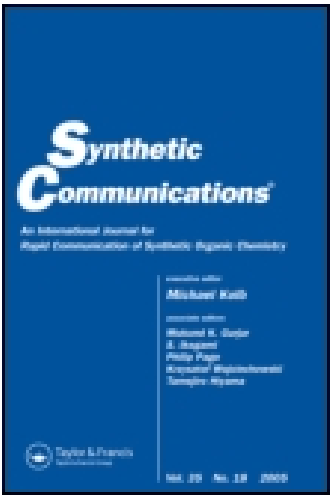

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A Facile Synthesis of 4-Ar-2-bromopyridine and Its 2,2′-Bipyridine Derivatives

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A Facile Synthesis of 4-Ar-2-bromopyridine and Its 2,2′-Bipyridine Derivatives

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ABSTRACT

By means of selective cross-coupling of ArMgBr with 2-bromo-4-iodopyridine in the presence of a catalytic amount of $Pd(PPh_3)_4$, 4-Ar-2-bromopyridines were facilely one-step synthesized. These pyridine compounds were smoothly transformed into their 2,2′-bipyridine derivatives via Stille-type cross-couplings.

Key Words: 4-Ar-2-bromopyridine; 2,2-Bipyridine; 2-Bromo-4-iodopyridine; Stille-coupling.

2,2′-Bipyridines have been extensively used in supermolecular chemistry, molecular biology, and photochemistry.[1,2] As a result, the efficient syntheses

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of these compounds have always attracted the attention of researchers. Among various synthetic approaches to these compounds,[3,4] modern palladium(0)-catalyzed Suzuki,[5] Negishi,[6], and Stille[7]-type cross-couplings provide the most effective methods.

As part of our investigations, we wished to prepare a series of 4-Ar-2,2′-bipyridines or 4-Ar-4′-Ar′-2,2′-bipyridines. Obviously 4-Ar-2-bromopyridines are the key building blocks for these bipyridine compounds because they can be conveniently and flexibly built up into the required bipyridines via the above-mentioned cross-couplings. For instance, transformations of 4-Ar-2-bromopyridines into symmetrical bipyridines can be easily achieved by homo-couplings,[8] while unsymmetrical bipyridines can be achieved in the following two ways: (1) directly coupled with 2-pyridyl organometallics; (2) transformed into the corresponding organometallics, then coupled with 2-pyridyl halides.

4-Ar-2-bromopyridines can be synthesized by reported procedures[9] involving: (a) preparation of 4-Ar-pyridines;[8] (b) 2-amination via the Chichibabin reaction; (c) Sandermeyer substitution of bromide. As a linear route with three steps, this synthetic strategy seems unattractive and inconvenient for a variety of 4-Ar-2-bromopyridines. Very recently Bouillon[10] reported a general synthetic approach to 4-Ar-2-bromopyridines based on the Suzuki couplings of 2-halopyridin-4-yl-boronic acids with aryl halides. Obviously these syntheses suffer from inconvenience of preparing boronic acids. Recently we developed an efficient and convenient synthesis of 2-bromo-4-iodopyridine via halogen-dance from 2-bromopyridine.[11] Therefore, we considered that a variety of 4-Ar-2-bromo-pyridines can be facilely one-step prepared by selective substitutions of 2-bromo-4-iodopyridine (at 4-position) through cross-couplings of ArMgX and 2-bromo-4-iodopyridine.

