Research Article

A Novel Regiospecific Synthesis of 1-Chloro-2-arylcyclohexenes

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An efficient high yielding chemoselective synthesis of eleven novel 1-chloro-2-arylcyclohexenes employing the Suzuki cross coupling of 1-bromo-2-chlorocyclohexene with eleven different aryl boronic acids and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ catalyst is reported.

1. Introduction

Cross-coupling reactions of unsaturated carbon centres bearing halogens/triflates with aryl boronic acids catalyzed by palladium metal complexes have become a powerful tool in organic synthesis for the formation of carbon-carbon bonds. One of the important cross-coupling reactions in this genre is the Suzuki reaction [1–4]. These organopalladium complex catalyzed couplings of unsaturated halides with boronic acids/esters have been employed in key steps to form a wide variety of pharmaceuticals and natural products [5–10].

1,2-Dihalocycloalkenes are precursors to cycloalkynes [11, 12]. However, there are very few reports for the conversion of 1,2-dihalocycloalkenes to substituted 1-halo-2-arylcycloalkenes. One report shows the chemoselective cross coupling of 2-bromo-3-chloronorbornadiene to 2-chloro-3-aryl-norbornadiene [13]. In this regard, the Suzuki coupling reaction of cyclohexenyl bromides with arylboronic acids is still almost unexplored. A recent report shows its importance in the synthesis of polysubstituted phenol derivatives [14].

Our laboratory is involved in the synthesis and reactions of some novel cyclic vinyl silanes. We employ the Wurtz-Fittig coupling reaction of corresponding cyclic vinyl halide with sodium and chlorotrimethylsilane in suitable solvent to prepare the cyclic vinylsilanes. Using the Wurtz-Fittig reaction, we have been able to synthesize a large number of simple and substituted cyclic vinylsilanes [15–19]. The organosilicon compounds are anionic synthons serving as the starting materials in the total synthesis of natural products [20–23].

Cyclic vinyl halides and 1,2-dihalocycloalkenes serve as precursors to the cyclic vinylsilanes. There are several protocols for the preparation of cyclic vinyl halides and 1,2-dihalocycloalkenes [24]. The protocols for 1,2-dihalocycloalkenes normally afford the two halogen atoms symmetrically attached to the carbon-carbon double bond [25, 26]. In comparison to the preparation of symmetrical 1,2-dihalocycloalkenes, there exist very few protocols for the synthesis of unsymmetrical 1,2-dihalocycloalkenes especially 1-bromo-2-chlorocycloalkenes [27–31]. We had earlier adopted the addition reaction of bromine chloride to 1-chlorocyclopentene followed by dehydrochlorination for the synthesis of 1-bromo-2-chlorocyclopentene [25].

In this paper, we report for the first instance the synthesis of 1-bromo-2-chlorocyclohexene (**2**) and the chemoselective Suzuki cross-coupling reaction with eleven different aryl boronic acids (**3a–k**) to form eleven novel 1-chloro-2-arylcyclohexenes (**4a–k**) in high yields.

2. Materials and Methods

All reactions were performed in oven dried apparatus. Reactions were monitored on Merck F-254 precoated TLC plastic sheets using hexane (60–80°C) fraction as mobile phase. GC was run on SE-30 SS 2 m $\times$ 1/8" column on Mayura 9800 gas chromatograph. IR spectra were recorded on Shimadzu FT-IR 8400S using NaCl flats as neat thin liquid film samples. The values are reported in wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR were obtained on a Bruker AMX 400 spectrometer using CDCl_3 with tetramethylsilane as internal standard.

Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). GC-MS spectra were obtained using a Shimadzu GC-MS QP 5050A instrument equipped with a 30 mm $\times$ 0.32 mm BP-5 capillary column. Elemental analyses were obtained using Elementar Vario Microcube-15106062 instrument. All yields refer to the isolated yields of the products.

2.1. Synthesis of 1-Bromo-2-chlorocyclohexene (2). To a stirred suspension of PCl_5 (1.4 g, 6.723 mmol) in 10 mL anhydrous ether was added a 10 mL ethereal solution of **1** (1.0 g, 5.525 mmol), dropwise over 30 min. The mixture was stirred for further 8 hours, when all the starting material disappeared as followed by GC. The reaction mixture was poured into crushed ice (50 g) and extracted with ether (3×30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to isolate 1.05 g of concentrate.

