JOC*Note*

A Tandem Elimination−Cyclization−Suzuki Approach: Efficient One-Pot Synthesis of Functionalized (*Z*)-3-(Arylmethylene)isoindolin-1-ones

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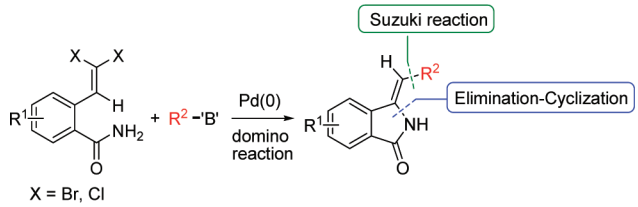

A novel and efficient one-pot regioselective elimination−cyclization−Suzuki approach was developed to afford (*Z*)-3-arylmethyleneisoindolin-1-ones in good to excellent yields from easily accessible *o*-*gem*-dihalovinylbenzamides and organoboron reagents.

3-Arylmethyleneisoindolin-1-ones represent important structural units frequently found in natural products, biologically active compounds, and other synthetic intermediates.[1] Considerable effort has been made to synthesize 3-arylmethyleneisoindolin-1-ones due to their wide application in pharmaceutical research. Among the various synthetic strategies, the majority of synthetic routes rely on nucleophilic addition to phthalimides[2] or phthalides,[3] condensation reaction from 3-(diphenylphosphinoyl)isoindolin-1-ones[1a,4] or phthalaldehyde,[4c,5] and base-promoted nucleophilic addition of *o*-(1-alkynyl)benzamides[6] or benzonitrile derivatives.[7] However, in the case of unsymmetrical substrates, these approaches often lead to a mixture of regioisomers.[1a,2,3c] Recently, a number of syntheses based on the palladium-mediated cyclization reactions described by Cossy and other groups have been proved to be some of the most efficient approaches.[8]

Remarkable progress has been made in metal-catalyzed reactions of *gem*-dihaloolefins,[9] which provide convenient and versatile routes to polysubstituted alkenes,[10] enynes,[11] polyynes,[12] and carbo- or heterocycles.[13−15] Ma et al. have developed the first transition metal-catalyzed bicyclic carbometalation reaction of *gem*-dibromides and afforded a prompt construction for fused bicycles from *gem*-dihaloolefins.[13] Recently, Lautens and co-workers reported several novel and elegant modular methods of indol synthesis via palladium- or copper-catalyzed C−N/C−N or C−N/C−C coupling sequence from *gem*-dihaloolefins.[15]

During our program aimed at the convenient construction of nitrogen-containing molecules and biochemical validation of various heterocycles,[16] our attention was drawn to 3-arylmethyleneisoindolin-1-ones. Thus, *gem*-dihaloolefins were explored as substrates to provide a general approach for a broad range of heterocycles under palladium-catalyzed reaction. Herein, we

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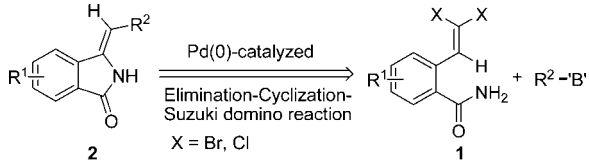
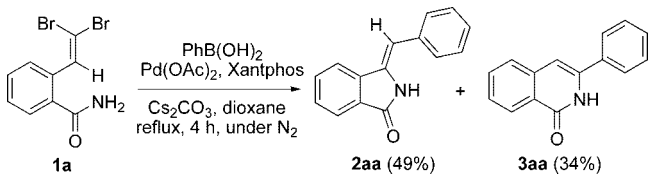
SCHEME 1



SCHEME 2

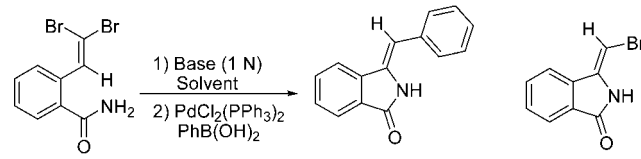


report a new synthetic strategy for the highly regioselective synthesis of substituted 3-arylmethyleneisoindolin-1-ones in a domino fashion from easily available *o-gem*-dihalovinylbenzamides and organoboron reagents (Scheme 1). To the best of our knowledge, this represents the first report of a one-pot synthesis of 3-arylmethyleneisoindolin-1-ones from the readily available *gem*-dihaloolefins.

