STUDIES ON ORGANOMETALLIC COMPOUNDS. IX.[1] SYNTHESIS OF BIPYRIDINE *N*-OXIDES AND TERPYRIDINES BY PALLADIUM CATALYZED CROSS-COUPLING REACTION OF TRIMETHYLSTANNYLPYRIDINES WITH BROMOPYRIDINES

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Abstract - Reaction of trimethylstannylpyridines with bromopyridines in the presence of $Pd(PPh_3)_4$ directed toward a practical use was accomplished, giving all nine pyridinylpyridine *N*-oxides in satisfactory yields. Similarly, nicotelline and 2,2':6',2"-terpyridine were produced in good yields.

There have been published many literatures concerning with pyridinylpyridine *N*-oxides owing to their potential intermediates.[2] However, the synthetic methods presently used possess some limitations in view of practical preparation. Thus, we initiated this investigation as an extension of previous work[3] and wish to report herein the synthesis of pyridinylpyridine *N*-oxides by cross-coupling reactions between trimethylstannylpyridines[4] and bromopyridine *N*-oxides along with synthesis of nicotelline and 2,2':6',2"-terpyridine.

Two methods to access to pyridinylpyridine *N*-oxide were considered; one was a cross-coupling between trimethylstannylpyridine *N*-oxide and halopyridine and another was from trimethylstannylpyridine and halopyridine *N*-oxide. Attempts of preparation of trimethylstannylpyridine *N*-oxide by the stannylation of bromopyridine *N*-oxide with trimethylstannyl sodium[5] (**1**) were unsuccessful,

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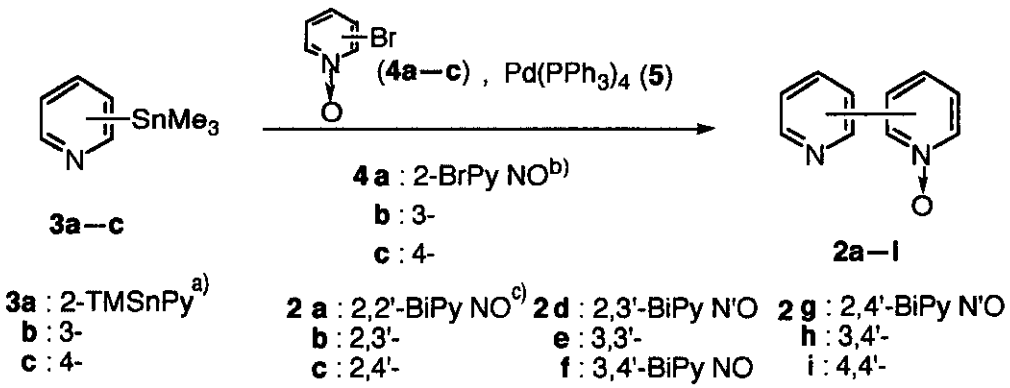
This paper is dedicated to the late Professor Yoshio Ban.

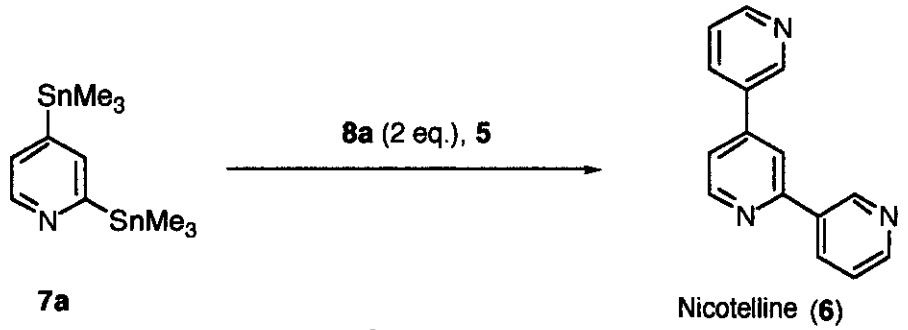
leading to only reduction of the *N*-oxide function with **1**. Hence, synthesis of pyridinylpyridine *N*-oxides (**2**) was alternatively accomplished by reaction of trimethylstannylpyridines (**3**) with bromopyridine *N*-oxide (**4**) in the presence of a palladium catalyst. The cross-coupling reaction proceeded more readily than that of bromopyridine with trimethylstannylpyridines previously described;[3] a solution of 4-trimethylstannylpyridine (**3c**) and 2-bromopyridine *N*-oxide (**4a**) in toluene was heated under reflux in a catalytic amount of $Pd(PPh_3)_4$ (**5**) for 5 h furnished 2-(4'-pyridinyl)pyridine *N*-oxide (**2c**) in good yield (Scheme 1). Tables I and II briefly summarize the results obtained. This method gives much advantages in synthesis of pyridinylpyridine *N*-oxides (**2**) because of their difficulty in alternative *N*-oxidation.



