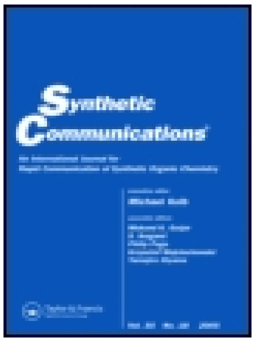

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Synthesis of some novel chloro-/aryl-substituted-5,5-dimethyl-2-cyclohexenones

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ABSTRACT
Two novel structural isomers: the dihalo-5,5-dimethyl-2-cyclohexenones were synthesized. Regioselective Suzuki-Miyaura cross coupling reaction of the isomers with nine different aryl boronic acids afforded eighteen novel compounds: the 2-aryl-3-chloro-5,5-dimethyl-2-cyclohexenones and the 3-aryl-2-chloro-5,5-dimethyl-2-cyclohexenones in 90–95% yields, which were characterized spectroscopically by IR, NMR and MS. The single crystal X-Ray diffraction ORTEP views of four representative compounds unambiguously confirm the formation of substituted cyclohexenones.

ARTICLE HISTORY
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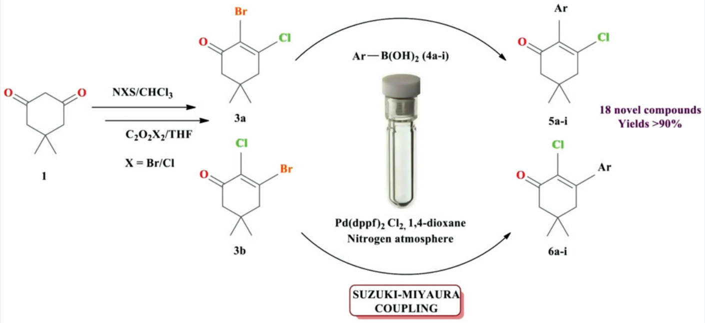
KEYWORDS
Aryl derivatives; cross coupling reaction; halogenated cyclohexenones; single crystal XRD

GRAPHICAL ABSTRACT



Introduction

Being starting materials for the synthesis of a wide range of natural products, substituted cyclohexenones form an important class of compounds in synthetic organic chemistry.[1] Earlier, we have reported the preparation of some substituted methylcyclohexenones,[2] and their conversion into novel anionic synthons.[3] Based on these results we are reporting in this communication new methodologies developed for the synthesis of a wide range of substituted cyclohexenones. To expand the scope and

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Supplemental data for this article can be accessed on the publisher's website.

the utility of our work, we were seeking commercially available less expensive compounds to prepare the substrates.[4]

Over the years, our laboratory has been involved in the study of some metal catalyzed cross-coupling reactions. For examples, (i) Heck-;[5] (ii) Sonagashira-;[6,7] (iii) Suzuki-Miyaura-;[5,8,9] (iv) Wurtz-Fittig-;[5,6,10] and (v) Buchwald – Hartwig cross-coupling reactions[11] have been reported from this laboratory. The starting compounds for these coupling reactions are cyclic vinyl halides/tosylates.[12]

Our earlier studies showed that 1-bromo-2-chlorocycloalkenes form excellent precursors for regioselective transformations. The vicinal olefinic halogens possess differing carbon-halogen bond strengths, the carbon-chlorine bond strength is 335 kJ mol^{-1} whereas, the carbon-bromine bond strength is 268 kJ mol^{-1}.[13] These results indicated that the bromo- group could be preferentially and regiospecifically replaced under suitable reaction conditions.[5,8,11,14]

There are few literature reports for the synthesis of 1,2-vicinal dihalocycloalkenes[15–19] and aryl-substituted cycloalkenes/cycloalkenones in short duration of time and high yields.[20,21] The use of vicinal olefinic 1,2-dibromo- substrates in the Suzuki-Miyaura cross coupling reactions lead to the formation of the 1,2-diaryl products. Similar reaction of 1,2-dichloro- substrates lead to the formation of 1-chloro-2-arylcycloalkenes, albeit employing costly catalysts.[22]

