Chinese Chemical Letters 25 (2014) 1296–1300

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Nickel-catalyzed cross-coupling reaction of alkynyl bromides with Grignard reagents

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ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form 3 April 2014
Accepted 4 April 2014
Available online 30 April 2014

Keywords:
1,2-Disubstituted acetylene
Nickel
(Bromoethynyl)benzene
Grignard reagent
Cross-coupling

ABSTRACT

We describe a convenient method for the synthesis of 1,2-disubstituted acetylenes *via* a cross-coupling reaction of (bromoethynyl)benzene with Grignard reagents. The reaction of (bromoethynyl)benzene (1 mmol) with Grignard reagent (1.3 mmol) mediated by $NiCl_2$ (4 mol%) and $(p\text{-}CH_3Ph)_3P$ (8 mol%) in THF could produce 1,2-disubstituted acetylenes in good yields at room temperature.

1. Introduction

Nickel-catalyzed cross-coupling reactions represent a versatile tool for the C–X (X = C, N, O, *etc.*) bond formation with aryl halides and analogs [1–6]. The palladium mediated Sonogashira coupling reaction [7] is one of the most widely used reactions in organic synthesis [8–12] for the preparation of potential bioactive compounds [13,14], new materials [15–17], and natural products [18–20], but the same transformation catalyzed by nickel has not been explored much. In the past decade, researchers have directed their efforts toward the development of more efficient or single metal catalyst systems with milder reaction conditions and other desirable attributes [19–25]. While these efforts have provided alternative methods for the synthesis of alkynes, the development of rapid and more efficient procedures for the preparation of alkynes by Sonogashira coupling still remains a challenge. Aryl halides, especially aryl iodides and bromides, and alkynes are the preferred coupling partners in these reactions. Particularly, (bromoethynyl)benzene (**1a**), which is easily synthesized from 1-ethynylbenzene, has been studied in cross-coupling reactions [26–29].

Grignard reagents are reactive nucleophilic reagents and can easily be prepared from the corresponding halides [30–32]. Although the synthesis of 1, 2-disubstituted alkynes by copper-catalyzed cross-coupling of Grignard reagents with alkynyl bromide has been described [33,34], the synthesis based on direct coupling of alkynyl halide with Grignard reagents using nickel catalysts has been rarely studied. Herein, we report a new method for the synthesis of 1,2-disubstituted alkynes *via* Nickel-catalyzed cross-couplings between (bromoethynyl)benzene (**1a**) and Grignard reagents in the presence of $NiCl_2$ (4 mol%) and $(p\text{-}CH_3Ph)_3P$ (8 mol%) at room temperature.

2. Experimental

^1H NMR and ^{13}CNMR spectra were recorded on a Varian 400 MHz spectrometer. The chemical shifts are reported relative to Me_4Si. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates. Flash column chromatography was carried out on silica gel (200–400 mesh). All reactions were carried out under a nitrogen atmosphere. The starting material (bromoethynyl)benzene was prepared according to literature procedures [35]. Chemical reagents and solvents were purchased from Aldrich or Alfa Aesar, and were used without further purification with the exception of the following reagents: THF, Et_2O, hexane and toluene were distilled from sodium under nitrogen, and dichloromethane was distilled from CaH_2. Mass spectra were carried out on a Finnigan MAT-4510 spectrometer.

General procedure for cross-coupling of (bromoethynyl)benzene with Grignard reagent: Under an atmosphere of nitrogen,

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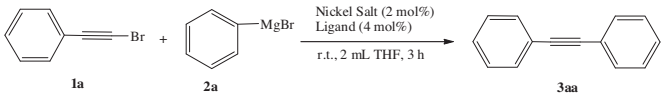
http://dx.doi.org/10.1016/j.cclet.2014.04.019

Table 1
Effect of the nickel source and ligand on the cross-coupling reaction.[a]



