (m, 1 H), 1.70 - 1.50 (m, 2 H).

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