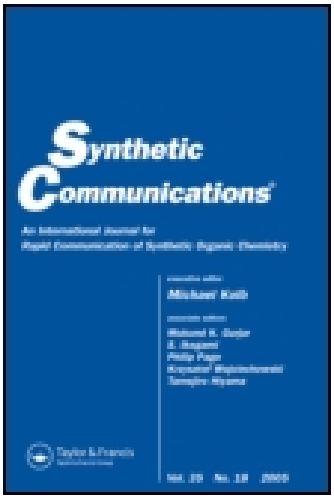

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Efficient Synthesis of Pyridylacrylonitriles via the Heck Reaction

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Efficient Synthesis of Pyridylacrylonitriles via the Heck Reaction

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Abstract: A new synthetic pathway to pyridylacrylonitriles has been developed based on a palladium-catalyzed Heck reaction. The optimized process and the preparation of related functionalized pyridylacrylonitriles are discussed.

Keywords: Heck reaction, palladium acetate, pyridylacrylonitrile

INTRODUCTION

Substituted pyridines, especially functionalized pyridines, exhibit a diverse range of effects when introduced into biological systems. Among them, pyridylacrylontriles (**2**) have attracted significant attention because of their potential as building blocks in medicinal chemistry.[1] Thus, the preparation of pyridylacrylontriles is of increasing interest.

There are several approaches for the synthesis of pyridylacrylonitriles, including the Knoevenagel condensation,[2] the Wittig reaction,[3] and the Peterson reaction.[4] However, these previously reported methods have

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certain disadvantages such as limited availability of starting materials, which limit their applications to some extent.

Recently Hutchinson et al.[5] and Berthiol et al.[6] described an efficient Heck coupling of 3-bromopyridine with acrylates. We herein report an improved synthesis of pyridylacrylonitriles via the Heck reaction between bromopyridines (**1**) and acrylonitrile (Scheme 1). Generally, a Heck coupling reaction system involves palladium acetate, ligand, base, solvent, and other additives. We investigated the effects of these factors and developed a practical synthesis of pyridylacrylonitriles.

RESULTS AND DISCUSSION

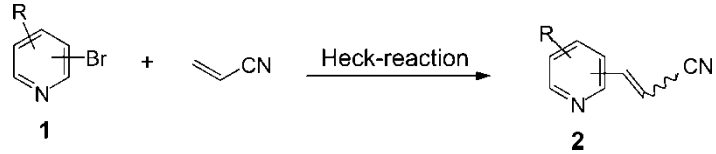
We selected 3-bromopyridine (**1a**) as the substrate in a model reaction and performed a comparative study of this coupling reaction under various conditions. The results are shown in Table 1.

From Table 1, it can be observed that temperature is important for this reaction. Different solvents worked well for this reaction, as long as they could sustain the reaction temperature; thus N-methyl-2-pyrrolidinone (NMP), toluene, and N,N-dimethylformamide (DMF) were good, but dioxane and acetonitrile gave low yields.

Generally, the ligands play important roles in Heck reaction. We screened four electron-rich phosphorous-based ligands including triphenylphosphine, tri-(*o*-tolyl)phosphine, tri-(2-furyl)phosphine, and tri-(2-thienyl)phosphine and found that tri-(*o*-tolyl)phosphine worked best (Entries 4 to 7).

The investigation of various bases was also performed. $NaHCO_3$ (66%) and triethylamine (TEA) (62%) gave much better results than Na_2CO_3, K_3PO_4, and NaOAc.

A number of reports have indicated that phase-transfer conditions are superior to Pd-catalyzed Heck reactions, and many reactions under Jeffery's conditions did give good yields.[7] Accordingly, we designed two reactions using tetra-n-butylammonium chloride as phase-transfer agent. We found that under these conditions the reactions completed faster and no ligand was necessary (Entries 9 and 10). Interestingly, the reaction worked well with TEA as base or in toluene (Entries 11 and 12). This fact suggests that tetra-n-butylammonium chloride in the reaction is not only the phase-transfer



Scheme 1.