Initial study was performed by examining the reaction of **1a**[17] with phenylboronic acid in the presence of $Pd(OAc)_2$ (5 mol %) and Xantphos (10 mol %) in dioxane with Cs_2CO_3 as a base. However, this reaction gave 5-*exo* product **2aa** in 49% yield together with 6-*endo* product **3aa** in 34% yield (Scheme 2). The structures of **2aa** and **3aa** were determined by spectra analysis and compared with authentic samples,[1b,8d] and the identity of **2aa** was further confirmed by X-ray crystallography. To identify optimal conditions for selective synthesis of **2aa**, various combinations of palladium source/ligand/base/solvent were screened with $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, or $Pd(OAc)_2$ as catalyst, BINAP, Tri-2-furylphosphine (TFP), Xantphos, or PPh_3 as ligand, and Na_2CO_3, K_3PO_4, or Cs_2CO_3 as base in toluene, DMF, or dioxane. However, all these reactions gave a mixture of **2aa** and **3aa**, or poor yield of **2aa**. We envisioned that the formation of **2aa** arose from the domino elimination−5-*exo*-cyclization−Suzuki reaction via alkynyl bromide[15g,18] and (*Z*)-3-(bromomethylene)isoindolin-1-one **4**. Thus, in order for **2aa** to be the major product, it is crucial to avoid the palladium-catalyzed intramolecular C−N formation,[15] which leads to **3aa**.

We speculated selective formation of the alkynyl bromide could be achieved by employing a base without addition of palladium catalyst.[15g,18] As expected, our attempts to use the NaOH/$PdCl_2(PPh_3)_2$ system in dioxane afforded **2aa** in 82% yield (Table 1, entry 1). Other inorganic bases such as LiOH or KOH in dioxane gave similar results, whereas Cs_2CO_3 retarded the reaction and the remaining unreacted **1a** could be recovered nearly quantitatively (Table 1, entries 2−4). When the solvent was switched to EtOH, toluene, or CH_3CN, the yield of **2aa** decreased (Table 1, entries 5 and 6) or gave only the 5-*exo*-cyclization intermediate **4** in 67% isolated yield (Table 1, entry 7). When the reaction was conducted with phenylboronic acid in THF with $PdCl_2(PPh_3)_2$ (5 mol %) as catalyst and NaOH (1 N) as base at 60 °C, **2aa** was isolated in 87% yield after being reacted about 10 min for the cyclization reaction and 30 min for the Suzuki cross-coupling reaction (Table 1, entry 8). Attempts to lower the loading of Pd catalyst to 1 mol % in THF or dioxane gave no significant change of yield but longer cross-coupling reaction times were needed (Table 1, entries 9 and 10). The addition of tetra-*n*-butylammonium bromide (TBAB) as an additive had no obvious effect (Table 1, entry 11); however, raising the temperature to reflux improved the reaction time and gave good yields (Table 1, compare entries 9 and 12).

TABLE 1. One-Pot Synthesis of (*Z*)-3-Benzylideneisoindolin-1-one under the Catalysis of $PdCl_2(PPh_3)_2$[a]



entry	Pd (%)	base	solvent	temp (°C)	time (*C*/*S*)[b] (min/min)	yield[c] (%)
1	5	NaOH	dioxane	80	10/7	82
2	5	LiOH	dioxane	80	10/5	77
3	5	KOH	dioxane	80	10/5	84
4	5	Cs_2CO_3	dioxane	80	>60	0[d]
5	5	NaOH	EtOH	80	10/10	55
6	5	NaOH	toluene	80	15/30	68
7	5	NaOH	CH_3CN	reflux	15/30	0[e]
8	5	NaOH	THF	60	10/30	87
9	1	NaOH	THF	60	10/70	83
10	1	NaOH	dioxane	60	10/35	77
11	1	NaOH	THF	60	10/150	79[f]
12	1	NaOH	THF	reflux	10/35	83

[a] All reactions were performed on a 0.1 mmol scale, using $PdCl_2(PPh_3)_2$, $PhB(OH)_2$ (2 equiv), and base (1 N, 3 equiv). [b] *C*: the reaction time for cyclization reaction. *S*: the reaction time for Suzuki coupling reaction. [c] Isolated yields. [d] Starting material **1a** was recovered. [e] Intermediate **4** was isolated in 67% yield. [f] TBAB (1 equiv) was added.

