SYNTHESIS OF 4-SILYL-SUBSTITUTED METHYL NICOTINATES *VIA* SILYLCUPRATION OF *N*-ACYLPYRIDINIUM SALTS†

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Abstract - A general synthetic method for the preparation of 4-silyl-substituted methyl nicotinates (**5**) is described. The reaction sequence includes a silylcupration of the *N*-acylated 3-methoxypyridinium salts (**2**) followed by oxidation of the resulting dihydropyridines (**3**) to give **5**.

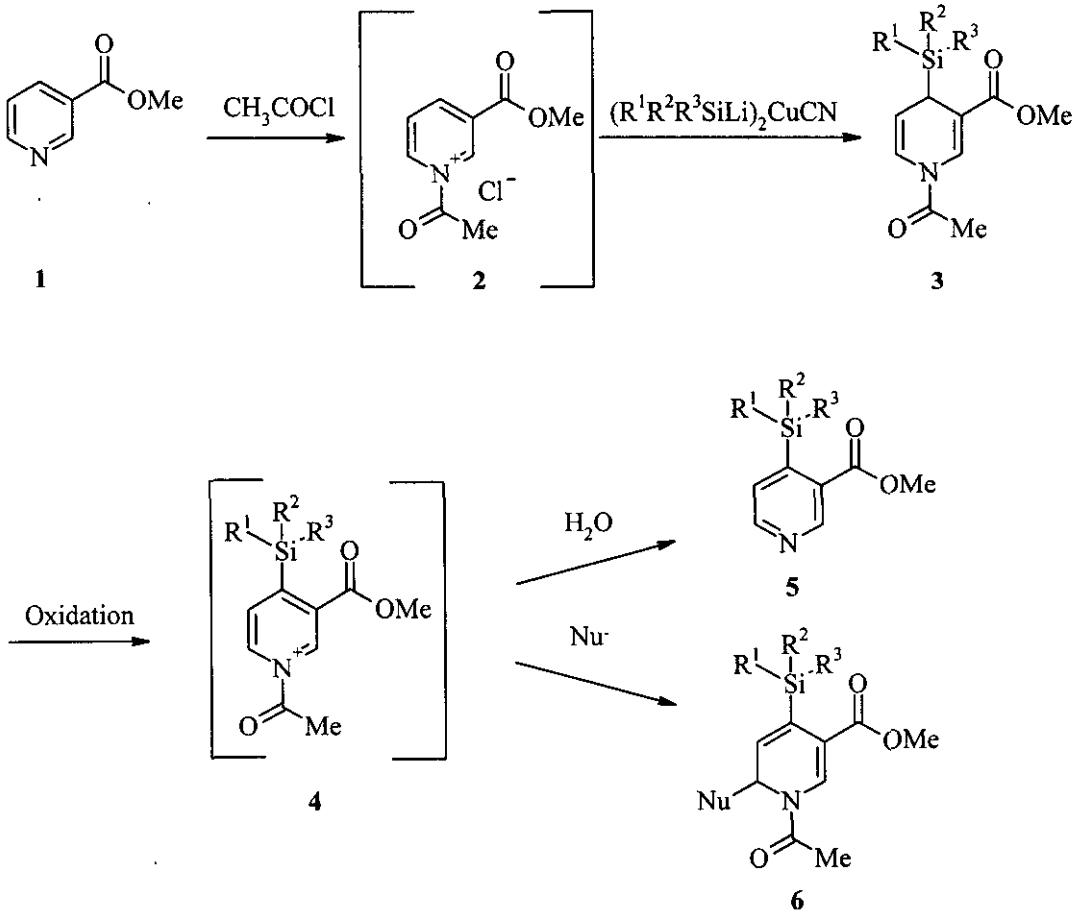
Within a project directed toward the development of new GABA uptake inhibitors[1] we needed a synthetic access to 4-silyl-substituted methyl nicotinates (**5**). Though the silyl group is widely used as a substituent or as a protective group for various functional groups as for hetero atoms, acetylenes, alkenes or aromatic compounds,[2] up to now no syntheses of the aforementioned 4-silyl-substituted methyl nicotinates (**5**) have been reported.