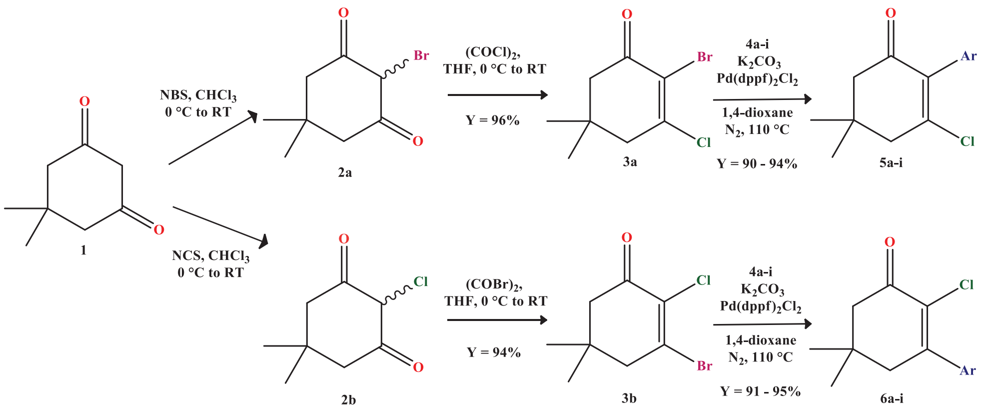
Our aim and protocol was preparation of substrates by regiospecific replacement of only one halogen atom, making use of the differential carbon-halogen bond strengths, eliminating the competition of substitution of both halogens. This strategy has been recently and successfully employed by other scientists for aryl systems.[14] In this context 2-bromo-3-chloro- and 3-bromo-2-chloro-5,5-dimethyl-2-cyclohexenones form excellent precursors in the regioselective Suzuki-Miyaura cross coupling reactions, where the bromo-group could be selectively replaced.

We now report, for the first instance of time, the synthesis of the novel structural isomers: 2-bromo-3-chloro-5,5-dimethyl-2-cyclohexenone (**3a**) and 3-bromo-2-chloro-5,5-dimethyl-2-cyclohexenone (**3b**) from dimedone, using simple and cost effective reagents. The Suzuki-Miyaura cross coupling reaction of **3a** and **3b** with nine different aryl boronic acids: **4a**-**i** afforded a diverse range of novel products: 2-aryl-3-chloro-5,5-dimethyl-2-cyclohexenones: **5a-i**, and 3-aryl-2-chloro-5,5-dimethyl-2-cyclohexenones: **6a-i**, by the *ipso*-substitution at the bromine bearing carbon. The isolated yields of products were 90–95% (Scheme 1). The novelty of our Suzuki-Miyaura reaction methodology approach is the isolation of compounds **5a-i** and **6a-i** in high yields.[23]

Results and discussion

During the course of our earlier studies, we have reported the conversion of a wide range of 2-bromo-1,3-cycloalkanediones to α-bromo-β-chlorocycloalkenones, employing oxalyl chloride.[24]

Reaction of dimedone (**1**) with N-halosuccinimide (NBS or NCS), *p*-TSA in $CHCl_3$ gave the corresponding halogenated compound **2a** and **2b** respectively. Reaction of **2a** and **2b** with oxalyl chloride or oxalyl bromide in THF gave the novel structural isomers: **3a** and **3b** in 96% and 94% respectively.



Scheme 1. Synthesis of some novel chloro-/aryl- substituted-5,5-dimethyl-2-cyclohexenones **5a-i** and **6a-i**.

