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Palladium-catalyzed arylation of aryl sulfonamides with cyclohexanones

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ABSTRACT

Pd-catalyzed intermolecular aerobic dehydrogenative aromatizations have been developed for the arylation of aryl sulfonamides with cyclohexanones. Various *N*-aryl sulfonamides were selectively obtained in good yields using molecular oxygen as oxidant. The reaction tolerated a wide range of functionalities.

1. Introduction

N-Aryl sulfonamides are of great importance as building blocks for pharmaceuticals and bioactive compounds [1]. In particular, they are widely used as antibacterial, anticancer, anti-inflammatory and antiviral agents and HIV protease inhibitors [2]. Thus, the search for general and efficient routes for construction of sulfonamides under mild conditions is of great continuing interest for organic chemists. Although many efforts have been put into the development of novel sulfonamide synthesis [3], the conventional synthesis mainly relies on the reaction of amino compounds and sulfonyl chlorides in the presence of organic or inorganic bases because of the reactivity and simplicity (Scheme 1a) [4]. Over the last few decades, the transition-metal-catalyzed cross coupling reactions of aryl halides or pseudohalides with sulfonamides has become a more attractive approach to form N-aryl sulfonamides. (Scheme 1b). Arguably, the most prominent reactions include Buchwald–Hartwig-coupling [5], Ullmann-type reactions [6] and Chan–Lam-type aminations [7]. For pharmaceutical purposes, the use of non-toxic coupling reagents under mild reaction conditions is highly desirable.

Recently, there has been significant interest in the transition-metal-catalyzed *N*-alkylation of amines using cheap, readily available and non-toxic alcohols as the alkylation reagent via hydrogen autotransfer (or borrowing hydrogen) strategy. In this process, the alcohol was oxidized in situ and two hydrides were transferred into the metal catalyst. The metal-hydride complex could be used as reducing reagent to reduce the imine intermediate [8]. Since the seminal work reported by Grigg et al. [9] and Watanable et al. [10], great progress has been made in the transition-metal-catalyzed direct amination of amines, sulfonamides [11] or even nitro arenes [12] with alcohols. However, the borrowing hydrogen methodology using alcohols as starting materials is limited for the alkylation of amines and not suitable for arylations. Inspired by pioneering work [13], the group of Stahl succeeded in the utilization of molecular oxygen in catalytic oxidative aromatization reactions. Cyclohexanone derivatives have been transferred into the corresponding phenols [14] and cyclic enones [15] in the presence of a Pd-catalyst under mild reaction conditions. We and others have developed the intermolecular arylation reactions of amines and alcohols using cyclohexanones as the reducing reagents and aryl sources via dehydrogenation and tautomerization [16]. Nitro arenes were also successfully used as the hydrogen acceptors to further form diaryl amines with cyclohexanones [17]. In continuation of our interest in using cyclohexanones as hydrogen donors and aryl sources, herein, we report a Pd-catalyzed arylation of aryl sulfonamides with cyclohexanones using molecular oxygen as oxidant (Scheme 1c).

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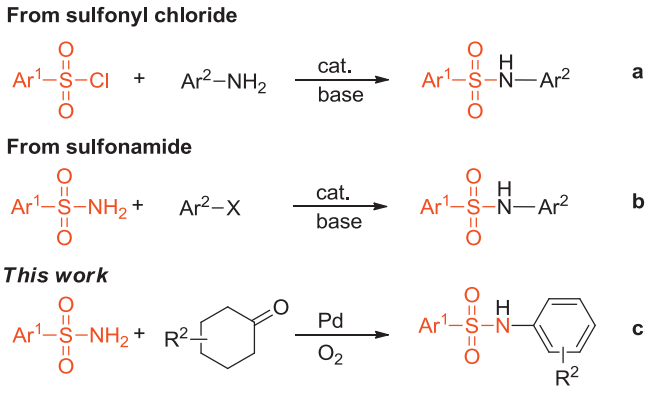

Scheme 1. Pathways for *N*-aryl sulfonamide formation.

2. Experimental

2.1. General remarks

All experiments were carried out under an atmosphere of oxygen. Flash column chromatography was performed over silica gel 48–75 μm. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-AV (400 and 100 MHz, respectively) instrument internally referenced to $SiMe_4$ or chloroform signals. MS analyses were performed on Agilent 5975 GC–MS instrument (EI). The new compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS. The structure of known compounds was further corroborated by comparing their ^{1}H NMR, ^{13}C NMR data and MS data with those of literature. All reagents were used as received from commercial sources without further purification. Palladium (II) trifluoroacetate was purchased from Alfa Aesar.

2.2. General procedure: 4-methyl-N-phenylbenzenesulfonamide (*3a*)

A 25 mL oven-dried reaction vessel was charged with $Pd(TFA)_2$ (2.3 mg, 0.01 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), *p*-toluene sulfonamide (**1a**, 34.2 mg, 0.2 mmol), cyclohexanone (**2a**, 32 μL, 0.3 mmol). The reaction vessel was flushed with oxygen three times and then sealed. Toluene (0.7 mL) was added by syringe and the resulting solution was stirred at 140 °C for 40 h. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give the corresponding product **3a** (39.9 mg) as white solid in 81% yield.