In search of a synthetic strategy for the preparation of compounds (**5**) we became aware of a method developed by Kelly and Kim[3] for the synthesis of methyl 4-trimethylstannylnicotinate. These authors employed nicotinic aldehyde as a starting material that they converted into the target compound in a three step sequence. Lithiation of this compound (in 4-position in the presence of *N,N,N'*-trimethylethylendiamine[4] with n-butyllithium) and reaction with trimethylstannyl chloride provided 4-trimethylstannylnicotinic aldehyde. Finally, upon oxidation with $KMnO_4$ and reaction with diazomethane, methyl 4-trimethylstannylnicotinate was obtained. Though this methodology is certainly a useful entry to 4-substituted nicotinic acid derivatives we were interested in a more direct route.

In this paper we describe a new and highly convenient approach to this class of compounds. Our entry is based on *N*-acylpyridinium ions as reactive intermediates. The reaction of these intermediates with silyl nucleophiles gives access to 4-silyl-substituted 1,4-dihydropyridines (**3**) which upon oxidation lead to the desired 4-silylated derivatives (**5**).

From many addition reactions of carbon nucleophiles[5] to *N*-activated pyridinium salts it is known that the regioselectivity of the addition reaction depends on the electronic nature of the nucleophile. According to the HSAB principle soft nucleophiles have to be employed to get an addition to the position 4 of the

pyridine nucleus.[5] Therefore we decided to utilize higher order silylcyanocuprates as nucleophiles for the silylation reaction. Such silylcupration reactions of *N*-acylpyridinium salts have not been conducted so far. Thus we were very pleased to find that a smooth addition reaction occurred when the *N*-acylpyridinium ion (**2**) (generated *in situ* from **1** and acetyl chloride) was treated with various silylcuprates providing the addition products (**3a-c**) in good yields (77-92%, see Table).



Scheme

		Yield of **3** (%)	Yield of **5** (%)	
a	$R^1 = R^2 = Me$, $R^3 = Ph$	78	66 [a]	75 [b]
b	$R^1 = R^2 = R^3 = Ph$	77	62 [a]	0 [b]
c	$R^1 = R^2 = Ph$, R^3 = *tert*-Bu	92	60 [a]	0 [b]

[a] oxidation by *p*-chloranil

[b] oxidation by triphenylcarbenium tetrafluoroborate

Table

Among these silyl substituents in **3a-c** the phenyldimethylsilyl group in **3a** is certainly especially useful as it may function as a protective group[2] that can be easily replaced by hydrogen (with tetrabutylammonium fluoride)[6] and this even chemoselectively in the presence of trialkylsilyl substituents[7] or acid sensitive groups,[6] and besides this it may be transformed into a hydroxyl group as well.[8]

Numerous oxidizing reagents have been reported to convert 1,4-dihydropyridines into pyridines like sulfur,[9] oxygen,[10] *o*-chloranil[11] and DDQ.[12] In addition, the transformation may also be performed by an electrochemical oxidation.[13] We first examined *p*-chloranil according to Weller[14] and found that it is well suited for this reaction providing the desired 4-silyl-substituted methyl nicotinates (**5a-c**) in yields from 60-66% (see Table).

Next we examined triphenylcarbenium tetrafluoroborate for this process. This reagent has successfully been employed for the oxidation of *N*-methyl-3,4-dihydroisoquinolines[15] and various chiral *N*-acyl-3,4-dihydroisoquinolines.[16] However to date, no studies using triphenylcarbenium tetrafluoroborate to oxidize 1,4-dihydropyridines have been reported. Such oxidation reactions with triphenylcarbenium tetrafluoroborate are usually performed in dichloromethane[16] and lead at first to the corresponding *N*-acyliminium ion (e.g. **4** with tetrafluoroborate as a counter ion). Due to the solvent and the chemical inertness of the side products formed during the oxidation reaction the solution with the *N*-acyliminium ion (BF_4^-) may be directly employed (without isolation of **4**) in subsequent trapping reaction with nucleophiles to give the corresponding addition product, for which reason this method is especially valuable. In the case of **4** this would lead to substituted dihydropyridines (**6**), whereas upon aqueous workup of **4** the pyridines (**5**) would be obtained.

Employing triphenylcarbenium tetrafluoroborate, however, we only succeeded in the oxidation of **3a** to give pyridine (**5a**), which was isolated in a yield of 77% (see Table). In contrast, the compounds (**3b**) and (**3c**) remained unaffected by triphenylcarbenium tetrafluoroborate which is presumably due to an increase in steric hindrance caused by the larger silyl groups.

In conclusion we have presented an efficient entry to the silyl derivatives (**5**) as a new class of compounds.