The compounds **3a** and **3b**, were subjected to the Suzuki-Miyaura cross coupling reaction with nine different aryl boronic acids **4a-i** using Pd(dppf)$_2$Cl$_2$ (0.32 mol%) catalyst, K$_2$CO$_3$ (6.32 m moles), and 5 mL of 1,4-dioxane as solvent, under nitrogen atmosphere in a 15 mL Sigma Ace pressure tube at 110 °C to isolate the 2-aryl-3-chloro-5,5-dimethyl-2-cyclohexenones **5a-i**; and the 3-aryl-2-chloro-5,5-dimethyl-2-cyclohexenones **6a-i** (Scheme 1).

Each coupling reaction was carried out for a minimum of three trials. The optimum yields of the isolated products were greater than 90% and are given in Table 1. The compounds were isolated as high boiling liquids/low melting off-white to yellow Colored solids. Distillation under reduced pressure of 0.01 mm Hg gave tarry material indicating the decomposition of the compounds. The compounds **5a-i** and **6a-i** were finally isolated in pure form using column chromatography or recrystallization from appropriate solvent and characterized spectroscopically.

X-ray structural analysis

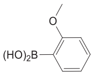
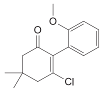
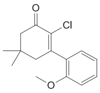
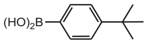
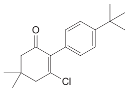
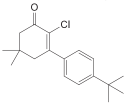
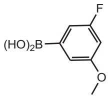
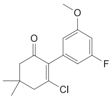
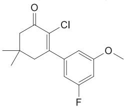
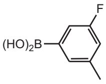
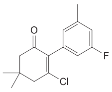
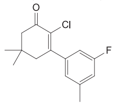
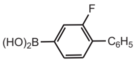
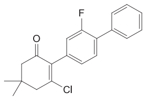
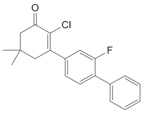
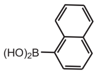
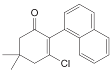
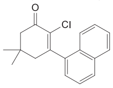
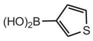
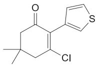
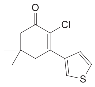
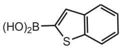
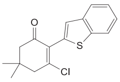
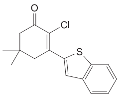
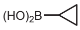
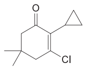
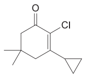
Slow evaporation techniques were employed to isolate good quality crystals in petroleum benzine (60–74 °C) solvent. Among all the compounds which were subjected to recrystallization, good quality crystals were isolated in the case of: **3a**,[24,25] **3b**, 3-chloro-2-napthyl-5,5-dimethyl-2-cyclohexenone (**5f**) and 2-chloro-3-(3′-fluoro-5′-methyl)phenyl-5,5-dimethyl-2-cyclohexenone (**6d**). These compounds were subjected to single crystal XRD studies and the ORTEP views are given in Figure 1.

To the best of our knowledge, there are no literature reports for the single crystal XRD analysis of this class of compounds. Now, first time we are reporting here the single crystal XRD data for the representative compounds **3a**, **3b, 5f** and **6d**.