To 0.63 g (5.614 mmol) of potassium *tert*-butoxide in 10 mL *tert*-butyl alcohol was added the 1.05 g of crude in 10 mL *tert*-butyl alcohol drop wise over 15 min and refluxed for 2 hours, when the aliquot indicated a single peak in gas chromatogram. The mixture was diluted with water (150 mL), extracted with ether (4×30 mL), washed with brine (20 mL), dried (an. Na_2SO_4), and concentrated. Distillation under reduced pressure gave pure **2** (0.62 g, 56%).

2.2. General Procedure for the Synthesis of 1-Chloro-2-arylcyclohexenes (4a–k). A mixture of 1-bromo-2-chlorocyclohexene **2** (196 mg, 1.0 mmol), aryl boronic acid (1.0 mmol), K_2CO_3 (3.0 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (5 mol%) in 10 mL 1,4-dioxane was heated in a sealed tube placed in an oil bath at 70–80°C for 2–3 hr. The reaction mixture was cooled to ambient temperature and filtered, and the solvent was removed *in vacuo*. The crude product was then subjected to column chromatography using silica gel (60–100 mesh) and 1:10 ethyl acetate/hexane (60–80°C fraction) to isolate **4a–k** in greater than 90% yield (Table 2).

2.3. Spectral Data for the Products

2.3.1. 1-Bromo-2-chlorocyclohexene (2). IR: 2941, 2862, 2839, 1641, 1434, 1325, 1006 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.70–1.80 (m, 4H), 2.40–2.45 (m, 2H), 2.53–2.58 (m, 2H); ^{13}C NMR (CDCl_3) δ : 23.30, 23.89, 34.60, 36.47, 119.50, 130.83; GC-MS *m/e* (*rel. int.*): 198 (0.29), 196 (1.22), 194 (0.80), 168 (0.18), 166 (0.17), 160 (0.42), 159 (0.33), 158 (0.27), 129 (0.24), 117 (2.63), 116 (1.06), 115 (7.30), 114 (0.72), 113 (0.57), 100 (0.94), 99 (1.14), 89 (1.16), 87 (3.19), 81 (2.18), 80 (8.05), 79 (100.00), 78 (7.21), 77 (29.9), 75 (3.88), 74 (3.40), 73 (3.66), 63 (7.03), 53 (5.90), 52 (12.56), 51 (34.76), 50 (20.39), 49 (4.31); Anal. Found: C, 36.95; H, 4.19. Calcd: C, 36.86; H, 4.12.

2.3.2. 1-Chloro-2-phenylcyclohexene (4a). IR: 698, 1004, 1440, 2858, 2929 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.70–2.84 (m, 4H), 2.36–2.47 (m, 2H), 2.48–2.57 (m, 2H), 7.24–7.60 (m, 5H); ^{13}C NMR (CDCl_3) δ : 22.68, 23.90, 32.95, 34.09, 126.09, 127.15,

127.23, 127.80, 128.03, 128.73, 134.40, 141.56; Anal. Found: C, 74.76; H, 6.75. Calcd: C, 74.80; H, 6.80.

2.3.3. 1-Chloro-2-phenyl-3'-methyl-cyclohexene (4b). IR: 1440, 1693, 2880, 2931 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.69–1.84 (m, 4H), 2.35 (s, 3H), 2.36–2.58 (m, 4H), 7.04–7.59 (m, 4H); ^{13}C NMR (CDCl_3) δ : 22.70, 23.34, 23.93, 33.02, 34.64, 119.56, 124.26, 125.12, 127.67, 127.94, 128.67, 137.59, 141.54; Anal. Found: C, 75.45; H, 7.27. Calcd: C, 75.53; H, 7.31.

