An Efficient and Easy Route to Trimethyl Derivatives of 2,2':6',2''-Terpyridine

Reza-Ali Fallahpour

Institut für Anorganische Chemie, Universität Basel, Spitalstrasse 51, CH-4056 Basel, Switzerland

E-mail: Reza.Fallahpour@unibas.ch

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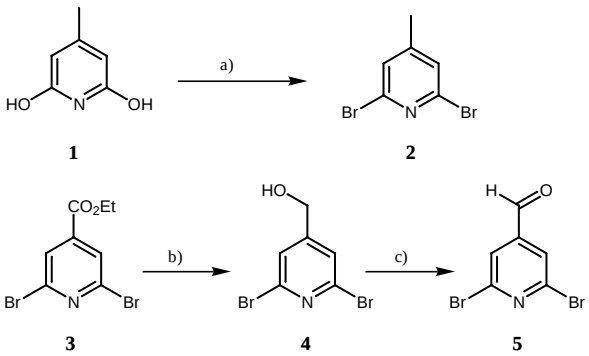
Abstract: By using the Stille coupling reaction, trimethyl derivatives of 2,2':6',2"-terpyridine have been prepared in good yields.

Key words: terpyridines, aldehydes, Stille coupling, tin, heterocycles

In continuation of our studies on functionalisation of oligopyridines,[1–6] generally, and 2,2':6',2''-terpyridine (tpy), especially, we would like to report a new synthetic approach to trimethyl derivatives of 2,2':6',2''-terpyridine. From the synthetic point of view there are few methods leading to this system. 2,2':6',2''-Terpyridines have been synthesised by the following methods: a) Ullman coupling of bromopyridines;[7] b) cross-coupling methods such as Stille reaction,[8] the Suzuki reaction[9] and nickel mediated reactions;[10] c) α-oxoketene dithioacetal methodology;[11] d) Kröhnke method;[12] e) Jameson method;[13] and f) Sauer method.[14]

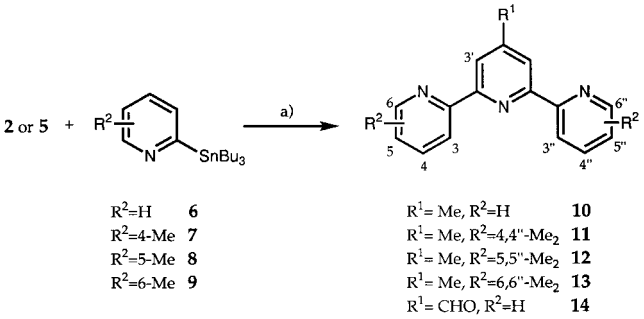
The functionalisation of the tpy ligand at C(4') and, simultaneously, at the terminal pyridine rings is of interest. We have already applied the Stille coupling reaction for the synthesis of functionalised oligopyridines.[3–6] Càrdenas and Sauvage have also applied this methodology for the synthesis of oligopyridines.[15] The Stille coupling reaction consists of the reaction of stannyl and bromo or triflate compounds in the presence of a catalytic amount of palladium(0) and palladium(II). The advantage of this method is that many functionalities such as nitro, carbonyl or carboxylate groups are inert under the reaction conditions.



Reagents and conditions: a) **1**/PBr_3, 175 °C, 6 h, 35%; b) **3**/$NaBH_4$/EtOH, 78 °C, 3 h, 79%; c) **4**/DMSO/$(COCl)_2$/Et_3N/CH_2Cl_2, −78 °C, 81 %

Scheme 1

The key compounds of the Stille coupling reaction are the 2,6-dibromo-4-methylpyridine (**2**) and 2,6-dibromopyridine-4-carbaldehyde (**5**) (Scheme 1). The commercially available 2,6-dihydroxy-4-methylpyridine (**1**) was reacted with PBr_3 to give the 2,6-dibromo-4-methylpyridine (**2**) in 35% yield.[16] Ethyl 2,6-dibromo-4-pyridinecarboxylate (**3**)[6] was reduced to 2,6-dibromo-4-hydroxymethylpyridine (**4**) followed by the Swern oxidation[17] to the aldehyde **5**.