Table 1. Heck reactions between 3-bromopyridine and acrylonitrile[a]

Entry	Temp. (°C)[b]	Ligand	Solvent	Base	Additive	Time (h)	Yield[c] (%)
1	90	(*o*-tol)$_3$P	DMA	TEA	—	24	18
2	110	(*o*-tol)$_3$P	DMA	TEA	—	24	54
3	140	(*o*-tol)$_3$P	DMA	TEA	—	24	46
4	110	(*o*-tol)$_3$P	DMF	TEA	—	24	62[d]
5	110	PPh_3	DMF	TEA	—	24	45
6	110	(2-thienyl)$_3$P	DMF	TEA	—	24	21
7	110	(2-furyl)$_3$P	DMF	TEA	—	24	17
8	110	(*o*-tol)$_3$P	DMF	$NaHCO_3$	—	24	66[d]
9	110	(*o*-tol)$_3$P	DMF	$NaHCO_3$	n-Bu_4NCl	4	85
10	110	—	DMF	$NaHCO_3$	n-Bu_4NCl	4	94
11	110	—	DMF	TEA	n-Bu_4NCl	16	85
12	110	—	Toluene	$NaHCO_3$	n-Bu_4NCl	16	90
13	110	—	Toluene	TEA	n-Bu_4NCl	16	74

[a]Unless otherwise noted, all reactions were performed with 2.0 mmol of 3-bromopyridine, 6.0 mmol of acrylonitrile, 0.04 mmol of $Pd(OAc)_2$.

[b]Oil bath temp.

[c]Isolated yield.

[d]When this reaction was run for 48 h, yield was not improved.

agent but also presumably the stabilizer of intermediate Pd^0 species, as reported previously.[8]

Overall, we found the following conditions were efficient for the Heck reaction of 3-bromopyridine with acrylonitrile: (a) $Pd(OAc)_2$, n-Bu_4NCl, DMF, $NaHCO_3$, 110 °C, 4 h; (b) $Pd(OAc)_2$, n-Bu_4NCl, toluene, $NaHCO_3$, 110 °C, 16 h; and (c) $Pd(OAc)_2$, n-Bu_4NCl, DMF, TEA, 110 °C, 16 h.

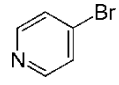
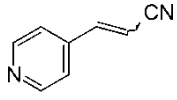
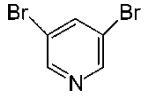
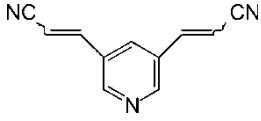
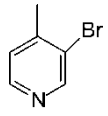
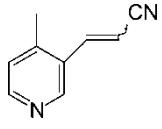
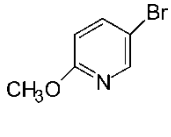
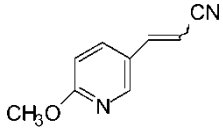
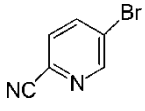
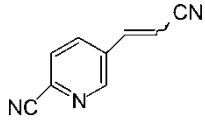
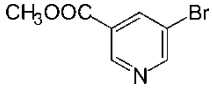
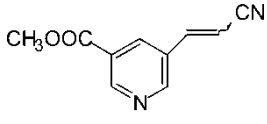
Under these optimized conditions, other substituted pyridyl bromides could be converted into the corresponding functionalized pyridylacrylonitriles (Table 2).

The Heck reaction of 4-bromopyridine in the presence of n-Bu_4NCl with TEA as the base (Entry 1b) was much better than the one with $NaHCO_3$. As expected, the Heck reaction of 3,5-dibromopyridine (Entry 1c) gave a mixture of three isomeric products determined by ^1H NMR. The reaction of 4-methyl-3-bromopyridine and 5-bromo-2-methoxypyridine (Entries 1d and 1e) required more catalyst $Pd(OAc)_2$ (6%) to achieve the acceptable yields.

