Inorganica Chimica Acta 369 (2011) 284–287

Contents lists available at ScienceDirect

Inorganica Chimica Acta

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

Rhodium-catalyzed arylation of α-amido sulfones with arylboronic acids in a water–toluene biphasic system

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ARTICLE INFO

Article history:
Available online 8 October 2010

Dedicated to R.G. Bergman and R.J. Puddephatt

Keywords:
Rhodium
Arylboronic acids
α-Amido sulfones
Imines
Aqueous media

ABSTRACT

An efficient method for the synthesis of *N*-protected diaryl-methyl-amines was developed through a rhodium-catalyzed arylation of α-amido sulfones with arylboronic acids in a water–toluene biphasic system. The use of a base combined with a surfactant played a key role in this biphasic reaction. A diverse range of α-branched amine derivatives bearing different functional groups were obtained within 10 min under the present conditions.

1. Introduction

The addition reactions of various organometallic reagents to the C=N bond of imines and their derivatives have attracted considerable attention of organic chemists [1,2]. Such reactions can provide practical methods for the synthesis of α-branched amines and their derivatives, which are prevalent and important building blocks of many biological and pharmaceutical agents. However, most imines are unstable and prone to decomposition during workup. Furthermore, many functional groups are not tolerated with the classical organometallic reagents and need to be protected. Thus, methods involving the generation of the imine in situ are highly desirable. α-Amido sulfones are stable precursors of reactive imino derivatives, which can be easily synthesized by the three-components coupling of carbamate, aldehyde, and sodium sulfinates under acidic conditions [3]. Subsequent elimination of sulfinic acid leads to the in situ generation of reactive *N*-acylimines, which can react with nucleophilic reagents to give the corresponding addition products [3–6]. Recently, Ollevier's group developed a $Bi(OTf)_3$ catalyzed addition of allylsilanes and silyl enolates to *N*-alkoxycarbonylamino sulfones [7–9].

With the advances in organic chemistry, many stable organometallic compounds are developed as substitutes for Grignard and organolithium reagents. Such alternative reagents can tolerate an array of sensitive functional groups and can even work well in water and air. Among them, arylboronic acids are extremely powerful organometallic reagents in organic synthesis because they are moisture-stable, easy to handle, commercially available and compatible with many functional groups. Additions of arylboronic acids to imines have already been intensively studied recently; however, they generally suffer from harsh reaction conditions, a long reaction time and poor functional group compatibility [10–23]. Such restrictions undoubtedly limited the application of these reactions.

Due to the abundance of water as well as the inherent advantages of using water as a solvent, recent interest has been growing in studying organic reactions in water [24–26]. Many reactions that are traditionally carried out in organic solvent can be conducted in water with additional beneficial features: (1) water-soluble substrates such as carbohydrates can be used directly without derivatization, (2) the aqueous catalyst solution can be recycled easily, and (3) water-insoluble products can be separated conveniently by simple phase separations. Among them, we and others have reported that organometallic reagents including organoboron, organotin, organobismuth and organolead reagents were effective for carbonyl addition and conjugated addition reactions in air and water [27–39]. In addition, we also reported the copper-mediated or catalyzed direct nucleophilic additions of alkynes to reactive *N*-acylimines and *N*-acyliminium ions (generated in situ from α-amido sulfones or methoxyl groups as stable precursors), affording propargylamine derivatives in aqueous media [40].

Based on our intensive interest in organic reactions in aqueous media and the excellent properties of boronic acids, we envisioned

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doi:10.1016/j.ica.2010.09.056

that arylation of α-amido sulfones with arylboronic acids in aqueous media will be a direct and practical method for the synthesis of α-branched amines and their derivatives. To the best of our knowledge, such a reaction has not been achieved. Herein, we reported our results on the rapid arylation of α-amido sulfones with arylboronic acids in a water–toluene biphasic system.

2. Experimental

2.1. General

All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) or Sorbent silica gel 60 F254 plates. The developed chromatography was analyzed by UV lamp (254 nm). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or Sorbent silica gel 30–60 μm. High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (ACPI). Nuclear magnetic resonance (NMR) spectra were recorded on Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz), a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz), or a Varian MERCURY plus-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. Unless stated otherwise, commercial reagents were used without further purification. All reagents were weighed and handled in air at room temperature. α-Amido sulfones were prepared according to the literature method [41].

2.2. A representative experimental procedure

A reaction vessel was charged with benzenesulfonyl-phenyl-methyl-carbamic acid benzyl ester **1a** (38.1 mg, 0.1 mmol), phenylboronic acid (18.3 mg, 0.15 mmol), sodium dodecyl sulfate (20 mg), $Rh(COD)_2BF_4$ (2.1 mg, 5 mmol%), water (0.3 mL), and toluene (0.5 mL); sealed and the resulting solution was stirred at 150 °C for 10 min. The resulting mixture was cooled to room temperature and the residue was extracted with ethyl acetate (3 × 5 mL). The combined organic extract was dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel (eluent: hexane/diethyl ether = 10:1) to give benzyl benzhydrylcarbamate **3a**.

2.3. ^{1}H, ^{13}C NMR spectra and HR/MS data

Compound **3a** was obtained as a white solid [42]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12 (s, 2H), 5.41 (bs, 1H), 6.00 (d, J = 7.6 Hz, 1H), 7.24–7.29 (m, 6H), 7.31–7.35 (m, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.8, 67.0, 127.2, 127.5, 128.2, 128.5, 128.6, 136.2, 141.6, 155.5.