Reagents and conditions:a) **2** or **5** (1.0 mol equiv)/2-pyridyl-$SnBu_3$ **6**-**9** (2.0 mol equiv)/$(Ph_3P)_4Pd$ (0.02 mol equiv)/toluene, 110 °C, 16 h; **10** (65%), **11** (55%), **12** (58%), **13** (50%), **14** (61%)

Scheme 2

2-Bromopyridine, 2-bromo-4-methylpyridine,[18] 2-bromo-5-methylpyridine[19] and 2-bromo-6-methylpyridine[19] were converted to derivatives of tributyl(pyridin-2-yl)stannanes **6**–**9** by reacting with butyllithium and tributyltin chloride in tetrahydrofuran.[6] Because of the toxicity of the stannyl compounds they have been prepared in situ and used immediately. The stannyl compounds were reacted with 0.5 equivalents of **2** and **5** in the presence of 0.02 equivalents of $(Ph_3P)_4Pd$ for 16 hours at reflux in toluene to give 4'-methyl-2,2':6',2''-terpyridine (**10**), trimethyl-2,2':6',2''-terpyridines **11**–**13** and 2,2':6',2''-terpyridine-4'-carbaldehyde (**14**) in 50–65% yields. The yields and data of compounds **2**–**5** and **10**–**14** are listed in the Table. All data are in accord with the previously known ones or with the proposed formulations of compounds.

Terpyridines **12** and **13** are new, while **10**,[11] **11**[21] and **14**[11] have already been prepared by different methods. Compound **14** has also been synthesised by the reduction of butyl 2,2':6',2''-terpyridine-4'-carboxylate.[22] The disad-

Table Pyridine Derivatives Prepared

Product[a]	Yield (%)	Mp (°C)	MS (*m*/*z*)	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ
2	35	74−75	251	7.29 (s, 2 H), 2.32 (s, 2 H)	153.19, 141.44, 128.63, 21.19
4	79	96−97	267	7.47 (s, 2 H), 4.72 (s, 2 H)	
5	81	80	265	9.96 (s, 1 H), 7.84 (s, 2 H)	188.00, 142.19, 125.95, 125.18
10	65	97	249	8.70 (d, 2 H, *J* = 7.80), 8.61 (d, 2 H, *J* = 7.80), 8.29 (s, 2 H), 7.84 (ddd, 2 H, *J* = 8.30, 7.80, 1.95), 7.32 (ddd, 2 H, *J* = 8.30, 7.80, 1.95), 2.53 (s, 3 H)	156.40, 155.24, 149.14, 149.03, 136.83, 123.64, 121.83, 121.32, 21.34
11	55	186	275	8.56 (d, 2 H, *J* = 7.80), 8.41 (s, 2 H), 8.27 (s, 2 H), 7.15 (dd, 2 H, *J* = 7.80, 1.95), 2.51 (s, 3 H), 2.49 (s, 6 H)	156.19, 155.43, 148.87, 148.05, 124.67, 123.54, 122.10, 122.03, 21.34, 21.17
12	58	178	275	8.54 (d, 2 H, *J* = 7.80), 8.52 (d, 2 H, *J* = 7.80), 8.24 (s, 2 H), 7.67 (dd, 2 H, *J* = 7.80, 1.95), 2.53 (s, 3 H), 2.44 (s, 6 H)	155.22, 153.90, 149.36, 137.46, 133.30, 121.26, 120.89, 21.33, 18.39
13	50	154	275	8.39 (d, 2 H, *J* = 7.80), 8.28 (s, 2 H), 7.72 (t, 2 H, *J* = 7.80), 7.18 (d, 2 H, *J* = 7.80), 2.66 (s, 6 H), 2.53 (s, 3 H)	157.73, 155.90, 155.47, 148.93, 136.96, 123.14, 121.65, 118.34, 24.67, 21.42
14	61	166	261	10.28 (s, 1 H), 8.88 (s, 2 H), 8.75 (d, 2 H, *J* = 7.80), 8.63 (d, 2 H, *J* = 7.80), 7.90 (ddd, 2 H, *J* = 8.30, 7.80, 1.95), 7.39 (ddd, 2 H, *J* = 8.30, 7.80, 1.95)	191.75, 157.22, 155.18, 149.40, 144.00, 137.02, 124.37, 121.33, 119.77

[a] Satisfactory microanalyses obtained: C ±0.22, H ±0.23, N ±0.47.

vantage of the published methods is that the starting materials are not easily accessible or the yield is low.

