Palladium-catalysed alkynylation of 2- or 3-bromopyridine

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2- or 3-Alkynylpyridines were prepared using a palladium complex, in the absence of copper ions or amines. The mild procedure tolerated a range of 1-alkynes giving 2- or 3-alkynylpyridine in moderate to good yield.

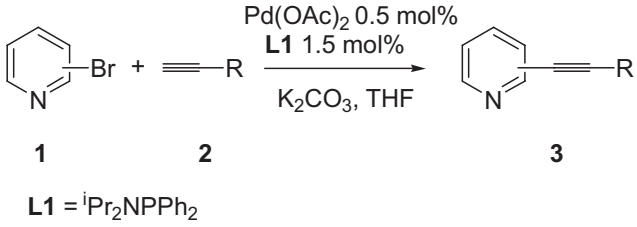
Keywords: palladium-catalysed alkynylation, 2- or 3-bromopyridine

Palladium-catalysed coupling of terminal alkynes with aryl or alkenyl iodides, is one of the most straightforward methods for the preparation of aryl alkynes and conjugated enynes.[1] Usually the coupling is carried out in the presence of catalytic amounts of a palladium complex as well as copper iodide in an amine as solvent in order to obtain good yield.[2, 3]

2- or 3-Alkynylpyridines are not only synthetically important intermediates for preparation of various compounds but also biologically important. However, less attention was paid in the comprehensive synthesis of 2- or 3-alkynylpyridine and the copper-free alkynylation of 2- or 3-bromopyridine was rarely reported. The Cu(I) acetylides formed *in situ* could undergo oxidative dimerisation to give diaryldiacetylenes when they are exposed to air or an oxidant (a reaction known as the Glaser coupling).[4] These by-products are generally difficult to separate from the desired products.

Zhang reported (diisopropylamino)diphenylphosphane **L1**, which is air-stable and easy to prepare, showed high efficiency in the Suzuki cross coupling reaction as well as in Sonogashira reaction.[5] Accordingly, we hope to enlarge the application scope of the ligand in the Sonogashira reaction. Here we report a copper and amine free alkynylation reaction of 2- or 3-bromopyridine employing aminophosphine ligand (Scheme 1).

For the study, based on Zhang's results,[5] THF was chosen as the solvent and potassium carbonate as the base. The reaction was run at 65°C under nitrogen in the presence of a combination of $Pd(OAc)_2$ and **L1** as catalyst.



Scheme 1

Treatment of a mixture of 3-bromopyridine **1a** (314 mg, 2 mmol), 1-ethynylbenzene **2a** (243 mg, 2.4 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), and **L1** (43.1 mg, 0.15 mmol) in dry THF (5 ml) at 65°C under inert atmosphere for 8 hours produced the desired product **3aa** in 82% yield. This is a promising result, since no copper salt and amine was required. Then a series of alkynes was tested in the reaction conditions. Results are summarised in Table 1. When 3-bromopyridine acted as substrate, all of the alkynes substrates that possess alkyls or aryls attached to the triple C–C bonds worked well under the reaction conditions in the absence of CuI or amine. Because the ligand will react with primary alcohol, prop-2-yn-1-ol was not a proper substrate in the procedure.[6] However, the 3^0 alcohol substrates, such as 2-methylbut-3-yn-2-ol (**2e**) and 1-ethynyl cyclohexanol (**2g**) were good substrates in the reaction and the yield reached 79% and 85%, respectively (Table 1, entries 4, 7). When the hydroxyl group of **2e** was protected by a methyl group, the coupling yield slightly

Table 1 Alkynylation of 2- or 3-bromopyridine

Entry	Bromopyridine	Alkyne	Yield/%[a]
1	3-bromopyridine	Ethnynlbenzene	82
	1a	**2a**	**3aa**
2	**1a**	Hex-1-yne	70
		2b	**3ab**
3	**1a**	Ethynyltrimethylsilane	86
		2c	**3ac**
4	**1a**	2-Methylbut-3-yn-2-ol	79
		2d	**3ad**
5	**1a**	3-Methoxy-3-methylbut-1-yne	89
		2e	**3ae**
6	**1a**	*N,N*-Diethylprop-2-yn-1-amine	54
		2f	**3af**
7	**1a**	1-Ethynylcyclohexanol	85
		2g	**3ag**
8	**1a**	1-Ethynylcyclohex-1-ene	96
		2h	**3ah**
9	2-Bromopyridine	**2a**	47
	1b		**3ba**
10	**1b**	**2e**	47 **3be**
11	**1b**	**2f**	59 **3bf**
12	**1b**	**2h**	95 **3bh**

[a]Isolated yield, all reactions were run with bromopyridines (2 mmol), alkynes (2.4 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), K_2CO_3 (828 mg, 6 mmol) and **L1** (43.1 mg, 0.15 mmol) in 5 ml of THF at 65°C for 8 h.