EXPERIMENTAL

General All reactions were carried out in vacuum dried glassware under nitrogen atmosphere. All reagents were used as commercially available. The solvents were dried and distilled. THF and toluene were freshly distilled from sodium metal/benzophenone ketyl prior to use. Acetyl chloride was freshly distilled from *N,N*-dimethylaniline. Melting points were determined on a Büchi melting point apparatus no. 510 (Dr. Tottoli) and are uncorrected. IR spectra were determined with a Perkin Elmer FT-IR spectrophotometer Paragon 1000, and NMR with a JEOL JNMR-GX 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) with TMS as internal standard. The spectra were recalculated with NUTS, 2D version 5.097. MS spectra were recorded on a Hewlett Packard 5989 with 59980 B particle beam LC/MS interface. CHN-analyses were determined with an elemental analysator Heraeus Rapid. TLC was

performed on Merck 60 F-254. Flash chromatography was performed on silica gel (Merck 60 F-254, 0.040–0.063 mm).

General procedure 1 for the synthesis of methyl 1-acetyl-4-silyl-1,4-dihydropyridine-3-carboxylates (3). To a suspension of CuCN in THF at 0 °C the respective silyllithium compound[17] was added. The resulting solution was stirred for 20 min, then cooled to - 78 °C and cannulated to a solution of methyl nicotinate (**1**) in THF (at -78 °C). After dropwise addition of acetyl chloride in THF over a period of 2 h the resulting dark solution was stirred for 18 h. Then the reaction was quenched by addition of phosphate buffer (1M, pH 7). Methylene chloride was added and the organic layer was washed with water. The methylene chloride layer was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography.

Methyl 1-acetyl-4-dimethylphenylsilyl-1,4-dihydropyridine-3-carboxylate (**3a**). Compound (**3a**) was obtained according to the general procedure 1 from 206 mg (1.50 mmol) of methyl nicotinate (**1**) in 47 mL of THF, 144 µL (2.00 mmol) of acetyl chloride in 6 mL of THF, 8.2 mL (4.00 mmol) of phenyldimethylsilyllithium[17] (0.37 M in THF) and 180 mg (2.00 mmol) of CuCN in 10 mL of THF as colorless oil (370 mg, 78%) after purification by flash chromatography (heptane : ethyl acetate 70 : 30). IR (film): $\tilde{\nu}$ = 1729 cm $^{-1}$, 1690, 1296, 703. – ^{1}H NMR ($CDCl_3$): δ = 0.25 (s, 2.4 H, $Si(CH_3)_2$), 0.55 (s, 3.6 H, $Si(CH_3)_2$), 1.98 (s, 1.2 H, CH_3CO), 2.14 (s, 1.8 H, CH_3CO), 2.88 (d, *J* = 5.8 Hz, 0.6 H, 4-H), 2.90 (d, *J* = 5.8 Hz, 0.4 H, 4-H), 3.55 (s, 1.2 H, CH_3O_2C), 3.65 (s, 1.8 H, CH_3O_2C), 4.98 (dd, *J* = 5.8 and 7.8 Hz, 0.4 H, 5-H), 5.03 (dd, *J* = 5.8 and 7.8 Hz, 0.6 H, 5-H), 6.10 (d, *J* = 7.8 Hz, 0.4 H, 6-H), 6.74 (d, *J* = 7.8 Hz, 0.6 H, 6-H), 7.23 - 7.52 (m, 5.4 H, phenyl protons, 2-H), 7.84 (s, 0.6 H, 2-H); ratio of rotamers = 0.6/0.4. – MS (CI); *m/z*: 316 (M^+ +1). – *Anal.* Calcd for $C_{17}H_{22}NO_3Si$: C, 64.52; H, 7.01; N, 4.43. Found: C, 64.71; H, 6.56; N, 4.69.