In conclusion, the method presented here allows the synthesis of derivatives of 2,2':6',2"-terpyridine not only at the central pyridine ring but also at the terminal pyridine rings. The methyl groups are very reactive, e.g. they can be oxidised and a 2,2':6',2"-terpyridine-4,4',4"-tricarboxylic acid obtained.[23] In addition, the yields are reasonable and the starting materials are either commercially available or easily accessible.

All reagents were used as supplied. Silica gel (0.060−0.200 mm) was obtained from Chemie Uetikon. Melting points were measured on Büchi 535 and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 250 spectrometer and referenced against TMS. Time of flight (Maldi) spectra were recorded using a PerPespective Biosystems Voyagers-RP Biospectrometry Workstation. 2,6-Dihydroxy-4-methylpyridine (**1**) was supplied by Merck.

2,6-Dibromo-4-methylpyridine (2)

A mixture of 2,6-dihydroxy-4-methylpyridine (**1**) (10.0 g, 0.080 mol) and PBr_3 (32.5 g, 0.012 mol) was heated at 175 °C in an autoclave for 6 h. The autoclave was cooled down over a period of 20 h. H_2O (300 mL) was cautiously added to the black product and filtered. The dark aqueous phase was extracted with CH_2Cl_2 (5 × 40 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed. Compound **2** was then purified on silica gel using CH_2Cl_2/hexane (4:1); yield: 7.0 g (35%) (Table).

2,6-Dibromo-4-hydroxymethylpyridine (4)

$NaBH_4$ (0.30 g, 0.079 mol) was added in portions to a solution of **3** (0.50 g, 0.016 mol) in EtOH (30 mL) at 0 °C and the mixture was refluxed for 3 h. EtOH was removed and H_2O (20 mL) was added. Excess $NaBH_4$ was destroyed by the addition of 1 N HCl (5 mL) and the solution was neutralised with Na_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and solvent was removed. Compound **4** was then purified on silica gel using CH_2Cl_2/EtOAc (3:1); yield: 0.34 g (79%) (Table).

2,6-Dibromopyridine-4-carbaldehyde (5)

To a solution of oxalyl chloride (0.17 g, 1.35 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added under N_2 a solution of DMSO (0.23 g, 2.94 mmol) in CH_2Cl_2 (2 mL). After 10 min a solution of **4** (0.33 g, 1.23 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 15 min and Et_3N (0.62 g, 6.13 mmol) was added. The cooling bath was removed and H_2O (20 mL) was added at r.t. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed. Compound **4** was then purified on silica gel using CH_2Cl_2/hexane (1:1); yield: 0.26 g (81%) (Table).

Stille Coupling Reaction; General Procedure

A mixture of 2,6-dibromopyridines **2** and **5** (200 mg), stannyl compounds **6**−**9** (2 mol equiv) and $(Ph_3P)_4Pd$ (0.02 mol equiv) was heated under N_2 in toluene (50 mL) for 16 h. Upon cooling to r.t., sat. NH_4Cl (20 mL) was added and the organic phase separated. The aqueous phase was extracted with toluene (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed. Concd HCl (20 mL) was added to the residue and extracted with CH_2Cl_2 (3 × 30 mL). The aqueous phase was cautiously neutralised with solid NaOH. After extraction with CH_2Cl_2 (3 × 30 mL) the combined organic phases were dried ($MgSO_4$) and the solvent was removed. The terpyridine ligands were then purified on silica gel with CH_2Cl_2/hexane (3:2). All compounds were recrystallised from EtOH (Table).

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