Cross-couplings of ArMgx to halopyridines performed under the catalysis of $Ni(PPh_3)_2Cl_2$ and $PdCl_2(dppb)_2$ have been reported.[9,12] During the selective cross-couplings of ArMgX to 2-bromo-4-iodopyridine (at 4-position) we selected three readily available catalysts to promote the couplings: (a) CuI; (b) $Ni(PPh_3)_2Cl_2$; (c) $Pd(PPh_3)_4$. Experiment results revealed that the best catalyst was $Pd(PPh_3)_4$ and the optimal temperature was $-40^{\circ}C$. When $Ni(PPh_3)_2Cl_2$ was used, the reaction consumed 2-bromo-4-iodopyridine almost completely at $-40^{\circ}C$ in tetrahydrofuran (THF); however, the substitutions of bromine (by ArMgX or homo-coupling) also occurred. On the other hand, in the presence of CuI, the coupling was sluggish and incomplete with excess ArMgX at $-10^{\circ}C$, and its optimized yield was only approximately 40%. We their prepared a series of 4-Ar-2-bromopyridines in 54%–70% using $Pd(PPh_3)_4$, as summarized in Table 1.

Having efficiently prepared 4-Ar-2-bromopyridines, we next synthesized 2,2′-bipyridines through homo-couplings and the Stille-type couplings, respectively. According to reported procedures[8] we found that the yields

of homo-couplings of **2a** did not exceed 30%.[11] We found debromination occurred seriously during the couplings. The preparations via the Stille couplings were accomplished in two ways, as illustrated in Sch. 1: (1) **2a** cross-coupled with 4-RC_5H_3N-2-$SnBu_3$; (2) the tributylstannyl derivative of **2a** cross-coupled with 2-Br-4-R-pyridine. These couplings were carried out according standard procedures,[7] and the yields were moderate (as summarized in Table 1).

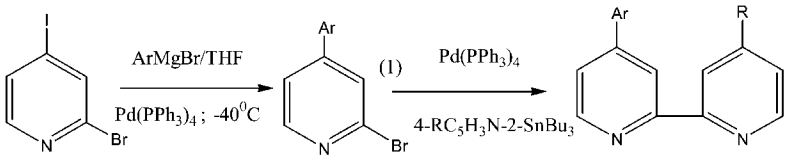
In summary, by virtue of the selective cross-couplings of ArMgBr with 2-bromo-4-iodopyridine, this synthetic strategy furnishes us with an efficient preparation of 2,2-bipyridine derivatives with only two or three steps.

EXPERIMENTAL

Melting points were measured using a RY-1 capillary melting point apparatus and uncorrected (China). ^1H and ^{13}CNMR spectra were recorded in $CDCl_3$ on a 500 MHz Brucker instrument (Germany) using tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a 60 FT-IR Vaatar3 spectrometer (Italy).

General Procedure for the Syntheses of 2-Bromo-4-Ar-pyridines

A solution of 2-bromo-4-iodopyridine (2.0 g, 7 mmol), $Pd(PPh_3)_4$ (400 mg, 0.35 mmol) in 50 mL THF was cooled to −40°C. A solution of



	Ar
2a	4-$CH_3C_6H_4$
2b	4-$CH_3OC_6H_4$
2c	4-ClC_6H_4
2d	1-$C_{10}H_9$

	3a	**3b**
Ar	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$
R	H	CH_3

Scheme 1.

Table 1. Syntheses of 2 via selective cross-couplings of ArMgBr with 2-bromo-4-iodiopyridine and 3 via Stille-couplings.