To explore the scope of this method, a variety of *o-gem*-dihalovinylbenzamides **1a**−**e** were prepared from substituted 2-methylbenzonitriles[17,19,20] (Scheme 3) and applied to the synthesis of 3-arylmethyleneisoindolin-1-ones under the optimized conditions (Table 1, entry 12), as shown in Table 2.

As illustrated in Table 2, the cyclization−coupling reaction proceeded readily to give the corresponding 5-*exo* products in good to excellent yields. Remarkably clean reactions were observed with functionalized arylboronic acids bearing ortho, meta, and para substitutions on the aryl ring (entries 2−15).

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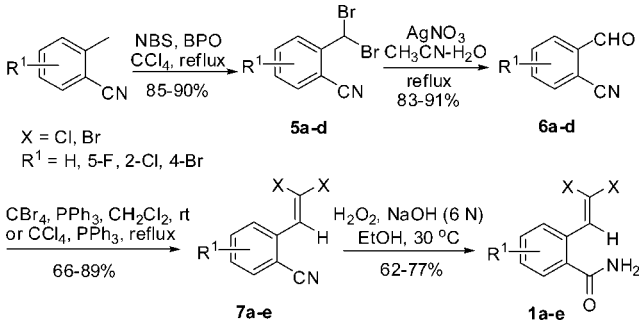
SCHEME 3. Synthesis of *o-gem*-Dihalovinylbenzamides

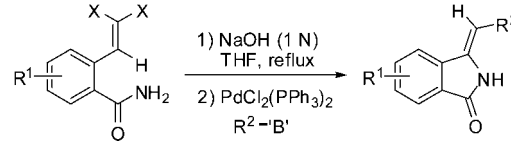


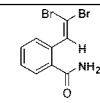
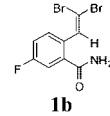
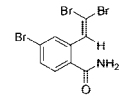
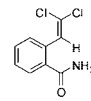
Boronic reagents containing electron-donating groups afforded products in high yields with short reaction time (entries 2−5 and 9−11), whereas the reagents with electron-withdrawing groups such as nitro, tosyl,[21] or trifluoromethyl groups gave slightly lower yields (entries 7 and 13−15). The reactions were generally performed with 1 mol % of palladium, with a few exceptions (entries 4, 10, 13, and 16). It was found that 4-hydroxyphenylboronic acid could give product in 96% yield with 5 mol % of Pd and 5 equiv of NaOH in the reaction (entry 10). This reaction was not limited to simple benzene-containing boronic acids, the naphthyl- and thiophen-containing substrates also afforded **2an** and **2ao** in 78% and 76% yields, respectively (entries 16 and 17). Additionally, dibutyl vinylboronate and phenethyl-9-BBN[22] were further investigated and afforded **2ap** and **2aq** in excellent yields (entries 19 and 20). The effect of substitution on aromatic ring was examined. Substrates consisting of a fluoro and a chloro group gave corresponding **2bh** and **2ch** in good yields when reacted with electron-rich *p*-tolylboronic acid (entries 21 and 23), whereas long reaction time was needed to complete the reaction when reacted with electron-deficient *p*-(trifluoromethyl)phenylboronic acid (entry 22). For bromo-containing substrate **1d**, a double Suzuki-coupling reaction was found and afforded (*Z*)-3-(4-methylbenzylidene)-5-(4-tolyl)-2,3-dihydro-1*H*-isoindolin-1-one (**2dh**) in 67% yield (entry 24), while the tosyl group in compound **10**[21] was untouched[23] during the Suzuki reaction (entry 13). It should be noted that high loading of palladium (3 mol %) (entries 8, 15, and 18) or using dioxane as cosolvent (entry 21) or solvent (entries 23−24) promoted the reaction. In particular, the use of *o-gem*-dichlorovinylbenzamide **1e** could also afford **2ah** in high yield with a long reaction time (entry 25).

The produced (*Z*)-3-arylmethyleneisoindolin-1-ones are versatile synthetic intermediates and could be further elaborated.[1] For example, compound **2aa** was transformed to N-substituent derivatives **8** and **9** in high yield by alkylation or benzylation reaction[24] (Scheme 4). Also, a potential Topo-I inhibitor **11** could be easily constructed from **2aa** by using literature reported methods (Scheme 4).[1b,25]

A tentative mechanism to rationalize this novel palladium-catalyzed tandem reaction is proposed in Scheme 5. The mechanism may involve dehydrobromination of **1** and furnish the alkynyl bromide intermediate **A**,[15g,18] which was then attacked by nitrogen of the amide group to provide (*Z*)-3-(bromomethylene)isoindolin-1-one **4** regioselectively via a 5-*exo*-cyclization process. The generated **4** will lead to 3-arylmethyleneisoindolin-1-ones **2** through the classic Suzuki cross-coupling reaction.[15g,26] Additional support for this mechanism was obtained by the high-yield formation of **2aa** (89%) from phenylboronic acid and **4** under optimized Suzuki reaction condition, and **4** was prepared from **1a** in 98% yield via a cyclization reaction.