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increased to 89% (Table 1, entry 5). If 2-bromopyridine acted as substrate, except for **2h**, only moderate yields were achieved (Table 1, entries 9, 10, 11). For substrate **2h**, which possesses both a C–C double bond and a C–C triple bond, only the Sonogashira cross-coupling product (**3ah**, **3bh)** was isolated in 96% and 95% yield, respectively, and no Heck reaction product was detected (Table 1, entries 8, 12).

In conclusion, we have developed a facile and mild way to the alkynylation of 3- or 2-bromopyridine in the absence of copper and amine. Aminophosphine was used as the ligand. The ligand is easy to prepare from commercially available material and is air-stable.

Experimental

General

All reactions were conducted under a nitrogen atmosphere using standard Schlenk techniques. Column chromatography was performed using EM Silica gel 60 (300–400 mesh), ^{1}H NMR was recorded on a 300 MHz spectrometer, and ^{13}C NMR was at 75 MHz. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard.

Materials

THF was distilled from sodium-diphenylacetone prior to use. K_2CO_3, 2-, 3-bromopyridine and alkynes were used directly as obtained commercially unless otherwise noted.

General procedure for alkynylation reaction

Under nitrogen atmosphere, a Schlenk reaction tube was charged with bromo pyridine **1** (2 mmol), alkyne **2** (2.4 mmol), K_2CO_3 (828 mg, 6 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), **L1** (43.1 mg, 0.15 mmol) and THF (5 ml). The reaction tube was purged with N_2 under a dry ice bath. After the mixture was heated at 65°C for 8 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel to give the product **3**.

3aa: *3-(2-phenylethynyl)pyridine*.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.57–8.55 (m, 1H), 7.83–7.80 (m, 1H), 7.57–7.54 (m, 2H), 7.39–7.36 (m, 3H), 7.31–7.27 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 148.5, 138.4, 131.7, 128.8, 128.4, 123.0, 122.5, 120.5, 92.6, 85.9.

3ab: *3-(hex-1-ynyl)pyridine*.[8] ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.49–8.47 (m, 1H), 7.69–7.65 (m, 1H), 7.26–7.19 (m, 1H), 2.43 (t, J = 7.1 Hz, 2H), 1.63–1.52 (m, 2H), 1.50–1.43 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 152.3, 147.9, 138.4, 122.8, 121.2, 94.0, 77.4, 30.6, 22.0, 19.1, 13.6.

3ac: *3-(2-(trimethylsilyl)ethynyl)pyridine*.[9] ^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1H), 8.52–8.50 (m, 1H), 7.72–7.69 (m, 1H), 7.22–7.19 (m, 1H), 0.22 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 152.6, 148.7, 138.8, 122.8, 120.3, 101.4, 98.2, –0.60.

3ad: *2-methyl-4-(pyridin-3-yl)but-3-yn-2-ol*.[10] ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.52–8.50 (m, 1H), 7.72–7.69 (m, 1H), 7.27–7.23 (m, 1H), 3.20 (br, 1H), 1.63 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 152.1, 148.3, 138.7, 123.0, 120.1, 97.7, 78.6, 65.3, 31.3.

3ae: *3-(3-methoxy-3-methylbut-1-ynyl)pyridine*. ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.51–7.50 (m, 1H), 7.70–7.68 (m, 1H), 7.25–7.20 (m, 1H), 3.41 (s, 3H), 1.53 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 152.3, 148.6, 138.6, 122.9, 120.3, 94.5, 80.7, 70.8, 51.7, 28.2. MS (EI) *m/z* 175(M^+); IR (cm^{-1}) 3029, 2958, 2161, 1579, 1475, 1408, 1185, 1022, 863. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.31; H, 7.63.