a) TMSnPy = trimethylstannylpyridine b) BrPy NO = bromopyridine *N*-oxide
c) BiPy NO = pyridinylpyridine *N*-oxide

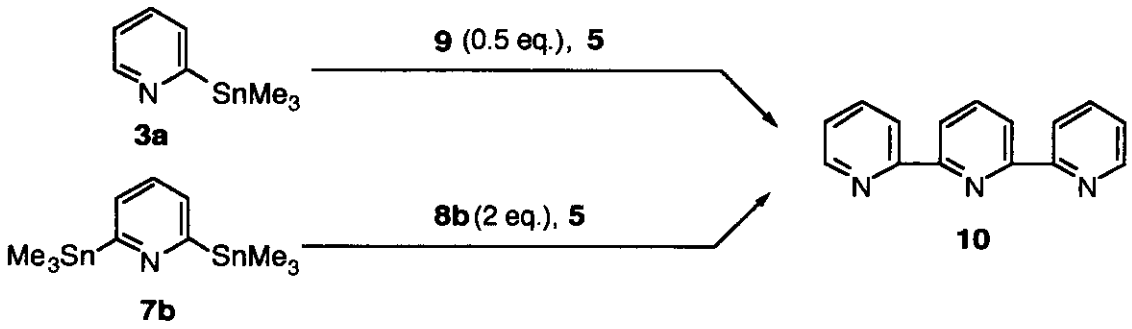
Scheme 1

Nicotelline (**6**) was similarly prepared in an improved yield from 2,4-bis(trimethylstannyl)pyridine (**7a**) and 3-bromopyridine (**8a**) (Scheme 2). Tables I and II summarize the result obtained.



Scheme 2

Terpyridine[6] also has attracted considerable attention because of the particular property of co-ordination, of which synthesis was carried out by use of both 2-trimethylstannylpyridine (**3a**) and 2,6-bis(trimethylstannyl)pyridine (**7b**) as the starting compounds; thus, when 2 eq of **3a** were treated with 2,6-dibromopyridine (**9**) in toluene under reflux in a catalytic amount of **5**, 2,2':6',2"-terpyridine (**10**) was obtained in good yield. Also, reaction of **7b** with 2 eq of 2-bromopyridine (**8b**) provided terpyridine **10** in high yield (Scheme 3). Tables I and II summarize the results obtained.



Scheme 3

Table I. Synthesis of Pyridinylpyridine *N*-Oxides (**2a-i**) and Terpyridines (**6** and **10**)

TMSnPy	BrPy (eq)	product	Yield (%)	solvent	Time (h)	Temp (°C)	mp (°C) [lit.]	Picrate mp (°C) [lit.]
3a	**4a** (1.1)	**2a**	78	xylene	3	120	45-50 [58-60][2g)]	188-189
3b	**4a** (1.1)	**2b**	68	toluene	4	reflux	116-117	—
3c	**4a** (1.1)	**2c**	65	toluene	5	reflux	115-117 [119-121][2g)]	190-193.5
3a	**4b** (1.1)	**2d**	62	toluene	6	reflux	139-140	—
3b	**4b** (1.1)	**2e**	58	toluene	4	110	149-151 [151-153][2g)]	156-160
3c	**4b** (1.1)	**2 f**	61	toluene	8	reflux	77-78 [78][2g)]	—
3a	**4c** (1.1)	**2g**	57	xylene	6	reflux	169-173	160-161
3b	**4c** (1.1)	**2h**	61	toluene	8	reflux	53-55	199-202
3c	**4c** (1.1)	**2 i**	70	xylene	6	reflux	169-172 [174-176][2g)]	215-218
7a	**8a** (2.0)	**6**	75	toluene	8	reflux	147-149 [147.5-148.5][7)]	214-215 [216-217][7)]
3a	**9** (0.5)	**10**	74	toluene	8	reflux	89-91 [84-86][6b)]	—
7b	**8b** (2.0)	**10**	72	toluene	8	reflux		