2.3.4. 1-Chloro-2-phenyl-4'-formyl-cyclohexene (4c). IR: 1209, 1602, 1701, 2731, 2837, 2860, 2933 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.26–1.87 (m, 4H), 2.38–2.41 (m, 2H), 2.48–2.52 (m, 2H), 7.41–7.44 (d, 2H, $J = 12$ Hz), 7.85–7.88 (d, 2H, $J = 12$ Hz), 10.00 (s, 1H); ^{13}C NMR (CDCl_3) δ : 22.48, 23.74, 32.52, 34.06, 128.36, 129.23, 129.60, 130.05, 130.26, 133.52, 135.02, 147.93; GC-MS *m/e* (*rel. int.*): 221.93 (32), 219.82 (100), 184.99 (28), 154.88 (32). Anal. Found: C, 70.77; H, 5.99. Calcd: C, 70.75; H, 5.94.

2.3.5. 1-Chloro-2-phenyl-2'-methoxy-cyclohexene (4d). IR: 1249, 1490, 1596, 2837, 2856, 2931 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.75–1.85 (m, 4H), 2.51 (br, 4H), 3.83 (s, 3H), 6.92–6.99 (m, 2H), 7.10–7.12 (m, 1H), 7.26–7.30 (m, 1H); ^{13}C NMR (CDCl_3) δ : 22.50, 23.97, 31.65, 33.71, 55.62, 111.15, 120.41, 128.28, 128.36, 130.00, 130.57, 132.60, 156.26; Anal. Found: C, 70.15; H, 6.72; Calcd: C, 70.11; H, 6.79.

2.3.6. 1-Chloro-2-phenyl-2'-methoxy-5'-isopropyl-cyclohexene (4e). ^1H NMR (CDCl_3) δ : 1.23–1.25 (d, 6H, $J = 6.8$ Hz), 1.75–1.90 (br m, 4H), 2.10–2.35 (br, 4H), 2.40–2.60 (br, 2H), 2.82–2.92 (sep, 1H), 3.79 (s, 3H), 6.83–6.85 (d, 1H, $J = 8.4$ Hz), 6.96–6.97 (d, 1H, $J = 2.4$ Hz), 7.10–7.12 (m, 1H); ^{13}C NMR (CDCl_3) δ : 22.99, 24.45, 24.59, 30.13, 32.17, 33.67, 34.23, 56.24, 111.48, 126.32, 128.56, 128.71, 130.73, 133.40, 141.18, 154.80; Anal. Found: C, 72.59; H, 7.97. Calcd: C, 72.57; H, 7.99.

2.3.7. 1-Chloro-2-phenyl-4'-ethoxy-cyclohexene (4f). IR: 1286, 1685, 2862, 2935 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.40–1.43 (t, 3H, $J = 7.2$ Hz), 1.74–1.82 (m, 4H), 2.35–2.49 (m, 4H), 4.01–4.06 (q, 2H, $J = 6.8$ Hz), 6.86–6.88 (d, 2H, $J = 8.4$ Hz), 7.18–7.20 (d, 2H, $J = 8.8$ Hz); GC-MS *m/e* (*rel. int.*): 237.80 (38), 235.81 (100), 207.70 (28), 200.82 (36), 172.76 (56). Anal. Found: C, 71.09; H, 7.30. Calcd: C, 71.03; H, 7.24.

2.3.8. 1-Chloro-2-phenyl-3', 4'-dimethoxy-cyclohexene (4g). IR: 1159, 1207, 1504, 1606, 2837, 2933 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.17–1.18 (broad m, 4H), 2.1–2.4 (broad s, 2H), 2.4–2.6 (broad s, 2H), 3.7 (s, 3H), 3.8 (s, 3H), 6.5 (s, 2H), 6.98–7.01 (d, 1H, $J = 12$ Hz), ^{13}C NMR (CDCl_3) δ : 22.59, 24.01, 31.89, 33.82, 55.28, 55.63, 99.00, 104.19, 106.19, 128.48, 130.39, 132.29, 157.35, 160.01; Anal. Found: C, 66.50; H, 6.72; Calcd: C, 66.53; H, 6.78.