However, we did not obtain coupling products when 2-bromopyridine was used as substrate, even with higher loading of catalyst or with tetrakis(triphenylphosphine)palladium. Probably the oxidative addition intermediate of Pd^0 dimerizes to form a stable complex,[9] which renders the palladium catalyst unavailable for further reaction.

In conclusion, we disclosed the Heck reaction between pyridyl bromides and acryonitrile for the synthesis of a variety of pyridylacryonitriles.

Table 2. Reaction of various bromopyridines with acrylonitrile[a]

Entry	Substrate **1**	Product **2**	Time[b] (h)	Yield[c] (%)	E/Z[d]
1b			12	94[e]	5/1
1c			4	91	3/3/1[f]
1d			12	85[g]	2.5/1
1e			12	71[g]	4/1
1f			4	84	2/1
1 g			4	75	2/1

[a]Unless otherwise noted, all reactions were performed with 2.0 mmol of bromopyridine, 6.0 mmol of acrylonitrile, 0.04 mmol of $Pd(OAc)_2$, 2.0 mmol n-Bu_4NCl, and 6.0 mmol $NaHCO_3$ in DMF at 110°C.

[b]Monitored by TLC until the bromopyridine reacted completely.

[c]Isolated yield.

[d]Determined by ^1H NMR.

[e]4-Bromopyridine hydrochloride salt was used, and the base was TEA (8.0 mmol).

[f]E-E/Z-E/Z-Z.

[g]$Pd(OAc)_2$ (6%) was used.

EXPERIMENTAL

General

All melting points were determined on a ShenGuang WRR apparatus and are uncorrected. ^1H NMR spectra was recorded on Mercury-300 (300 MHz) using TMS as internal reference in $CDCl_3$ or in CD_3OD. The liquid

chromatography-mass spectrometry (LC/MS) was equipped with a Symmetry C_{18} (0.46 mm × 50 mm) column. Mass spectra were recorded by atmospheric pressure chemical ionization (APCI). The CHN elemental analyses were performed at Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

General Procedure for a Heck Coupling between Bromopyridine and Acrylonitrile

A mixture of bromopyridine (2 mmol), acrylonitrile (6 mmol), $Pd(OAc)_2$ (0.04 mmol), ligand (0.08 mmol, if necessary), n-Bu_4NCl (2 mmol, when present), and base (6 mmol) in 5 ml of solvent was stirred under nitrogen (for reaction time and temperature, see Tables 1 and 2). After removing the solvent in a vacuum, the residue was extracted with methylene chloride (10 ml × 3) and washed with water (10 ml × 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (silica, petroleum ether/ethyl acetate) to afford the pure desired compound.

Data

3-(3-Pyridyl)acrylonitrile (2a). White solid [E/Z ca. 5/1 (^{1}H NMR)]: mp 82–84 °C. ^{1}H NMR (CD_3OD): δ 6.4 (d, J = 16.8 Hz, 1H), 7.5 (m, 1 H), 7.6 (d, J = 16.8 Hz, 1H), 8.1 (m, 1H), 8.5 (m, 1H), 8.7 (m, 1H), 5.8 (d, J = 12.3 Hz, 0.2H), 7.3 (d, J = 12.3 Hz, 0.2H), 7.5 (m, 0.2H), 8.3 (m, 0.2H), 8.6 (m, 0.2H), 8.8 (m, 0.2H). Elemental analysis calcd. (%) for $C_8H_6N_2$: C, 73.83; H, 4.65; N, 21.52; found: C, 73.63; H, 4.67; N, 20.99. MS (APCI): m/e = 131.1 $[M + H]^+$. Recrystallized with petroleum ether gave pure E-isomer: mp 105–107 °C (lit.[10] 106–107 °C). ^{1}H NMR (CD_3OD): δ 6.4 (d, J = 16.8 Hz, 1H), 7.5 (dd, J = 4.8, 8.2 Hz, 1H), 7.6 (d, J = 16.8 Hz, 1H), 8.1 (m, 1H), 8.5 (dd, J = 2.1, 4.8 Hz, 1H), 8.7 (d, J = 2.1 Hz, 1H).