Compound **3b** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (bs, 3H), 1.38 (bs, 2H), 1.61 (bs, 2H), 4.08 (t, J = 6.4 Hz, 2H), 5.31 (bs, 1H), 5.98 (d, J = 6.0 Hz, 1H), 7.24–7.28 (m, 6H), 7.31–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 31.0, 58.6, 65.0, 127.2, 127.4, 128.6, 141.8, 155.9. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{18}H_{22}O_2N$, 284.16451; found, 284.16441.

Compound **3c** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 5.16 (bs, 1H), 5.91 (bs, 1H), 7.23–7.27 (m, 6H), 7.30–7.34 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 58.4, 79.8, 127.2, 127.3, 128.6, 142.0, 155.0. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{18}H_{22}O_2N$, 284.16451; found, 284.16457.

Compound **3d** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (bs, 3H), 4.10–4.16 (q, J = 7.2 Hz, 2H), 5.28 (bs, 1H), 5.97 (d, J = 6.8 Hz, 1H), 7.23–7.28 (m, 6H), 7.31–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 58.6, 61.1, 127.2, 127.4, 128.6, 141.8, 155.8. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{16}H_{18}O_2N$, 256.13321; found, 256.13323.

Compound **3e** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H), 5.32 (bs, 1H), 5.98 (d, J = 6.8 Hz, 1H), 7.23–7.28 (m, 6H), 7.31–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.3, 58.8, 127.2, 127.5, 128.6, 141.6, 156.2. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{15}H_{16}O_2N$, 242.11756; found, 242.11779.

Compound **3f** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (bs, 3H), 1.36 (bs, 2H), 1.57 (bs, 2H), 2.32 (s, 3H), 4.07 (t, J = 6.4 Hz, 2H), 5.25 (bs, 1H), 5.92 (bs, 1H), 7.13 (s, 4H), 7.23–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 21.0, 31.0, 58.4, 65.0, 127.1, 127.3, 128.5, 129.3, 137.1, 138.9, 142.0, 155.9. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{19}H_{24}O_2N$, 298.18016; found, 298.18022.

Compound **3g** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (bs, 3H), 1.36 (bs, 2H), 1.56 (bs, 2H), 4.07 (t, J = 6.4 Hz, 2H), 5.24 (bs, 1H), 5.92 (bs, 1H), 7.18–7.20 (m, 4H), 7.25–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 30.9, 58.2, 65.1, 127.2, 127.7, 128.5, 128.7, 128.8, 133.2, 140.3, 141.2, 155.8. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}O_2NCl$, 318.12553; found, 318.12548.

Compound **3h** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (bs, 3H), 1.36 (bs, 2H), 1.58 (bs, 2H), 4.07 (t, J = 6.4 Hz, 2H), 5.25 (bs, 1H, 5.90 (bs, 1H), 7.13(d, J = 8.4 Hz, 2H), 7.21 (d, J = 6.8 Hz, 2H),7.26–7.35 (m, 3H), 7.43–7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 18.09, 30.9, 58.2, 65.1, 121.3, 127.2, 127.7, 128.7, 128.8, 131.6, 140.9, 141.1, 155.8. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}O_2NBr$, 362.07502; found, 362.07573.

Compound **3i** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 6.8 Hz, 3H), 1.37–1.39 (m, 2H), 1.58–1.59 (m, 2H), 2.31 (s, 3H), 4.08 (t, J = 6.8 Hz, 2H), 5.26 (d, J = 6.4 Hz, 1H), 6.15 (d, J = 7.6 Hz, 1H), 7.14–7.23 (m, 6H), 7.25–7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 19.4, 31.0, 55.5, 65.0, 126.2, 126.5, 127.3, 127.4, 128.6, 130.7, 136.0, 139.8, 140.9, 141.2, 155.8. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{19}H_{24}O_2N$, 298.18016; found, 298.17998.

Compound **3j** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 6.8 Hz, 3H), 1.36–1.38 (m, 2H), 1.59 (bs, 2H), 3.77 (s, 3H), 4.07 (t, J = 6.8 Hz, 2H), 5.29 (bs, 1H), 5.93 (d, J = 6.8 Hz, 1H), 6.79–6.84 (m, 3H), 7.22–7.34 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 31.0, 55.2, 58.6, 65.0, 112.5, 113.1, 119.5, 127.2, 127.4, 128.6, 129.6, 141.6, 143.4, 155.9, 159.7. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{19}H_{24}O_3N$, 314.17507; found, 314.17558.

Compound **3k** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (bs, 3H), 1.38 (bs, 2H), 1.59 (bs, 2H), 4.08 (t, J = 6.4 Hz, 2H), 5.29 (bs, 1H), 6.00 (bs, 1H), 7.20–7.22 (m, 2H), 7.27–7.40 (m, 5H), 7.59 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 30.9, 58.5, 65.2, 125.5, 125.6, 127.3, 127.9, 128.9, 129.4, 140.8, 145.8, 155.8. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{19}H_{21}O_2NF_3$, 352.15189; found, 352.15213.

Compound **3l** was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (bs, 3H), 1.39 (bs, 2H), 1.61 (bs, 2H), 4.10 (t, J = 6.8 Hz, 2H), 5.42 (bs, 1H), 6.14 (bs, 1H), 7.26–7.36 (m, 6H), 7.45–7.50 (m, 2H), 7.73 (s, 1H), 7.79–7.83 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 19.0, 31.0, 58.8, 65.1, 125.4, 125.7, 126.0, 126.3, 127.4, 127.5, 127.6, 128.0, 128.5, 128.7, 132.7, 133.2, 139.1, 141.6, 156.0. HRMS APCI (m/z): $[M+H]^+$ calcd for $C_{22}H_{24}O_2N$, 334.18016; found, 334.18052.