Methyl 1-acetyl-4-triphenylsilyl-1,4-dihydropyridine-3-carboxylate (**3b**). Compound (**3b**) was obtained according to the general procedure 1 from 275 mg (2.00 mmol) of methyl nicotinate (**1**) in 70 mL of THF, 287 µL (4.00 mmol) of acetyl chloride in 7 mL of THF, 18.9 mL (8.00 mmol) of triphenylsilyllithium[17] (0.42 M in THF) and 360 mg (4.00 mmol) of CuCN in 13 mL of THF as colorless crystals (678 mg, 77%) after purification by flash chromatography (heptane : ethyl acetate 70 : 30), mp 135 °C. – IR (KBr): $\tilde{\nu}$ = 1708 cm^{-1}, 1670, 1587, 1485, 738. – ^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 1.4 H, CH_3CO), 1.93 (s, 1.6 H, CH_3CO), 3.35 (s, 3 H, CH_3O_2C), 3.81 (d, *J* = 6.0 Hz, 0.6 H, 4-H), 3.84 (d, *J* = 6.0 Hz, 0.4 H, 4-H), 5.31 (dd, *J* = 6.0 and 7.4 Hz, 1 H, 5-H), 6.06 (d, *J* = 7.4 Hz, 0.4 H, 6-H), 6.75 (d, *J* = 7.4 Hz, 0.6 H, 6-H), 7.27 (s, 0.6 H, 2-H), 7.33-7.44 (m, 9 H, phenyl protons), 7.61-7.65 (m, 6 H, phenyl protons), 7.87 (s, 0.4 H, 2-H); ratio of rotamers = 0.6/0.4. – MS (CI); *m/z*: 440 (M^+ +1). – *Anal.* Calcd for $C_{27}H_{24}NO_3Si$: C, 73.94; H, 5.52; N, 3.19. Found: C, 73.78; H, 5.79; N, 3.08.

Methyl 1-acetyl-4-(2,2-dimethylethyl)diphenylsilyl-1,4-dihydropyridine-3-carboxylate (**3c**). Compound (**3c**) was obtained according to the general procedure 1 from 275 mg (2.00 mmol) of methyl nicotinate (**1**)

in 75 mL of THF, 214 µL (3.00 mmol) of acetyl chloride in 8 mL of THF, 14.2 mL (6.00 mmol) of *t*-butyldiphenylsilyllithium[17] (0.42 M in THF) and 270 mg (3.00 mmol) of CuCN in 15 mL of THF as colorless crystals (771 mg, 92%) after purification by flash chromatography (heptane : ethyl acetate 50 : 50), mp 147 °C. – IR (KBr): $\tilde{\nu}$ = 1693 cm^{-1}, 1659, 1318, 1240, 709. – ^{1}H NMR ($CDCl_3$): δ = 1.04 (s, 4.2 H, $(CH_3)_3C$), 1.06 (s, 4.8 H, $(CH_3)_3C$), 1.65 (s, 1.4 H, CH_3CO), 1.83 (s, 1.6 H, CH_3CO), 3.56 (s, 1.6 H, CH_3O_2C), 3.66 (s, 1.4 H, CH_3O_2C), 3.72 (d, *J* = 6.4 Hz, ~ 0.5 H, 4-H), 3.76 (d, *J* = 6.4 Hz, ~ 0.5 H, 4-H), 5.20 (dd, *J* = 6.4 and 7.7 Hz, ~ 0.5H, 5-H), 5.32 (dd, *J* = 6.4 and 7.7 Hz, ~ 0.5 H, 5-H), 5.93 (d, *J* = 7.7 Hz, ~ 0.5 H, 6-H), 6.65 (d, *J* = 7.7 Hz, ~ 0.5 H, 6-H), 7.14 (s, ~ 0.5 H, 2-H), 7.22-7.43 (m, 6 H, phenyl protons), 7.58-7.69 (m, 4H, phenyl protons), 7.73 (s, ~ 0.5 H, 2-H); ratio of rotamers ~ 0.5/0.5. – MS (70 eV); *m/z*: 419 (M^+). – *Anal.* Calcd for $C_{25}H_{29}NO_3Si$: C, 71.56; H, 6.97; N, 3.34. Found: C, 71.43; H, 7.10; N, 3.34.

General procedure 2 for the oxidation of the methyl 1-acetyl-4-silyl-1,4-dihydropyridine-3-carboxylates (3) with *p*-chloranil

Toluene was added to methyl 1-acetyl-4-silyl-1,4-dihydropyridine-3-carboxylates (**3**) and *p*-chloranil and the reaction mixture was refluxed for 6 h. After cooling to rt 2N NaOH was added. The aqueous phase was extracted with methylene chloride. The combined organic layers were washed with 2N NaOH, dried ($MgSO_4$) and evaporated to dryness. The resulting residue was purified by flash chromatography.