1a 2a 3aa

Entry	Nickel salt (2 mol%)	Ligand (4 mol%)	Yield of **3aa** (%)[b]
1	–	–	0
2	$NiCl_2$	–	72
3	$NiCl_2$	PPh_3	78
4	$NiBr_2$	PPh_3	68
5	$Ni(acac)_2$	PPh_3	75
6	$Ni(ClO_4)_2$	PPh_3	77
7	$Ni(OAc)_2$	PPh_3	73
8	$Ni(NO_3)_2$	PPh_3	66
9	$NiCl_2$	CH_3Ph_2P	78
10	$NiCl_2$	PCy_3	67
11	$NiCl_2$	$(p\text{-}CH_3Ph)_3P$	82
12	$NiCl_2$	$(o\text{-}CH_3Ph)_3P$	77
13	$NiCl_2$	$(C_6F_5)_3P$	77
14	$NiCl_2$	$(2\text{-Furanly})_3P$	78
15	$NiCl_2$	dppm	74
16	$NiCl_2$	dppe	66

[a] 1.0 mmol **1a**, 1.3 mmol **2a**, 2 mL THF, 3 h.
[b] The yield of **3aa** was determined by ^1H NMR of the crude reaction mixture.

$NiCl_2$ (6.6 mg, 0.04 mmol), $(p\text{-}CH_3Ph)_3P$ (0.08 mmol), and THF (2 mL) were mixed in a Schlenk flask. Shortly afterwards, the reaction mixture was cooled to 0 °C and a solution of ArylMgBr or AlkylMgBr (1.3 mmol) was added with a syringe pump, and subsequently the (bromoethynyl)benzene was added. After the addition, the reaction mixture was allowed to stir for an additional 3–4 h at room temperature. After the completion of the reaction, the reaction mixture was diluted with 1 mol/L aqueous HCl solution (10 mL) and extracted with Et_2O (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (hexane gradient) to afford the corresponding products.

Diphenylacetylene (**3aa**) [36]. White solid, mp 60–61 °C (lit. [35] 59–60 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.52 (m, 4H), 7.36–7.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.2, 128.3, 128.2, 123.4, 89.3; EI-MS (m/z): 178 (M^+).

1-Phenyl-2-(*o*-tolyl)acetylene (**3ab**) [36]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.48 (m, 3H), 7.38–7.31 (m, 3H), 7.24–7.14 (m, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 131.8, 131.5, 129.4, 128.3, 128.1, 125.6, 123.5, 123.0, 93.3, 88.3, 20.7; EI-MS (m/z): 192 (M^+).

1-Phenyl-2-(*m*-tolyl)acetylene (**3ac**) [23]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60–7.48 (m, 2H), 7.45–7.30 (m, 5H), 7.24 (t, 1H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.6 Hz), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 132.3, 131.7, 129.3, 128.8, 128.4, 128.3, 128.3, 121.7, 121.5, 89.7, 89.1, 21.4; EI-MS (m/z): 192 (M^+).

1-Phenyl-2-(*p*-tolyl)acetylene (**3ad**) [23]. White solid, mp 70–71 °C (lit. [23] 71–72 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.49 (m, 2H), 7.43 (d, 2H, J = 8.1 Hz), 7.37–7.30 (m, 3H), 7.14 (d, 2H, J = 8.1 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 131.5, 131.4, 129.1, 128.3, 128.0, 123.4, 120.1, 89.5, 88.7, 21.5; EI-MS (m/z): 192 (M^+).

1-Phenyl-2-(*m*-methoxyphenyl)acetylene (**3ae**) [37]. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.57 (m, 2H), 7.35–7.37 (m, 1H), 7.25–7.29 (m, 3H), 7.15 (d, 1H, J = 8.0 Hz), 7.08 (s, 1H), 6.90–6.92 (m, 1H), 3.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 131.6, 129.4, 128.33, 128.28, 124.24, 124.16, 123.2, 116.3, 114.9, 89.3, 89.2, 55.3; EI-MS (m/z): 208 (M^+).

1-Phenyl-2-(*p*-methoxyphenyl)acetylene (**3af**) [36]. White solid, mp 55–56 °C (lit. [36] 55 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 –7.45 (m, 4H), 7.37–7.26 (m, 3H), 6.88 (d, 2H, J = 9.0 Hz), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 133.0, 131.4, 128.3, 127.9, 123.6, 115.4, 114.0, 89.3, 88.0, 55.3; EI-MS (m/z): 208 (M^+).

1-(3,5-Dimethylphenyl)-2-phenylacetylene **(3ag)** [36]. White solid, mp 44–45 °C (lit. [36] 45 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55–7.43 (m, 2H), 7.36–7.27 (m, 3H), 7.30 (s, 2H), 7.15 (s, 1H), 2.28 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 132.3, 131.7, 129.3, 128.8, 128.4, 128.3, 128.3, 89.7, 89.1, 21.4; EI-MS (m/z): 206 (M^+).