3-(4-Pyridyl)acrylonitrile (2b). White solid [E/Z ca. 5/1 (^{1}H NMR)]: mp 48–51 °C. ^{1}H NMR (CD_3OD): δ 6.5 (d, J = 16.8 Hz, 1H), 7.5–7.6 (m, 3H), 8.5 (m, 2H); 5.9 (d, J = 12.3 Hz, 0.2H), 7.3 (d, J = 12.3 Hz, 0.2H), 7.7 (dd, J = 1.8, 4.5 Hz, 0.4H), 8.6 (dd, J = 1.8, 4.5 Hz, 0.4H). Elemental analysis calcd. (%) for $C_8H_6N_2$: C, 73.83; H, 4.65; N, 21.52; found: C, 73.70; H, 4.58; N, 21.15. MS (APCI): m/e = 131.3 $[M + H]^+$. Recrystallized with petroleum ether gave pure E-isomer: mp 71–72 °C (lit.[10] mp 70–71 °C). ^{1}H NMR (CD_3OD): δ 6.5 (d, J = 16.8 Hz, 1H), 7.5 (m, 2H), 7.6 (d, J = 16.8 Hz, 1H), 8.5 (m, 2H).

3-[5-(2-Cyanovinyl)(3-pyridyl)]acrylonitrile (2c). White solid [E-E/Z-E/Z-Z ca. 3/3/1 (^{1}H NMR)]: mp 181–184° C. ^{1}H NMR (CD_3OD): δ 6.5

(d, $J = 16.8$ Hz, 2H), 7.6 (d, $J = 16.8$ Hz, 2H), 8.3 (t, $J = 2.1$, 2.1 Hz, 1H), 8.7 (d, $J = 1.8$ Hz, 2H); 5.9 (d, $J = 12.6$ Hz, 1H), 6.4 (d, $J = 16.8$ Hz, 1H), 7.4 (d, $J = 12.6$ Hz, 1H), 7.7 (d, $J = 16.8$ Hz, 1H), 8.5 (t, $J = 2.1$ Hz, 1.8 Hz, 1H), 8.8 (d, $J = 2.1$ Hz, 1H), 8.9 (d, $J = 2.1$ Hz, 1H), 6.0 (d, $J = 12.3$ Hz, 0.6H), 7.4 (d, $J = 12.3$ Hz, 0.6H), 8.6 (t, $J = 1.8$ Hz, 2.4 Hz, 0.3H), 8.9 (d, $J = 2.4$ Hz, 0.6H). Elemental analysis calcd. (%) for $C_{11}H_7N_3$: C, 72.85; H, 3.86; N, 23.18; found: C, 72.82; H, 3.85; N, 22.87. MS (APCI): $m/e = 182.0$ $[M + H]^+$.

3-(4-Methyl(3-pyridyl))acrylonitrile (2d). White solid [E/Z ca. 2.5/1 (^{1}H NMR)]: mp 70–72 °C. ^{1}H NMR (CD_3OD): δ 2.4 (s, 3H), 6.32 (d, $J = 16.8$ Hz, 1H), 7.3 (d, $J = 4.2$ Hz, 1H), 7.8 (d, $J = 16.8$ Hz, 1H), 8.4 (d, $J = 5.4$ Hz, 1H), 8.7 (s, 1H), 2.3 (s, 1.2H), 5.9 (d, $J = 12.0$ Hz, 0.4H), 7.4 (d, $J = 5.4$ Hz, 0.4H), 7.6 (d, $J = 12.0$ Hz, 0.4H), 8.4 (d, $J = 5.4$ Hz, 0.4H), 8.8 (s, 0.4H). Elemental analysis calcd. (%) for $C_9H_8N_2$: C, 74.95; H, 5.55; N, 19.43; found: C, 74.60; H, 5.32; N, 19.44. MS: $m/e = 145.2$ $[M + H]^+$. Recrystallized with petroleum ether gave pure E-isomer: mp 102–104 °C. ^{1}H NMR (CD_3OD): δ 2.4 (s, 3H), 6.3 (d, $J = 16.8$ Hz, 1H), 7.3 (d, $J = 4.2$ Hz, 1H), 7.8 (d, $J = 16.8$ Hz, 1H), 8.4 (d, $J = 5.4$ Hz, 1H), 8.7 (s, 1H).

