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Heck–Suzuki–Miyaura Domino Reactions Involving Ynamides. An Efficient Access to 3-(Arylmethylene)isoindolinones

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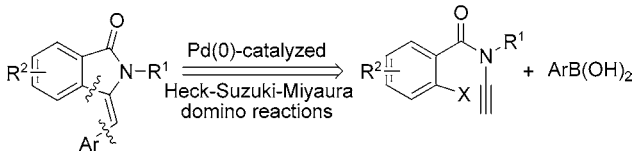
ABSTRACT



Substituted 3-(arylmethylene)isoindolin-1-ones can be efficiently synthesized in a stereoselective manner from various ynamides and boronic acids by palladium-catalyzed Heck–Suzuki–Miyaura domino reactions.

Substituted 3-methyleneisoindolin-1-ones of type **A** (Figure 1) are present in a number of naturally occurring and biologically active compounds.[1,2] Existing methods for their preparation often rely on nucleophilic additions to phthalimides of type **B** followed by dehydration, but this can produce mixtures of regioisomers in the case of unsymmetrical substrates.[1−3]

Several recent synthetic developments that have improved the situation include some Pd-catalyzed three-component processes that exploit a carbonylation reaction,[4] Pd-catalyzed heteroannulations involving 2-iodobenzamides and terminal alkynes,[1a,5] and the Horner condensation of 3-(diphenylphosphinoyl)isoindolin-1-ones with aldehydes.[1b,6]

In recent years, the synthetic application of ynamides has expanded enormously,[7] these stable electron-deficient variants of ynamines having been demonstrated to undergo several transformations usually carried out with alkynes such as metal-catalyzed cycloadditions,[7,8] metathesis,[9] sigmatropic rearrangements,[10] and addition reactions[11,12] eventually followed by cross-couplings.[13,14] However, to our knowledge, reports dealing with palladium-catalyzed reactions directly involving ynamides appear to be restricted, so far, to hydrostannation.[14]

Herein, we would like to report an alternative synthetic strategy toward a variety of (*E*)-3-(arylmethylene)isoindolin-

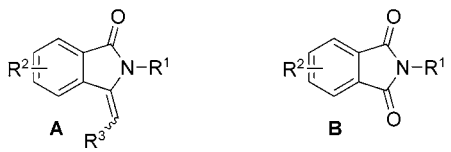


Figure 1.

(1) (a) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777−4792. (b) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313−10330 and references therein.

(2) Dihydroanalogues (3-alkylisoindolin-1-ones) also constitute an important class of biologically active products; see: Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651−1657 and references therein.

(3) For some examples, see: (a) Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707−7710. (b) Ha, D.-C.; Yuun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577−2580. (c) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003−2006. (d) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060−2062. (e) Islam, A. M.; El-Sharief, A. M. S.; Bedair, A. H.; Hammad, N. E. *Egypt. J. Chem.* **1983**, *25*, 251−261. (f) Islam, A. M.; El-Sharief, A. M. S.; El-Maghraby, A. A.; Bedear, A. H. *Indian J. Chem., Sect. B* **1978**, *16*, 301−304. (g) Marsili, A.; Scartoni, V. *Gazz. Chim. Ital.* **1972**, *102*, 806−817. (h) Marsili, A.; Scartoni, V. *Tetrahedron Lett.* **1968**, 2511−2516.

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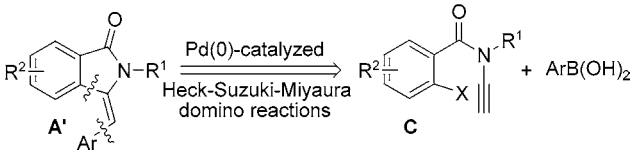
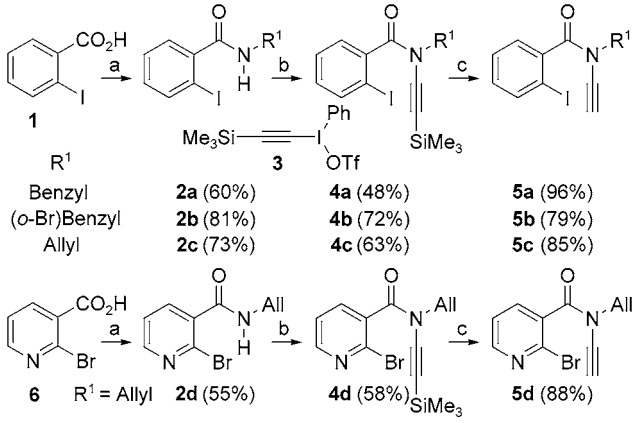
Scheme 1



1-ones of type **A′** that proceeds from ynamides of type **C** and arylboronic acids, which relies on Pd(0)-catalyzed Heck−Suzuki−Miyaura domino reactions for success (Scheme 1).