1-Phenyl-2-(*p*-chloro)acetylene (**3ah**) [36]. White solid, mp 82–83 °C (lit. [36] 84 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.51 (m, 2H), 7.47–7.45 (d 2H, J = 8.4 Hz,), 7.37–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2, 132.8, 131.6, 128.6, 128.4, 128.0, 122.9, 121.7, 90.3, 88.2; EI-MS (m/z): 212 (M^+).

1-Phenyl-2-(*p*-floro)acetylene **(3ai)** [36]. Pale yellow solid, mp 109–110 °C (lit. [36] 110 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60–7.45 (m, 4H), 7.40–7.32 (m, 3H), 7.08–7.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 161.0, 133.6 (d, J = 8.60 Hz), 131.7, 128.5 (d, J = 2.87 Hz), 123.2, 119.5, 115.7 (d, J = 21.5 Hz), 89.1, 88.4; EI-MS (m/z): 196 (M^+).

1-Phenyl-2-(*p*-trifloromethyl)acetylene (**3aj**) [38]. White solid, mp 125–126 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61–7.64 (m, 4H), 7.55–7.59 (m, 2H), 7.36–7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.9, 131.8, 129.9 (J = 32.4 Hz), 128.9, 128.5, 127.1 (J = 1.4 Hz), 125.2 (J = 3.9 Hz), 123.9 (J = 270.1 Hz), 122.6, 91.8, 87.9; EI-MS (m/z): 246 (M^+).

1-Phenyl-2-(*p*-trimethylsilane)acetylene **(3ak)** [24]. White solid, mp 119–121 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57–7.53 (m, 6H), 7.38–7.35 (m, 3H), 7.14 (d, 2H, J = 8.1 Hz), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 133.2, 131.6, 130.6, 129.2, 128.4, 128.3, 123.5, 89.5, 88.7, 2.5; EI-MS (m/z): 250 (M^+).

1-(1-Naphthyl)-2-phenylacetylene **(3al)** [24]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, J = 7.5 Hz), 7.85 (t, 2H, J = 8.1 Hz), 7.77 (dd, 1H, J = 7.2 Hz, 1.2 Hz), 7.67–7.63 (m, 2H), 7.60 (dt, 1H, J = 6.9 Hz, 1.5 Hz), 7.53 (dt, 1H, J = 6.9 Hz, 1.5 Hz), 7.45 (dd, 1H, J = 8.4 Hz, 7.2 Hz), 7.43–7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 133.2, 131.7, 130.4, 128.8, 128.4, 128.3, 128.2, 126.8, 126.4, 126.2, 125.3, 123.4, 120.9, 94.3, 87.5; EI-MS (m/z): 228 (M^+).

1-Phenyl-1-octyne **(3am)** [36]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 2H), 7.31–7.24 (m, 3H), 2.40 (t, 2H, J = 7.04 Hz), 1.66–1.52 (m, 2H), 1.50–1.38 (m, 2H), 1.38–1.26 (m, 4H), 0.91 (t, 3H, J = 6.53 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6, 128.3, 127.5, 124.2, 90.6, 80.6, 31.5, 28.8, 28.7, 22.7, 19.5, 14.2; EI-MS (m/z): 186 (M^+).

Table 2
Effect of the solvent and the molar ratio of $NiCl_2/(p\text{-}CH_3Ph)_3P$ on the cross-coupling reaction.[a]

Entry	$NiCl_2$ (mmol%)	$(p\text{-}CH_3Ph)_3P$ (mmol%)	Solvent	Yield of **3aa** (%)[b]
1	2	4	DME	78
2	2	4	Et_2O	61
3	2	4	Hexane	73
4	2	4	Toluene	40
5	2	4	CH_2Cl_2	75
6	2	2	THF	77
7	2	6	THF	75
8	4	8	THF	82
9	6	12	THF	78
10[c]	4	8	THF	79

[a] 1.0 mmol **1a**, 1.3 mmol **2a**, 2 mL THF, 3 h.
[b] The yield of **3aa** was determined by ^1H NMR of the crude reaction mixture.
[c] 1.0 mmol **1a**, 1.5 mmol **2a**.