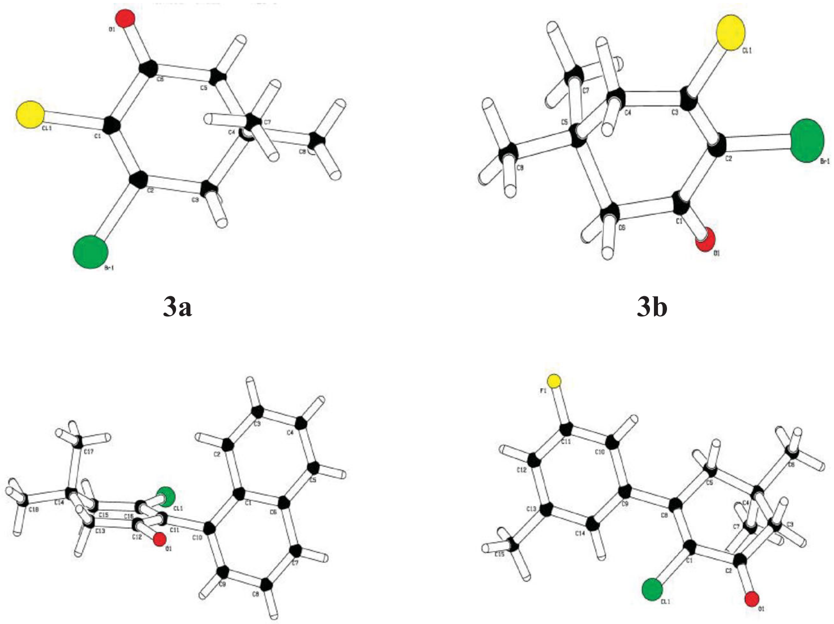
Mechanism

We expect the reaction mechanism for the formation of products **5a-i** and **6a-i**, to traverse through well established routes earlier reported by scientists for the

Table 1. Chloro-/aryl-substituted-5,5-dimethyl-2-cyclohexenones **5a-i** and **6a-i**.

Entry	Boronic acids	2-Aryl-3-chloro-5,5-dimethyl-2-cyclohexenones (Reaction duration and % yields)	3-Aryl-2-chloro-5,5-dimethyl-2-cyclohexenones (Reaction duration and % yields)
1	 **4a**	 **5a** (3 hrs, 92%)	 **6a** (2 hrs, 94%)
2	 **4b**	 **5b** (3 hrs, 93%)	 **6b** (3 hrs, 95%)
3	 **4c**	 **5c** (4 hrs, 91%)	 **6c** (2 hrs, 92%)
4	 **4d**	 **5d** (4 hrs, 91%)	 **6d** (2 hrs, 92%)
5	 **4e**	 **5e** (4 hrs, 94%)	 **6e** (2 hrs, 95%)
6	 **4f**	 **5f** (3 hrs, 92%)	 **6f** (2 hrs, 94%)
7	 **4g**	 **5g** (4 hrs, 90%)	 **6g** (2 hrs, 92%)
8	 **4h**	 **5h** (4 hrs, 91%)	 **6h** (4 hrs, 92%)
9	 **4i**	 **5i** (4 hrs, 90%)	 **6i** (3 hrs, 91%)

Suzuki-Miyaura cross coupling reactions. The oxidative addition of the C-Br bond of the vinyl halide **3a** or **3b** to the Pd (0) takes precedence over C-Cl bond, inducing the regioselective formation of products.[14] Our bench-work have also indicated that the reactions of **3b** were faster than **3a** and occur in much shorter duration of time (Table 1). We reason that oxidative addition of C-Br bond of **3b** is faster than **3a**, due to steric constraints in the latter. Trans-metallation and reductive elimination of the palladium intermediate yields the novel regioselective products **5a-i** and **6a-i**.



3a **3b**

5f **6d**

Figure 1. ORTEP view of compounds **3a**, **3b**, **5f** and **6d**.

Experimental section

General procedure for the preparation of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (2a) and 2-chloro-5,5-dimethylcyclohexane-1,3-dione (2b)

To a solution of dimedone (14 g, 0.1 moles) and *p*-toluenesulfonic acid (100 mg, 0.58 m moles) in 100 mL $CHCl_3$, maintained at 0 °C, was added N-halosuccinimide [NBS (21.35 g, 0.12 moles) or NCS (16.02 g, 0.12 moles)] over a period of 1 hour, followed by allowing the reaction mixture to attain room temperature. The progress of reaction was monitored by thin layer chromatography (TLC). After complete disappearance of the starting material as indicated by thin layer chromatograms using 0.5% methanol/CH_2Cl_2 as mobile phase, the reaction mixture was quenched with 250 mL of 20% sodium metabisulphite to remove any by-products. The aqueous layer was extracted with CH_2Cl_2 (3×70 mL), washed with water (3×70 mL), brine solution (2×70 mL) and dried over anhydrous Na_2SO_4 crystals. The organic extract was stripped of solvent under vacuum and the crude compound purified by column chromatography using 60–120 silica gel as stationary phase and 0.5% methanol/CH_2Cl_2 as mobile phase to isolate 94% of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (**2a**); or 91% of 2-chloro-dimethylcyclohexane-1,3-dione (**2b**) respectively.