TABLE 2. Scope of Organoboron Reagents and *o-gem*-Dihalovinylbenzamides[a]



entry	amide	R^2-"B"	Pd (%)	time (*C*/*S*)[b] min/h	yield[c] (%)
1	 **1a**	$PhB(OH)_2$	1	20 / 1	84 (**2aa**)
2		*o*-$MeC_6H_4B(OH)_2$	1	20 / 1	86 (**2ab**)
3		*o*-$MeOC_6H_4B(OH)_2$	1	20 / 1	87 (**2ac**)
4		*m*-$NH_2C_6H_4B(OH)_2$	3	20 / 1	87 (**2ad**)
5		*m*-$MeOC_6H_4B(OH)_2$	1	20 / 1	84 (**2ae**)
6		*m*-$FC_6H_4B(OH)_2$	1	20 / 1.5	85 (**2af**)
7		*m*-$NO_2C_6H_4B(OH)_2$	1	20 / 2	63 (**2ag**)
8			3	20 / 1	72 (**2ag**)
9		*p*-$MeC_6H_4B(OH)_2$	1	20 / 1	96 (**2ah**)
10		*p*-$HOC_6H_4B(OH)_2$	5	20 / 3	96[d] (**2ai**)
11		*p*-$MeOC_6H_4B(OH)_2$	1	20 / 1	94 (**2aj**)
12		*p*-$ClC_6H_4B(OH)_2$	1	20 / 1	91 (**2ak**)
13		*p*-$TsOC_6H_4B(OH)_2$	3	20 / 2	77 (**2al**)
14		*p*-$CF_3C_6H_4B(OH)_2$	1	20 / 2	55 (**2am**)
15			3	20 / 1	68 (**2am**)
16		2-NaphthylB$(OH)_2$	3	20 / 0.5	78 (**2an**)
17		3-ThienylB$(OH)_2$	1	20 / 2	76 (**2ao**)
18			3	20 / 0.25	91 (**2ao**)
19		CH_2=CHB$(O^nBu)_2$	3	20 / 1	91[e] (**2ap**)
20		$PhCH_2CH_2BBN$	3	20 / 1	93[e] (**2aq**)
21	 **1b**	*p*-$MeC_6H_4B(OH)_2$	1	10 / 0.5	87[f] (**2bh**)
22		*p*-$CF_3C_6H_4B(OH)_2$	3	30 / 2	80 (**2bm**)
23	 **1c**	*p*-$MeC_6H_4B(OH)_2$	3	5 / 0.17	70[g] (**2ch**)
24	 **1d**	*p*-$MeC_6H_4B(OH)_2$	3	15 / 0.33	0 (67)[g,h] (**2dh**)
25	 **1e**	*p*-$MeC_6H_4B(OH)_2$	1	240 / 2	92 (**2ah**)

[a] All reactions were performed on a 0.5 mmol scale, using $PdCl_2(PPh_3)_2$, $ArB(OH)_2$ (2 equiv), and NaOH (1 N, 3 equiv) in THF (c = 0.1 M) under reflux unless otherwise noted. [b] *C*: the reaction time for cyclization reaction. *S*: the reaction time for the Suzuki reaction. [c] Isolated yields. [d] NaOH (1 N, 5 equiv) was used under N_2. [e] Under N_2. [f] THF/dioxane (2.5:1) as solvent. [g] Dioxane as solvent at 80 °C under N_2. [h] The yield in parentheses is for product **2dh**, which was given via double Suzuki reaction.

(21) For preparation of 4-(tosyloxy)phenylboronic acid (**10**), see the Supporting Information.