Compound ***3a***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.65 (d, J = 8.0 Hz, 2H), 7.26–7.23 (m, 5H), 7.15–7.12 (m, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.42 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.9, 136.7, 136.1, 129.7, 129.3, 127.3, 125.2, 121.4, 21.5; MS (EI) *m*/*z* (%) 247, 182, 155, 91 (100).

Compound ***3b***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.77 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H),7.45–7.41 (m, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.14–7.05 (m, 3H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 139.2, 136.5, 133.0, 129.3, 129.0, 127.3, 125.5, 121.8; MS (EI) *m*/*z* (%) 233, 168, 92 (100), 77, 65.

Compound ***3c***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.69 (d, J = 8.0 Hz, 2H), 7.24–7.22 (m, 4H), 7.11–7.07 (m, 3H), 6.79 (s, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 149.9, 136.7, 136.5, 129.3, 128.5, 127.4, 125.2, 121.5, 28.8, 14.9; MS (EI) *m*/*z* (%) 261, 105 (100), 92, 77, 65.

Compound ***3d***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.70 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.11–7.07 (m, 3H), 6.68 (s, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.8, 136.8, 136.3, 129.3, 127.1, 126.0, 125.1, 121.3, 35.1, 31.0; MS (EI) *m*/*z* (%) 289, 168, 133 (100), 92, 65.

Compound ***3e***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.78–7.74 (m, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.16–7.05 (m, 5H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.3 (d, J = 253.8 Hz), 136.2, 135.2 (d, J = 2.9 Hz),130.0 (d, J = 9.4 Hz), 129.4, 125.7, 122.0, 116.3 (d, J = 22.5 Hz); MS (EI) *m*/*z* (%) 251, 186, 159, 92 (100), 65.

Compound ***3f***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.70 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.14 (s, 1H), 7.07 (d, J = 7.6 Hz, 2H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 139.6, 137.6, 136.2, 129.5, 129.4, 128.7, 125.8, 121.9; MS (EI) *m*/*z* (%) 267, 168, 111, 92 (100), 65.

Compound ***3g***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61–7.56 (m, 3H), 7.29–7.25 (m, 3H), 7.16 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 7.6 Hz, 2H), 6.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.2, 136.0, 132.3, 129.5, 128.8, 128.1, 125.9, 122.1; MS (EI) *m*/*z* (%) 313, 168, 156, 92 (100), 65.

Compound ***3h***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.4 Hz, 2H), 7.29–7.20 (m, 4H), 7.15 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.4 (d, J = 1.9 Hz), 137.4, 136.1, 129.7, 125.8, 120.2 (q, J = 258.0 Hz), 122.0, 120.8 (d, J = 1.1 Hz), 118.9; MS (EI) *m*/*z* (%) 317, 225, 161, 92 (100), 65; HRMS calcd. for: $C_{18}H_{20}NaO$ $[M+Na]^+$ 275.1406, found 275.1409.

Compound ***3i***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.96 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.32–7.19 (m 4 H), 7.07 (t, J = 7.3 Hz, 2H), 7.01 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.6, 137.2, 136.5, 133.1, 132.6, 130.0, 129.3, 126.3, 125.0, 120.8, 29.7; MS (EI) *m*/*z* (%) 247, 182, 155, 92 (100), 65.

Compound ***3j***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.99 (d, J = 8.0 Hz, 1H), 7.51–7.43 (m, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.12–7.07 (m, 3H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 136.3, 135.8, 134.0, 132.0, 131.6, 131.4, 129.3, 127.2, 125.8, 121.7; MS (EI) *m*/*z* (%) 267, 168, 111, 92 (100), 65.

Compound ***3k***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34–7.11 (m, 4H), 7.14–7.12 (d, J = 3.8 Hz, 2H), 6.84–6.83 (d, J = 2.0 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.9, 137.4, 135.8, 132.3, 129.5, 126.7, 126.2, 122.1; MS (EI) *m*/*z* (%) 273, 181, 174, 92 (100), 65.

Compound ***3l***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39–7.35 (t, J = 7.5 Hz, 2H), 7.24–7.19 (m, 3H), 6.57 (s, 1H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 136.9, 129.7, 125.5, 120.9, 39.3; MS (EI) *m*/*z* (%) 171, 140, 106, 92 (100), 65.

Compound ***3m***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.38 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.7, 136.0, 135.2, 133.9, 129.8, 129.6, 127.3, 122.2, 21.6, 20.9; MS (EI) *m*/*z* (%) 261, 106 (100), 91, 77.

Compound ***3n***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.67 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 3H), 7.13 (t, J = 7.6 Hz, 1H), 6.95–6.91 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.48 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.8, 139.3, 136.6, 136.2, 129.7, 129.1, 127.3, 126.0, 122.0, 118.2, 21.6, 21.4; MS (EI) *m*/*z* (%) 261, 106 (100), 91, 77.

Compound ***3p***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.39 (s, 1H), 2.59 (q, J = 7.6 Hz, 2H), 2.40 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.7, 141.6, 136.3, 134.1, 129.6, 128.6, 127.3, 122.2, 28.2, 21.6, 15.4; MS (EI) *m*/*z* (%) 275, 260, 120 (100), 91, 77.

Compound ***3q***: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.62 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.47 (s, 1H), 2.52 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.58–1.53 (m, 2H), 1.32–1.25 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 146.9, 143.6, 136.6, 133.7, 129.5,