2.3.9. 1-Chloro-2-phenyl-3'-acetyl-cyclohexene (4h). IR: 1286, 1685, 2862, 2935 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.73–1.86 (m, 4H), 2.38–2.42 (m, 2H), 2.48–2.51 (m, 2H), 2.61 (s, 3H), 7.46 (s, 1H), 7.42–7.48 (m, 1H), 7.85–7.86 (q, 2H); ^{13}C NMR (CDCl_3) δ : 22.57, 23.81, 26.64, 32.77, 34.04, 126.91, 128.11, 128.34, 128.77,

TABLE 1: Suzuki cross coupling of **2** with **3a** using different palladium catalysts/solvents.

Entry	Catalyst	Base	Ligand	Solvent	% Yield

01	Pd(OAc) ₂	K ₂ CO ₃	PPh ₃	Ethanol	40	—
02	Pd(OAc) ₂	K ₂ CO ₃	P(<i>t</i> -Bu) ₃	Ethanol	25	—
03	Pd(OAc) ₂	TEA	P(<i>o</i> -tol) ₃	Ethanol	30	—
04	(PPh ₃) ₂ PdCl ₂	K ₂ CO ₃	PPh ₃	Toluene	35	5
05	(PPh ₃) ₂ PdCl ₂	K ₂ CO ₃	P(<i>o</i> -tol) ₃	Ethanol	25	10
06	(PPh ₃) ₂ PdCl ₂	Cs ₂ CO ₃	P(<i>t</i> -Bu) ₃	Toluene	30	15
07	Pd(PPh ₃) ₂ Cl ₂	TEA	P(<i>o</i> -tol) ₃	Dioxane	35	30
08	Pd(PPh ₃) ₄	Cs ₂ CO ₃	—	Dioxane	20	45
09	Pd(dppf)Cl ₂ · CH ₂ Cl ₂ *	K ₂ CO ₃	—	Dioxane	20	60
					<5	>90

* Reactions were carried out both at reflux condition and in sealed tube.

SCHEME 1

132.98, 133.56, 137.05, 141.94, 198.04; Anal. Found: C, 71.60; H, 6.40. Calcd: C, 71.64; H, 6.44.

2.3.10. 1-Chloro-2-phenyl-3'-chloro-cyclohexene (4i). IR: 1438, 1703, 2860, 2935 cm⁻¹; ¹H NMR (CDCl₃) δ: 1.69–1.84 (m, 4H), 2.33–2.58 (m, 4H), 7.12–7.58 (m, 3H); ¹³C NMR(CDCl₃) δ: 23.34, 23.94, 34.64, 36.51, 119.56, 126.38, 127.04, 127.88, 128.30, 129.34, 130.12, 130.89; Anal. Found: C, 63.49; H, 5.38. Calcd. C, 63.46; H, 5.33.

2.3.11. 1,3',4'-Trichloro-2-phenyl-cyclohexene (4j). ¹H NMR (CDCl₃) δ: 1.72–1.84 (m, 4H), 2.32–2.35 (m, 2H), 2.45–2.49 (m, 2H), 7.08–7.11 (q, 1H, *J* = 4 Hz) 7.35–7.63 (m, 2H); ¹³C NMR (CDCl₃) δ: 22.49, 23.71, 32.61, 34.04, 126.15, 127.72, 128.80, 129.33, 130.07, 130.21, 130.96, 141.34; Anal. Found: C, 55.15; H, 4.29; Calcd. C, 55.10; H, 4.24.

2.3.12. 1-Chloro-2-(2'-benzo[b]furano)-cyclohexene (4k). ¹H NMR (CDCl₃) δ: 1.82–1.84 (m, 4H), 2.61–2.73 (m, 4H), 7.23–7.32 (m, 3H), 7.47–7.49 (d, 1H, *J* = 7.6 Hz), 7.60–7.62 (d, 1H, *J* = 7.6 Hz); ¹³C NMR (CDCl₃) δ: 22.39, 23.99, 28.703, 35.82, 106.85, 111.35, 121.50, 123.14, 124.62, 124.67, 129.18, 131.34, 153.97, 154.38; Anal. Found: C, 72.30; H, 5.68. Calcd. C, 72.26; H, 5.63.