Table II. Spectral Data of Pyridinylpyridine *N*-Oxides (**2a—l**) and Terpyridines (**6** and **10**)

product	Ir (cm^{-1})	Nmr ($CDCl_3$) δ (J = Hz)	El—ms (*m/z*)	Analysis (%) calcd (found) C	H	N
2a	1220 1580	7.23-7.42 (3H, m), 7.66-8.36 (3H, m), 8.65-8.93 (2H, m)	—		—	
b	1245 1587	7.16-8.83 (4H,m), 8.20-8.50 (2H,m), 8.60-8.85 (1H,m), 8.90-9.00 (1H,m)	172	69.76 (69.66	4.68 4.65	16.27 16.10)
c	1240 1590	7.26-7.55 (3H,m), 7.76 (2H, d, J = 6), 8.26-8.39 (1H, m), 8.71(2H, d, J = 2)	—		—	
d	1245 1587	7.33-7.65 (4H, m), 8.33-8.60 (2H, m), 8.70 (1H, d, J = 2), 9.00 (1H, d, J = 2)	172	69.76 (69.86	4.68 4.75	16.27 16.37)
e	1210 1600	7.36-7.75 (3H,m), 8.03-8.30 (2H, m), 8.66 (2H, m), 8.91 (1H, d, J =2)	—		—	
f	1230 1586	7.33-7.85 (4H, m), 8.33-8.60 (2H, m), 8.90 (1H, d, J = 2), 9.00 (1H, d, J =2)	—		—	
g	1240 1590	7.25-7.41 (1H,m), 7.75-8.19 (2H,m), 7.93 (2H, d, J =6), 8,38 (2H, d, J =6), 8.67-8.74 (1H, m)	172	69.76 (69.66	4.68 4.54	16.27 16.10)
h	1230 1590	7.35-7.96 (4H,m), 7.71 (2H, d, J = 6), 8.50 (2H, d, J = 6)	172	69.76 (69.96	4.68 4.78	16.27 16.56)
i	1230 1600	7.61-7.84 (4H, m), 8.34 (2H, d, J = 6), 8.70 (2H, d, J = 6)	—		—	
6	1600	7.20-7.70 (3H.m), 7.75 -8.10 (2H, m), 8.20-8.50 (1H, m), 8.50-9.10 (4H, m), 9.25-9.30 (1H, m)	—		—	
10	1595	7.15-7.50 (2H, m), 7.66-8.15 (3H, m), 8.33-8.81 (6H, m)	—		—	

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Ir spectra were taken with a PERKIN ELMER 1600 series FT-ir and Shimadzu ir-400. ^{1}H-Nmr spectra were recorded on a JEOL JNM PMX-60 and 60Si. Chemical shifts are recorded in δ (ppm) from TMS (internal standard). The following abbreviations are used : d = doublet, m = multiplet. Ms spectra were measured on a JEOL-DX303. All analytical data were measured on a PERKIN ELMER 2400 CHN Elemental Analyzer. Toluene and xylene were distilled from $CaCl_2$ and dried over sodium wire.

2-(2'-Pyridinyl)pyridine *N*-Oxide (2a); General procedure for 2b - i

A mixture of **3a** (2 g, 8.27 mmol), **4a** (1.4 g, 8.86 mmol), and **5** (0.12 g, 0.104 mmol) in xylene (60 ml) was heated under reflux for 12 h, then the solvent was removed *in vacuo*. The residue was extracted with hot 15% hydrochloric acid (HCl). The HCl layer was allowed to cool at room temperature, then filtered. The filtrate was concentrated *in vacuo*, made alkaline with solid Na_2CO_3, and extracted with chloroform ($CHCl_3$, 30 ml x 3). The $CHCl_3$ layer was dried over K_2CO_3, then allowed to stand at room temperature for 1 h. The $CHCl_3$ layer was filtered followed by concentration of the filtrate *in vacuo*. The residue was purified by column chromatography on alumina (eluted with ether) to give **2a**. Yield : 1.10 g (78%).

Nicotelline (6)

A mixture of **7a** (0.40 g, 1.0 mmol), **8a** (0.31 g, 2.0 mmol), and **5** (0.06 g, 0.05 mmol) in toluene (60 ml) was heated under reflux for 8 h. The resulting mixture was worked up by the same procedure as described above for **2a** to give **6**. Yield : 0.17 g (75%).

2,2': 6',2"-Terpyridine (10)

Method A : A mixture of **3a** (2.43 g, 5.0 mmol), **9** (1.57 g, 2.5 mmol), and **5** (0.28 g, 0.25 mmol) in toluene (60 ml) was heated under reflux for 8 h. The resulting mixture was worked up by the same procedure as described above for **2a** to give **10**. Yield : 0.84 g (74%).

Method B : A mixture of **7b** (0.40 g, 1.0 mmol), **8b** (0.31 g, 2.0 mmol), and **5** (0.06 g, 0.05 mmol) in toluene (60 ml) was heated under reflux for 8 h. The resulting mixture was worked up by the same procedure as described above for **2a** to give **10**. Yield : 0.16 g (72%).

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