3af: *N,N-diethyl-3-(pyridin-3-yl)prop-2-yn-1-amine*.[7] ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.51–8.49 (m, 1H), 7.71–7.68 (m, 1H), 7.24–7.22 (m, 1H), 3.65 (s, 2H), 2.61 (q, J = 7.2 Hz, 4H), 1.11 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 152.4, 148.3, 138.6, 122.9, 120.4, 88.2, 81.6, 47.3, 41.5, 12.6.

3ag: *1-(2-(pyridin-3-yl)ethynyl)cyclohexanol*. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.51–8.49 (m, 1H), 7.71–7.68 (m, 1H), 7.24–7.22 (m, 1H), 3.66 (br, 1H), 2.01–1.90 (m, 2H), 1.76–1.52 (m, 6H), 1.33–1.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 148.2, 138.6, 123.0, 120.3, 97.0, 80.6, 68.7, 39.8, 25.1, 23.3. MS (EI) *m/z* 201(M^+); IR (cm^{-1}) 3363, 2933, 2141, 1563, 1475, 1408, 1185, 1075, 863. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.87; H, 7.60.

3ah: *3-(2-cyclohexenylethynyl)pyridine*. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.47–8.44 (m, 1H), 7.69–7.65 (m, 1H), 7.25–7.18 (m, 1H), 6.25–6.22 (m, 1H), 2.01–1.90 (m, 2H), 2.22–2.13 (m, 4H), 1.67–1.58 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 152.0, 148.0, 138.2, 136.3, 122.9, 120.9, 120.3, 94.5, 83.3, 29.0, 25.8, 22.2, 21.4. MS (EI) *m/z* 183(M^+); IR (cm^{-1}) 3027, 2931, 2859, 2203, 1672, 1560, 1475, 1410, 842, 704. Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15. Found: C, 85.44; H, 7.30.

3ba: *2-(2-phenylethynyl)pyridine*.[11] ^{1}H NMR ($CDCl_3$) δ 8.64–8.63 (m, 1H), 7.69–7.66 (m, 1H), 7.63–7.59 (m, 2H), 7.55–7.52 (m, 1H), 7.38–7.36 (m, 3H), 7.27–7.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 150.1, 143.5, 136.1, 132.0, 128.9, 128.4, 127.1, 122.7, 122.3, 89.2, 88.6.

3be: *2-(3-methoxy-3-methylbut-1-ynyl)pyridine*. ^{1}H NMR ($CDCl_3$) δ 8.56–8.55 (m, 1H), 7.63–7.62 (m, 1H), 7.42–7.40 (m, 1H), 7.20–7.17 (m, 1H), 3.44 (s, 3H), 1.55 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 149.9, 143.0, 136.1, 127.2, 122.8, 91.0, 83.6, 70.8, 51.9, 28.1. MS (EI) *m/z* 175(M^+); IR (cm^{-1}) 3052, 2985, 2235, 1582, 1463, 1428, 1172, 1073, 863. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.31; H, 7.63.

3bf: *N,N-diethyl-3-(pyridine-2-yl)prop-2-yn-1-amine*.[7] ^{1}H NMR ($CDCl_3$) δ 8.54–8.52 (m, 1H), 7.59–7.57 (m, 1H), 7.39–7.36 (m, 1H), 7.19–7.15 (m, 1H), 3.65 (s, 2H), 2.62 (q, J = 7.2 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 149.8, 143.3, 136.0, 127.1, 122.6, 84.9, 84.6, 47.4, 41.3, 12.6.

3bh: *2-(2-cyclohexenylethynyl)pyridine*. ^{1}H NMR ($CDCl_3$) δ 8.53–8.51 (m, 1H), 7.60–7.55 (m, 1H), 7.37–7.34 (m, 1H), 7.15–7.11 (m, 1H), 7.30–7.28 (m, 1H), 2.23–2.21 (m, 2H), 2.13–2.11 (m, 2H), 1.68–1.57 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 149.8, 143.7, 137.2, 136.0, 126.8, 122.2, 120.1, 91.3, 86.2, 28.8, 25.8, 22.2, 21.4. MS (EI) *m/z* 183(M^+); IR (cm^{-1}) 3027, 2931, 2204, 1579, 1462, 1148, 1076, 842, 778. Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15. Found: C, 85.29; H, 7.26.

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