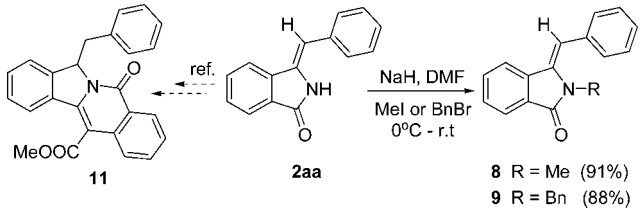
(22) For in situ preparation of phenethyl-9-BBN, see the Supporting Information.

(23) For the OTs group involved in Suzuki reaction, see: Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

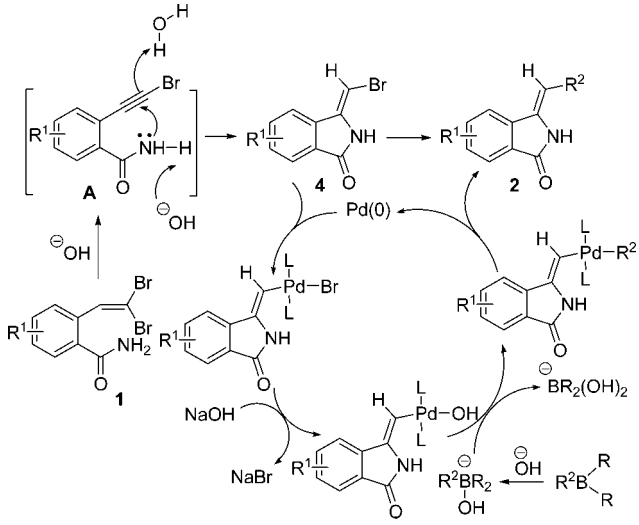
(24) Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pavé, G.; Roulland, E.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 8151.

(25) Pin, F.; Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 1975.

SCHEME 4



SCHEME 5. Plausible Mechanism Tandem Elimination−Cyclization−Suzuki Reaction



In summary, we have developed an efficient one-pot procedure for the regioselective synthesis of (*Z*)-3-arylmethyleneisoindolin-1-ones from easily accessible *o-gem*-dihalovinylbenzamides and organoboron reagents. This operationally facile reaction can be performed open to air and is compatible with many functional groups. The scope of this reaction and its application in the synthesis of bioactive compounds are currently under investigation in our laboratory and will be reported in due course.

(26) For reviews of the Suzuki cross-coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

Experimental Section

Representative Procedure for the Synthesis of (*Z*)-3-Benzylidene-2,3-dihydro-1*H*-isoindolin-1-one (2aa). To a solution of 2-(2,2-dibromovinyl)benzamide (**1a**) (152 mg, 0.50 mmol) in THF (3.5 mL) was added NaOH (1 N, 1.5 mL, 1.5 mmol) at room temperature. After the mixture was stirred for 20 min under reflux, the phenylboronic acid (122 mg, 1.0 mmol) and $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) were added. The resulting mixture was heated for 1 h under reflux with the reaction system open to air. After the reaction was cooled to room temperature, saturated NH_4Cl solution was added. The mixture was extracted with EtOAc (3 × 10 mL), washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The given crude product was purified with column chromatography (EtOAc/petroleum ether = 1:5) to afford **2aa** as a yellow solid (93 mg, 84%). Mp 182−183 °C; IR (KBr, cm^{-1}) 3452, 3264, 2922, 1705, 1650; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.58 (br, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8 Hz, 1H), 7.63 (td, J = 7.5, 1 Hz, 1H), 7.52 (td, J = 7.5, 0.5 Hz, 1H), 7.50−7.41 (m, 4H), 7.34−7.28 (m, 1H), 6.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 138.4, 135.1, 133.2, 132.4, 129.32, 129.29, 128.8, 128.7, 127.8, 123.7, 119.9, 106.2; EI-MS *m*/*z* (%) 221 (100) [M^+], 220 (51), 193 (30), 165 (25). Crystal data for **2aa**: $C_{15}H_{11}NO$, MW = 221.25, monoclinic, space group $P2(1)/c$, final R indices [$I > 2\sigma(I)$], R_1 = 0.0469, wR_2 = 0.1035, a = 11.660 (2) Å, b = 16.607(3) Å, c = 11.854(2) Å, α = 90°, β = 90.921(2)°, γ = 90°, V = 2295.1(7) $Å^3$, crystal size 0.25 × 0.20 × 0.16 mm, T = 273(2) K, Z = 8, reflections collected/unique 11401/4033 (R_{int} = 0.0369), no. of data 4033, no. of restraints 0, no. of parameters 308.

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Supporting Information Available: Characterization data and copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all compounds, and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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