Synthesis of 2-bromo-1H-indenes via copper-catalyzed intramolecular cross-coupling of gem-dibromoolefins

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Indene scaffolds are valuable synthetic targets as they exist in many molecules with diverse bioactivities\textsuperscript{1} and are also present in various metallocene complexes used for the catalysis of olefin polymerizations.\textsuperscript{2} In addition, indene derivatives are also of interest in the field of material science.\textsuperscript{3} As a result, a number of synthetic methods for the construction of indene ring systems have been developed.\textsuperscript{4} However, less attention has been paid to the synthesis of haloindenes which can be easily transformed into functionalized indene derivatives through subsequent coupling reactions. The preparation of haloindenes usually involves the bromination of indanes or indenes\textsuperscript{5} and Hi-mediated cyclization of o-(alkynyl)styrenes.\textsuperscript{6} These traditional approaches to haloindenes often suffer from either long reaction sequences or strong acidic conditions under which many functional groups cannot be tolerated. Recently, several protocols for the synthesis of the haloindenes have been developed. These methods include Lewis-acid catalyzed cyclization of iodinated allylic alcohols,\textsuperscript{7} iodonium-promoted carbocyclization of 2-substituted ethynylmalonates,\textsuperscript{8} Pd-catalyzed carbocyclization of 2-alkenylphenylacetylenes in the presence of copper halide\textsuperscript{9} and halocyclization of o-(alkynyl)styrenes.\textsuperscript{10} Very recently, an efficient strategy for the synthesis of substituted \textit{N}-(2-haloinden-1-yl)arenesulfonamides from propargyl alcohols and sulfonamides has been reported.\textsuperscript{11}

The chemistry of gem-dihaloolefins,\textsuperscript{12} once limited mainly to the synthesis of terminal alkynes, has made remarkable progress in organic synthesis especially in transition metal-catalyzed reactions. A number of novel and elegant reactions using gem-dihaloolefins as building blocks have been developed and compounds such as dienes,\textsuperscript{13} enynes,\textsuperscript{14} heterocycles\textsuperscript{15}, and carbocycles\textsuperscript{16} are prepared efficiently from various gem-dihaloolefins. In conjunction with our study of gem-dibromoolefins for the synthesis of heterocycles,\textsuperscript{17} we have developed a straightforward and efficient method for the synthesis of 2-bromo-1H-indenes via copper-catalyzed intramolecular C–C cross-coupling reaction of activated methylene aromatic compounds bearing gem-dibromoolefins, and herein we report these results.

Scheme 1. Preparation of diethyl 2-\{(2,2-dibromovinyl)phenyl\}malonate 1a.
Diethyl 2-(2-(2,2-dibromovinyl)phenyl)malonate 1a, readily prepared from 2-iodobenzaldehyde through β-arylation of malonate\(^{18}\) and subsequent \(\text{gem-dibromoolefination}\) of the aldehyde (Scheme 1),\(^{19}\) was chosen as the model substrate to optimize the reaction conditions. The results are shown in Table 1. The substrate 1a was first subjected to the following reaction conditions: CuI (20 mol %), Cs\(_2\)CO\(_3\) (3 equiv) in THF at 75 °C under an argon atmosphere without any ligand. The desired cyclized product 2a was obtained in a 68% yield (entry 1), while other reaction conditions gave lower yields (entries 2–7). Treating substrate 1a with Cs\(_2\)CO\(_3\) in the absence of the catalyst led to a lower yield of the desired product 2a (entry 8). In addition, treating substrate 1a with DBU gave the elimination product diethyl 2-(2-bromoethyl)phenyl)malonate exclusively, while the desired product 2a was not observed even after a prolonged reaction time (entry 9). To further optimize the reaction conditions, we then investigated the reaction in the presence of various ligands including L-proline (L\(_1\)), N,N-dimethylglycine (L\(_2\)), 2-picolinic acid (L\(_3\)), 1,10-phenanthroline (L\(_4\)), and 2-acetylcyclohexanone (L\(_5\)) (entries 10–15). Ligand 1,10-phenanthroline (L\(_4\)) was found to be the most suitable additive for this coupling reaction (entries 13 and 14). Reduction of L\(_4\) and CuI loading gave very similar results (entry 14). Thus, the optimized conditions included the use of 10 mol % CuI as the catalyst, 20 mol % of 1,10-phenanthroline (L\(_4\)) as the ligand, and 3 equiv of Cs\(_2\)CO\(_3\) as the base in THF at 75 °C under an argon atmosphere.