3. Results and Discussion

Reaction of 2-bromocyclohexanone (**1**) [32–35] with PCl₅ in anhydrous ether gave a mixture of chloro-compounds [26],

which without further purification was subjected to dehydrohalogenation using potassium *tert*-butoxide/*tert*-butyl alcohol to isolate pure **2** in 50% overall yield from **1**.

The nonsymmetrical 1-bromo-2-chlorocyclohexene **2** was subjected to the Suzuki cross-coupling reaction with phenyl boronic acid (**3a**) in the presence of palladium acetate catalyst [36]. The reaction however yielded biphenyl as the major product, instead of the expected cross-coupled product 1-chloro-2-phenylcyclohexene (**4a**).

Literature survey indicated several reports which show the use of differing palladium catalysts for the cross-coupling reactions. Some of the catalysts reported are Pd(OAc)₂ [36], PdCl₂ [37], (PPh₃)₂PdCl₂ [38], (PPh₃)₄Pd [39], Pd(dppf)Cl₂ [40], and Pd(dppf)Cl₂·CH₂Cl₂ [41]. We employed all the above catalysts for the Suzuki cross-coupling reaction in an effort to prepare 1-chloro-2-aryl cyclohexenes **4a–k** (Table 1).

Our investigations have shown that the best catalyst for the cross-coupling reaction of **2** to be Pd(dppf)Cl₂·CH₂Cl₂ under inert nitrogen atmosphere and sealed tube conditions (Scheme 1).

In a typical reaction **2** (1 mmol), phenylboronic acid **3a** (1 mmol), potassium carbonate (3 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (5 mol%) in 8–10 mL 1,4-dioxane solvent were heated on an oil bath at 80°C in a sealed tube for 3 hours. Monitoring using TLC and GC indicated the completion of reaction. The reaction mixture was filtered and subjected to column chromatography using silica gel (60–100 mesh) and 1:10 ethyl acetate/hexane (60–80°C fraction) to isolate **4a** in 95% isolated yield.

The reaction of **2** was extended to a wide variety of aryl boronic acids **3b–k** to isolate the products **4b–k**. Each

TABLE 2: Cross coupling of 1-bromo-2-chlorocyclohexene (**2**) with differing aryl boronic acids (**3a–k**). Preparation of novel 1-chloro-2-arylcyclohexenes (**4a–k**).

Entry	Aryl boronic acids (3a–k)	Products (4a–k)	Time (hr)	% Yield
01	3a	4a	3	95
02	3b	4b	2.5	90
03	3c	4c	3	91
04	3d	4d	2	93
05	3e	4e	2	90
06	3f	4f	2	92
07	3g	4g	2	95
08	3h	4h	3	95
09	3i	4i	2.5	94
10	3j	4j	2.5	92

TABLE 2: Continued.

Entry	Aryl boronic acids (3a–k)	Products (4a–k)	Time (hr)	% Yield
11	3k	4k	2.5	93

coupling reaction was repeated for a minimum of three trials and the optimum yields of the products are indicated in Table 2. All products **4a–k** were characterised completely by IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, GC-MS, and elemental analysis.

The mechanism for the formation of the 1-chloro-2-arylcyclohexenes may be explained based on the bond dissociation energies of the carbon-bromine and carbon-chlorine which are 289 and 335 kJ mol $^{-1}$, respectively. In the first step, due to the lower bond energy between carbon and bromine, oxidative addition of the Pd(dppf)Cl $_2$ ·CH $_2$ Cl $_2$ catalyst to **2** occurs across the carbon-bromine bond. In presence of potassium carbonate/arylboronic acid **3a–k**, the species eliminates KBr, CO $_2$, and KOB(OH) $_2$ followed by reductive elimination of the 1-chloro-2-arylcyclohexene **4a–k**. The restored palladium catalyst further continues the cycle.

4. Conclusion

A general methodology for the regiospecific replacement of bromine in 1-bromo-2-chlorocycloalkenes and formation of some novel 1-chloro-2-arylcyclohexenes using the Suzuki cross-coupling reaction are reported. The method is simple and cost efficient and yields the 1-chloro-2-aryl-cyclohexenes in high yields in short duration of time.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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