To investigate the feasibility of this Pd(0)-catalyzed process, several ynamides of type **C** were prepared from 2-iodobenzoic acid **1**. Thus, coupling with benzylamine, 2-bromobenzylamine, and allylamine afforded the corresponding 2-iodobenzamides **2a** (60%), **2b** (81%), **2c** (73%), respectively. Their conversion to ynamides was achieved by formation of the potassium amides (KHMDS, toluene, rt) and condensation with alkynyliodonium salt **3**[15] to afford compounds **4a** (48%), **4b** (72%), and **4c** (63%), respectively, in acceptable yields.[16] Subsequent desilylation using TBAF in THF finally provided **5a** (96%), **5b** (79%), and **5c** (85%), respectively. A structurally related ynamide **5d** possessing a pyridine ring was also prepared from the readily available 2-bromonicotinic acid **6**[17] and allylamine according to a similar strategy (28% overall yield) (Scheme 2).

Scheme 2. Preparation of Ynamides of Type **C**[a]



[a] Reagents and conditions: (a) R^1NH_2, EDCI, cat. DMAP, Et_3N, CH_2Cl_2, rt; (b) KHMDS, **3**, toluene, rt; (c) TBAF, THF, rt.

Since the planned strategy toward 3-(arylmethylene)-isoindolin-1-ones of type **A′** involved two different Pd(0)-catalyzed steps, it was of interest to initially examine the feasibility of the Heck reaction. Thus, ynamides **5b** and **5c** (Scheme 3) were treated with a catalytic amount of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) in DMF at 80 °C, and to regenerate the Pd(0) catalyst from the intermediate σ-vinylpalladium complexes of type **D**, the reaction was carried out in the presence of ammonium formate (1.5 equiv).[18] Under these conditions, the desired 3-methyleneisoindolin-1-ones **7** and **8**[4b] were cleanly generated in 56% and 62% yields, respectively. Worthy of note is the fact that the presence of an arylbromide in substrate **5b** did not alter the

Scheme 3

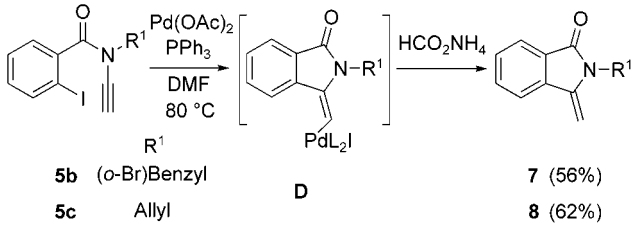


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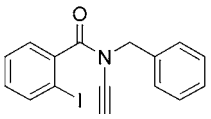
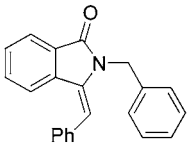
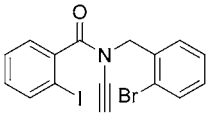
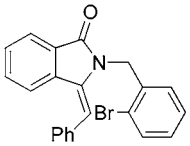
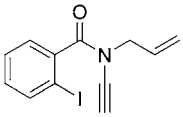
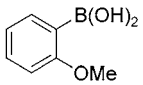
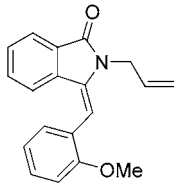
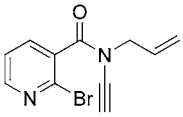
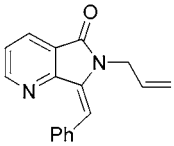
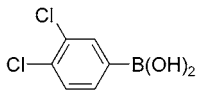
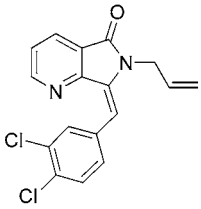
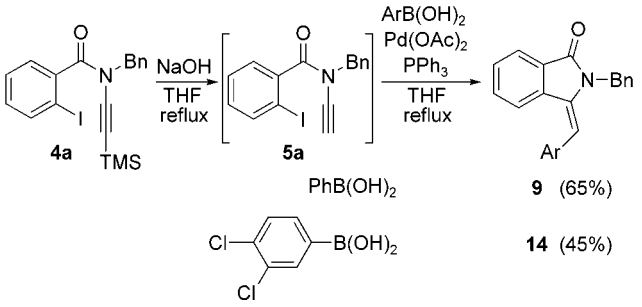
Table 1. Heck−Suzuki−Miyaura Domino Reactions

substrate	reagents: boronic acid Pd catalyst (5 mol%), base, solvent	product (yield)
	$PhB(OH)_2$	
5a	$Pd(PPh_3)_4$, NaOH, DME/H_2O	**9** (48%)
	$Pd(dba)_2$, NaOH, THF/H_2O	**9** (59%)
	$Pd(OAc)_2$ + 2 PPh_3, NaOH, THF/H_2O	**9** (70%)
	Pd/C, NaOH, THF/H_2O	**9** (56%)
	$PhB(OH)_2$	
5b	$Pd(OAc)_2$ + 2 PPh_3, NaOH, THF/H_2O	**10** (51%)
		
5c	$Pd(OAc)_2$ + 2 PPh_3, NaOH, THF/H_2O	**11** (67%)
	$PhB(OH)_2$	
5d	$Pd(OAc)_2$ + 2 PPh_3, NaOH, THF/H_2O	**12** (52%)
	Pd/C, NaOH, THF/H_2O	**12** (0%)
5d		
	$Pd(OAc)_2$ + 2 PPh_3, NaOH, THF/H_2O	**13** (68%)

course of the reaction, it remaining intact in the final product **7** (Scheme 3).