With the optimal reaction conditions in hand, we set to investigate the generality of this coupling reaction. As shown in Table 2, a broad range of substrates underwent this coupling reaction smoothly to afford the corresponding desired products in moderate to good yields. For example, substrates bearing different acti-
vated methylenes at 2-position of the aromatic ring smoothly pro-
ceeded to furnish the corresponding indenes (entries 1–3). Among
these results, the substrate 1b gave the highest yield (entry 1). The
presence of a more sterically hindered isopropyl malonate led to a
lower yield for the cyclized product (entry 3). Meanwhile, sub-
strate bearing a nitro substituent on the aromatic ring gave a poor
result (entry 13). Interestingly, while chloro and fluoro substitu-
teons on the aromatic ring were well tolerated (entries 6–9), a reac-
tive iodo derivative (2o) also afforded the desired product with
high chemoselectivity (entry 14).21 No iodo reduction was detected
from the reaction mixture.

A possible mechanism of the reaction is depicted in Scheme 2. It
is likely that the malonate is deprotonated transiently under the
reaction conditions. The anion is then coordinated with copper,

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*a* Reactions were carried out using 0.5 mmol of substrate 1, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, and 3 equiv of Cs2CO3 in THF (5 mL) at 75 °C under an argon atmosphere.

*b* Isolated yield.

directing Cu insertion into the ‘cis’-Br, and leading to the desired product. This mechanism explains the high selectivity over the distal iodo substitution (Table 2, entry 14).

In conclusion, we have developed an efficient method for the synthesis of 2-bromo-1H-indenes via copper-catalyzed intramolecular C–C cross-coupling reaction. A variety of 2-bromo-1H-indenes were obtained in moderate to good yields. This method may provide a new way for the synthesis of highly functionalized indenes.

Acknowledgment

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Supplementary data


References and notes


4. Typical procedure for the synthesis of diethyl 2-[(2,2-dibromovinyl)phenylmalonate (1a): To a well-stirred mixture of ethyl 2-(2-formylphenyl)malonate (2.60 g, 9.85 mmol) CBr4 (6.60 g, 19.90 mmol) in DCM (100 mL) was added dropwise a solution of PPh3 (10.40 g, 39.65 mmol) in DCM (50 mL) over 2 h. After 2 h stirring, hexane was added to precipitate as much PbP2O as possible, and the suspension was filtered through silica (washed with EtOH). The solution was concentrated under reduced pressure, and the residue was purify by column chromatography on silica gel (petroleum ether-EtOAc = 15:1) to give 1a as a colorless oil (2.96 g, 72%). 1H NMR (400 MHz, CDCl3): δ 7.58 (s, 1H), 7.50 (d, J = 7.1 Hz, 1H), 7.35–7.40 (m, 2H), 4.78 (s, 1H), 4.02 (s, 4H, 4H), 3.99 (s, 4H, 4H), 1.56 (s, 6H), 1.41 (s, 6H). 13C NMR (100 MHz, CDCl3): δ 167.7, 136.2, 136.0, 130.9, 129.5, 126.4, 124.8, 123.8, 123.0, 122.2, 119.9, 119.4, 118.2, 117.8, 116.6, 111.4, 111.2, 102.4, 97.9, 76.6, 62.6, 56.2, 53.3, 14.0; HRMS (ESI) exact mass calculated for [M+H]+ 339.0232, found 339.0232.


6. For comprehensive reviews, see: (a) Xu, B.; Ma, S. Org. Lett. 2005, 7, 3034–3037.