S.N.	Yield (%)	M.p. (°C)	Spectroscopic data					
			E. A. (%)	Calc.	(Found)	MS M/z (%)	^{1}HNMR δ_H (500 MHz, $CDCl_3$)	^{13}CNMR δ_C (500 MHz, $CDCl_3$)
			C	H	N			
2a[a]	65	68–70 54–55						
2b	54		54.57 (54.48)	3.79 (3.30)	5.31 (4.90)	265 ([M + 1]$^+$,43), 263 (47), 184 (62), 169 (53), 140 (100)	8.38 (1H, d, J = 5.2), 7.68 (1H, d, J = 0.96), 7.59 (2H, d, J = 8.7), 7.44 (1H, dd, J = 1.4; 5.2), 7.03 (2H, d, J = 8.5), 3.89 (3H,s).	161.5, 151.2, 150.7, 143.3, 129.3, 128.7, 125.5, 120.6, 115.1, 55.8
2c	70	129–131	49.18 (49.16)	2.61 (2.22)	5.22 (4.84)	269 (M$^+$, 74), 267 (61), 188 (100), 153 (87)	8.4 (1H, d, J = 5.0), 7.69 (1H, d, J = 1.1), 7.56 (2H, dd, J = 1.8; 8.0), 7.5 (2H,d, J = 8.0), 7.45 (1H, dd, J = 1.5; 5.2).	150.9, 150.4, 143.5, 136.5, 135.6, 129.9, 128.7, 126.1, 121.0
2d	55	112–113	63.40 (63.33)	3.52 (3.42)	4.93 (4.78)	285 ([M + 1]$^+$, 77), 283 (84), 204 (100)	8.52 (1H, d, J = 4.8); 7.95 (2H, d, J = 8.0), 7.81 (1H, d, J = 8.3), 7.68 (1H,s), 7.52 ~ 7.58 (3H, m), 7.42 ~ 7.44 (3H, m).	152.1; 150.5, 142.8, 136.2, 134.2, 130.9, 129.9, 129.5, 129.0,127.4, 126.8, 125.7, 125.2, 124.7

3a[b]	45 (52)	117–118	82.93 (83.22)	5.69 (5.56)	11.38 (11.2)	(ESI): 269.1 $(MNa)^+$247.1 $(MH)^+$	8.74 (2H,s), 8.69 (1H, t, J = 1.0); 8.48 (1H, dd, J = 1.0; 8.0), 7.87 (1H, dd, J = 1.5; 7.5), 7.71 (2H, d, J = 8.0), 7.56 (1H, dd, J = 1.5; 5.0), 7.32 ~ 7.37 (3H, m); 2.45 (3H, s)	157.0, 156.6, 149.7, 149.5, 139.6, 137.4, 135.7, 130.2, 127.4, 124.2, 121.8, 121.7, 119.2, 21.7
3b	48	147–147.5	83.08 (83.48)	6.15 (6.07)	10.77 (10.45)	(ESI): 283.2 $(MNa)^+$261.2 $(MH)^+$	8.73 (1H, d, J = 5.0), 8.69 (1H, s), 8.60 (1H, d, J = 5.0), 8.32 (1H,s), 7.72 (2H, d, J = 8.0), 7.56 (1H, dd, J = 2.0; 5.0), 7.32 (2H, d, J = 8.0), 7.19 (1H, d, J = 4.0), 2.49 (3H,s), 2.45 (3H, s)	149.9, 149.2, 139.6, 135.7, 130.2, 127.4, 125.2, 122.6, 121.7, 119.4, 21.7, 21,6

[a]**2a** has been reported in Ref.[8].

[b]The yield in the parentheses represents that of Stille coupling carried out in (2) manner.

ArMgBr (0.74 mmol) in THF was added and kept at that temperature. After completion of the coupling [monitored by thin layer chromatography (TLC)], the reaction was quenched by a saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2. After dried over anhyd K_2CO_3, CH_2Cl_2 was evaporated and the resulting crude product was purified by flash chromatography (petroleum-ethyl acetate-triethylamine; 180 : 10 : 1).

General Procedure for the Syntheses of 4-Ar-4′-R-2,2′-pyridines via Stille-Coupling

To a solution of 2-tributylstannyl-4-R-pyridine[7] [or 4-(4-MeC_6H_4)-2-tributylstannyl-pyridine] (12 mmol), $Pd(PPh_3)_4$ (500 mg, 0.44 mmol) in 50 mL xylene was added 2-bromo-4-(4-MeC_6H_4)pyridine (or 4-R-pyridine) (10 mmol). The reaction mixture was stirred at 120°C–130°C under an Ar atmosphere. After completion of the coupling (monitored by TLC), the reaction was quenched by a saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2. After being dried over anhyd K_2CO_3, CH_2Cl_2 was evaporated and the resulting crude product was purified by flash chromatography (petroleum-ethyl acetate-triethylamine; 180 : 10 : 1).

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