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

Yutaka Yamamoto*, Takuo Tanaka, Masayoshi Yagi, and Masayuki Inamoto

Tohoku College of Pharmacy, 4-1, Komatsushima 4 chome, Aoba-ku, Sendai 981, Japan

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 work³ and wish to report herein the synthesis of pyridinylpyridine *N*-oxides by cross-coupling reactions between trimethylstannylpyridines⁴ 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 sodium⁵ (**1**) were unsuccessful, 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.





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.



Terpyridine⁶ 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 2,6bis(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

TMSnPy	B (e	rPy 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] ² g)	188-189
Зb	4a	(1.1) 2b	68	toluene	4	reflux	116-117	_
3c	4a	(1.1) 2c	65	toluene	5	reflux	115-117 [119-121] ² 9)	190-193.5
3a	4 b	(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] ² g)	-
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) 21	70	xylene	6	reflux	169-172 [174-176] ² 9)	215-218
7a	8a	(2.0) 6	75	toluene	8	reflux	147-149 (147 5-149 517)	214-215
3a	9	(0.5) 10	74	toluene	8	reflux	89-91 [84-8616b]	
7b	8b	(2.0) 10	72	toluene	8	reflux	[0+ 00]	

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

product	Ir (cm ⁻¹)	Nmr (CDCl ₃) δ (<i>J</i> = Hz)	El—ms (m/z)	An C	alysis calcd found) H	(%) N
2a	1220	7.23-7.42 (3H, m), 7.66-8.36 (3H, m),			<u> </u>	
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, $J \approx 2$), 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, I=2)			—	
g	1240 1590	7.25-7.41 (1H,m), 7.75-8.19 (2H,m), 7.93 (2H, d, <i>J</i> =6), 8,38 (2H, d, <i>J</i> =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, $J \approx 6$)	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. If spectra were taken with a PERKIN ELMER 1600 series FT-ir and Shimadzu ir-400. ¹H-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 \approx 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 CaCl₂ and dried over sodium wire.

2-(2'-Pyridinyi)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 (HCi). The HCI layer was allowed to cool at room temperature, then filtered. The filtrate was concentrated *in vacuo*, made alkaline with solid Na₂CO₃, and extracted with chloroform (CHCl₃, 30 ml × 3). The CHCl₃ layer was dried over K₂CO₃, then allowed to stand at room temperature for 1 h. The CHCl₃ 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%).

ACKNOWLEDGEMENT

The Authors are indebted to Dr. S. Suzuki and Mr. S. Sato of this College for mass spectral and elemental analysis measurements.

REFERENCES AND NOTES

1. Part VIII : Y. Yamamoto, H. Ouchi, and T. Tanaka, Chem. Pharm. Bull., submitted.

2. (a) F. H. Burstall, J. Chem. Soc., 1938, 1662. (b) J. C. Craig and K. K. Purushothaman, J. Org.

Chem., 1970, 35, 1721. (c) D. E. Butler, P. Base, I. C. Nordin, F. P. Hauck, Jr., and Y. J. L'Italien,
J. Med. Chem., 1971, 14, 575. (d) R. Fielden and L. A. Summers. J. Heterocycl. Chem., 1974, 11,
299. (e) I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, and S. Martelli, J. Med.
Chem., 1981, 24, 1181. (f) D. Wenkert and R. B. Woodward, J. Org. Chem., 1981, 48, 283. (g) D.
B. Moran, G. O. Morton, and J. D. Albright, J. Heterocycl. Chem., 1986, 23, 1071.

- 3. Y. Yamamoto, Y. Azuma, and H. Mitoh, Synthesis, 1986, 564.
- 4. Trimethylstannylpyridines were prepared according to the reported procedure; Y. Yamamoto and A. Yanagi, *Chem. Pharm. Bull.*, 1982, **30**, 1731.
- 5. The method of employing trimethylstannyl sodium is more satisfactory than the others presently available as the stannylating agent.
- (a) E. C. Constable, M. D. Ward, and S. Corr, *Inorganica. Chimi. Acta*, 1988, 141, 201. (b) D. L. Jameson and L. E. Guise, *Tetrahedron Lett.*, 1991, 32, 1999. (c) R. G. Newkome, F. Cardullo, E. C. Constable, C. N. Moorefield, and A. M. W. Cargill Thompson, *J. Chem. Soc., Chem. Commun.*, 1993, 925. (d) F. Bargelletti, L. Flamigini, V. Balzani, J. -P. Collin, J. -P. Sauvage, A. Sour, E. C. Constable, and A. M. W. Cargill Thompson. *J. Chem. Soc., Chem. Commun.*, 1993, 925. (d) F. Bargelletti, L. Flamigini, V. Balzani, J. -P. Collin, J. -P. Sauvage, A. Sour, E. C. Constable, and A. M. W. Cargill Thompson. *J. Chem. Soc., Chem. Commun.*, 1993, 942.
- 7. J. Thesing and A. Müller, Chem. Ber., 1957, 90, 711.

Received, 18th November, 1994