General procedure for the preparation of 2-bromo-3-chloro-5,5-dimethyl-2-cyclohexenone (3a) and 3-bromo-2-chloro-5,5-dimethyl-2-cyclohexenone (3b)

To a magnetically stirred suspension of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (**2a**, **2g**, 9.1 m moles); or 2-chloro-5,5-dimethylcyclohexane-1,3-dione (**2b**, **2g**, 11.45 m moles) was added oxalyl chloride (18.25 m moles); or oxalyl bromide (22.91 m moles) dissolved individually in 20 mL THF, over a period of 30 minutes, at 0 °C. The reaction mixture was allowed to attain ambient temperature over a period of two hours. The contents were then transferred to 100 g of crushed ice and extracted with $CHCl_3$ (2 × 30 mL). The combined organic extract was washed with saturated $NaHCO_3$ (2 × 30 mL), brine solution (2 × 30 mL) and dried over anhydrous $MgSO_4$. The organic extract was stripped of solvent under vacuum to isolate pure compounds 2-bromo-3-chloro-5,5-dimethyl-2-cyclohexenone (**3a**) in 96% and 3-bromo-2-chloro-5,5-dimethyl-2-cyclohexenone (**3b**) in 94% yields respectively.

General procedure for the preparation of 2-aryl-3-chloro-5,5-dimethyl-2-cyclohexenones (5a-i) and 3-aryl-2-chloro-5,5-dimethyl-2-cyclohexenones (6a-i)

A suspension of 2-bromo-3-chloro-5,5-dimethyl-2-cyclohexenone (**3a**, 0.5 g, 2.11 m moles); or 3-bromo-2-chloro-5,5-dimethyl-2-cyclohexenone (**3 b**, 0.5 g, 2.11 m moles), aryl boronic acid (**4a-i**, 1.1 m molar equivalent), K_2CO_3 (0.87 g, 6.32 m moles), $Pd(dppf)_2Cl_2$ catalyst (5 mg, 0.0068 m moles, 0.32 mol%) in 6 mL of 1,4-dioxane was taken in a 15 mL Sigma-Aldrich ace pressure tube along with a magnetic pellet. The suspension was purged over 5 minutes with nitrogen gas and sealed. The pressure tube was introduced into a pre-heated oil bath at 110 °C and magnetically stirred for a period of 4 hours. Aliquots indicated the reaction to be completed within the duration of time as indicated in Table 1. The reaction was allowed to attain ambient temperature, transferred to a beaker and diluted with ethyl acetate (20 mL). The extract was filtered over a bed of Celite®. The filtrate was concentrated on a rotary evaporator and the crude product was purified by column chromatography using using silica gel (Merck, 60–120 mesh) as the stationary phase and ethyl acetate: petroleum benzine (60–74 °C) as mobile phase to isolate the compounds 2-aryl-3-chloro-5,5-dimethyl-2-cyclohexenones **5a-i** and 3-aryl-2-chloro-5,5-dimethyl-2-cyclohexenones **6a-i** in greater than 90% yields. The novel compounds were characterized by spectral analysis and the yields are reported in Table 1.

Conclusion

The current work describes an easy protocol for the direct synthesis of chloro-/aryl-substituted-5,5-dimethyl-2-cyclohexenones in short duration of time and accompanied with high yields, by the Suzuki-Miyaura cross coupling reaction. The spectroscopic analyses of all compounds and the single crystal XRD data of four representative compounds unambiguously confirm the formation of compounds.

Supplementary data associated with this article can be found as a separate word file, which includes: ^{1}H-NMR, ^{13}C-NMR, FT-IR, Mass spectra of all the novel compounds: **3a**, **3b**, **5a-i**, **6a-i**; and crystal data of **3a**, **3b**, **5f** and **6d**.

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