3-(6-Methoxy(3-pyridyl))acrylonitrile (2e). White solid [E/Z ca. 4/1 (^{1}H NMR)]: mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 3 H), 5.7 (d, $J = 16.6$ Hz, 1H), 6.7 (d, $J = 9.0$ Hz, 1H), 7.3 (d, $J = 16.6$ Hz, 1H), 7.7 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.2 (d, 2.4 Hz, 1H); 4.0 (s, 0.75H), 5.4 (d, $J = 12.3$ Hz, 0.25H), 6.8 (d, $J = 8.7$ Hz, 0.25H), 7.0 (d, $J = 12.3$ Hz, 0.25H), 7.2 (m, 0.25H), 8.3 (m, 0.25H). Elemental analysis calcd. (%) for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49; found: C, 67.14; H, 4.95; N, 17.07. MS (APCI): $m/e = 161.1$ $[M + H]^+$. Recrystallized with petroleum ether gave pure E-isomer: mp 106–108 °C. ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 3H), 5.7 (d, $J = 16.6$ Hz, 1H), 6.7 (d, $J = 9.0$ Hz, 1H), 7.3 (d, $J = 16.6$ Hz, 1H), 7.7 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.2 (d, 2.4 Hz, 1H).

5-(2-Cyanovinyl)pyridine-2-carbonitrile (2f). Pale yellow solid [E/Z ca. 2/1 (^{1}H NMR)]: mp 145–147 °C. ^{1}H NMR (CD_3OD): δ 6.5 (d, $J = 16.8$ Hz, 1H), 7.6 (d, $J = 16.8$ Hz, 1H), 7.8 (d, $J = 8.4$ Hz, 1H), 8.2 (dd, $J = 8.4$, 2.1 Hz, 1H), 8.7 (d, $J = 2.1$ Hz, 1H); 6.0 (d, $J = 12.3$ Hz, 0.5H), 7.4 (d, $J = 12.3$ Hz, 0.5H), 7.9 (d, $J = 8.4$ Hz, 0.5H), 8.4 (dd, $J = 8.4$, 2.4 Hz, 0.5H), 8.9 (d, $J = 2.1$ Hz, 0.5H). Elemental analysis calcd. (%) for $C_9H_5N_3$: C, 69.67; H, 3.25; N, 27.08; found: C, 69.58; H, 3.35; N, 26.79.

Methyl 5-(2-cyanovinyl)pyridine-3-carboxylate (2 g). White solid [E/Z ca. 2/1 (^{1}H NMR)]: mp 130–133 °C. ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 3H), 6.5 (d, $J = 16.5$ Hz, 1H), 7.6 (d, $J = 16.5$ Hz, 1H), 8.6 (m, 1H), 8.9 (d, $J = 2.1$ Hz, 1H), 9.1 (d, $J = 2.1$ Hz, 1H), 4.0 (s, 1.5H), 5.9 (d, $J = 12.3$ Hz, 0.5H), 7.4 (d, $J = 12.3$ Hz, 0.5H), 8.8 (m, 0.5H), 9.0 (d, $J = 2.1$ Hz, 0.5H), 9.1 (d, $J = 1.5$ Hz, 0.5H). Elemental analysis calcd. (%) for $C_{10}H_8N_2O_2$: C,

63.80; H, 4.25; N, 14.88; found: C, 63.98; H, 4.35; N, 14.70. MS (APCI): m/e = 189.1 $[M + H]^+$.

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