Having demonstrated that ynamides were viable substrates for the carbopalladation process, we investigated the achievement of the Heck−Suzuki−Miyaura domino reactions (Table 1).[18] When ynamide **5a** was treated with benzeneboronic acid in the presence of aqueous sodium hydroxide as a base and a catalytic amount of $Pd(PPh_3)_4$ (5 mol %) in refluxing 1,2-dimethoxyethane (DME), the corresponding 3-benzylideneisoindolin-1-one **9** was obtained in acceptable yield (48%) and as a single stereoisomer.[19] Additional experiments indicated that other palladium catalysts could also be used and that THF was a suitable solvent for this

Scheme 4



reaction. The use of $Pd(dba)_2$ led to a slightly increased yield of **9** (59%), but the optimal result (70%) was obtained when $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) in THF were used to catalyze the process. Interestingly, Pd on C was also an effective catalyst for this reaction, although **9** was obtained in slightly diminished yield (56%).

The Pd(0)-catalyzed Heck−Suzuki−Miyaura domino reactions were applied to ynamides **5b**−**d** in the presence of various boronic acids under optimized conditions [$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), aqueous NaOH, THF, reflux], and the resulting 3-(arylmethylene)isoindolin-1-ones **10** (51%) and **11** (67%), as well as the pyrrolopyridinones **12** (52%) and **13** (68%), were obtained in moderate to good yields, as single geometric isomers.[19] It is worth mentioning that the use of the heterogeneous catalyst Pd on C was unsatisfactory in the case of ynamide **5d**, presumably due to poisoning of the catalyst by the nitrogen atom of the pyridine ring.

The (*E*)-configuration of the 3-benzylideneisoindolin-1-one **9** was assigned by ^1H NMR and comparison with the literature data.[1,3,5] The (*E*)-configurations of the isoindolinone **10** and the pyrrolopyridinone **12** were also unambiguously confirmed by an independent preparation of authentic samples of their corresponding (*Z*)-isomers.[20] The configurations of the other 3-(arylmethylene)isoindolin-1-ones were determined on the basis of these results, which were in agreement with the fact that carbopalladation of alkynes involves a syn addition process, whereas the cross-coupling with σ-vinylpalladium complexes proceeds with net retention of the olefinic configuration.[18]

As the Suzuki−Miyaura cross-coupling reactions require the presence of a base,[21] and because alkynylsilanes are known to be deprotected under these conditions, it was envisaged that we could advantageously carry out a one-pot transformation starting from the trimethylsilylynamide **4a**. Thus, treatment of **4a** with aqueous NaOH in THF at reflux generated the terminal ynamide **5a** in situ, which underwent the subsequent Heck−Suzuki−Miyaura domino reactions by addition of benzeneboronic acid or 3,4-dichlorobenzene-

(19) Apparently, the Heck−Suzuki−Miyaura domino reactions afforded the 3-(arylmethylene)isoindolin-1-ones described herein as single geometric isomers. However, we cannot rule out that for some substrates of this class, depending on the aryl group and the nitrogen substituent, equilibration may further occur especially by acid-catalyzed, hydration−dehydration, or photochemical processes.

(20) Authentic samples of the (*Z*)-isomers of compounds **10** and **12** were prepared from amides **2b** and **2d**, respectively, by Sonogashira coupling with phenylacetylene and subsequent base-induced ring-closure (EtONa/EtOH). The stereochemical outcome of this literature procedure has been unambiguously established (see ref 1a).

(21) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

boronic acid and the palladium catalyst. Under these conditions, the 3-(arylmethylene)isoindolinones **9** and **14** were respectively obtained in 65% and 45% overall yields (Scheme 4).

In conclusion, we have reported an efficient stereoselective access to (*E*)-3-(arylmethylene)isoindolin-1-ones by using Pd(0)-catalyzed Heck−Suzuki−Miyaura domino reactions involving ynamides and arylboronic acids. This process, which further expands the synthetic utility of ynamides, will be applied to the preparation of natural and/or biologically active products.

Acknowledgment. We thank Johnson & Johnson for financial support (Focused Giving Award to J.C.).

Supporting Information Available: Characterization data for compounds **5a**−**d**, **7**−**14**, and the (*Z*)-isomers of **10** and **12**, copies of the ^{1}H NMR spectra of new compounds, and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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