Methyl 4-dimethylphenylsilylpyridine-3-carboxylate (**5a**). A) Compound (**5a**) was obtained according to the general procedure 2 from 196 mg (0.621 mmol) of **3a** and 168 mg (0.683 mmol) of *p*-chloranil in 5 mL of toluene as colorless crystals (111 mg, 66%) after purification by flash chromatography (heptane : ethyl acetate 70 : 30), mp 60 °C. – IR (KBr): $\tilde{\nu}$ = 1724 cm^{-1}, 1577, 1428, 1303. – ^{1}H NMR ($CDCl_3$): δ = 0.60 (s, 6 H, CH_3Si), 3.70 (s, 3 H, CH_3O_2C), 7.30 - 7.38 (m, 4 H, phenyl protons, 5-H pyridine), 7.43 - 7.47 (m, 2 H, phenyl protons), 8.62 (d, *J* = 4.8 Hz, 1 H, 6-H pyridine), 9.12 (d, *J* = 1.0 Hz, 1 H, 2-H pyridine) . – ^{13}C NMR ($CDCl_3$): δ = 52.4 (CH_3O), 128.1 (phenyl carbon atoms), 129.4 (phenyl carbon atoms), 130.9 (5-C), 131.6 (3-C), 134.1 (phenyl carbon atoms), 138.1 (phenyl carbon atoms), 150.6 (4-C), 150.8 (2-C), 152.0 (6-C), 167.5 (CO). – MS (70 eV); *m/z*: 272 (M^+). – *Anal.* Calcd for $C_{15}H_{17}NO_2Si$: C, 66.39; H, 6.31; N, 5.16. Found: C, 66.51; H, 6.32; N, 5.03.

B) To a solution of 362 mg (1.143 mmol) of **3a** in 11 mL of methylene chloride 415 mg (1.257 mmol) of tritylium tetrafluoroborate in 20 mL of methylene chloride was added and the reaction mixture was stirred for 18 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$. The aqueous phase was extracted with methylene chloride. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by flash chromatography to give 233 mg (75%) of colorless crystals.

Methyl 4-triphenylsilylpyridine-3-carboxylate (**5b**). Compound (**5b**) was obtained according to the general procedure 2 from 486 mg (1.108 mmol) of **3b** and 300 mg (1.218 mmol) of *p*-chloranil in 10 mL of toluene as colorless crystals (272 mg, 62%) after purification by flash chromatography (heptane : ethyl

acetate 60 : 40), mp 143 °C. – IR (KBr): $\tilde{\nu}$ = 1724 cm^{-1}, 1576, 1428, 1296, 700. – ^1H NMR ($CDCl_3$): δ = 3.16 (s, 3 H, CH_3O_2C), 7.28 (dd, *J* = 0.7 and 4.8 Hz, 1 H, 5-H), 7.35 - 7.53 (m, 15 H, phenyl protons), 8.67 (d, *J* = 4.8 Hz, 1 H, 6-H), 9.26 (d, *J* = 0.7 Hz, 1 H, 2-H). – MS (CI); *m/z*: 396 (M^+ +1). – *Anal.* Calcd for $C_{25}H_{21}NO_2Si$: C, 75.92; H, 5.35; N, 3.54. Found: C, 75.86; H, 5.47; N, 3.48.

Methyl 4-(2,2-dimethylethyl)diphenylsilylpyridine-3-carboxylate (**5c**). Compound (**5c**) was obtained from 150 mg (0.357 mmol) of **3c** and 97 mg (0.357 mmol) of *p*-chloranil in 3 mL of toluene as colorless crystals (85 mg, 60%) after purification by flash chromatography (heptane : ethyl acetate 70 : 30), mp 130 °C. – IR (KBr): $\tilde{\nu}$ = 1731 cm^{-1}, 1426, 1303, 701. – ^1H NMR ($CDCl_3$): δ = 1.15 (s, 9 H, $(CH_3)_3C$)), 2.97 (s, 3 H, CH_3O_2C), 7.32 - 7.43 (m, 6 H, phenyl protons), 7.54 - 7.59 (m, 4 H, phenyl protons), 7.97 (d, *J* = 4.9 Hz, 1 H, 5-H), 8.79 (d, *J* = 4.9 Hz, 1 H, 6-H), 9.02 (s, 1 H, 2-H). – MS (CI); *m/z*: 376 (M^+ +1). – *Anal.* Calcd for $C_{23}H_{25}NO_2Si$: C, 73.59; H, 6.71; N, 3.73. Found: C, 73.39; H, 6.93; N, 3.71.

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