Tetrahedron Letters 52 (2011) 5508–5511

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave assisted copper-free Sonogashira coupling/5-exo-*dig* cycloisomerization domino reaction: access to 3-(phenylmethylene)isoindolin-1-ones and related heterocycles

Malik Hellal, Gregory D. Cuny *

Laboratory for Drug Discovery in Neurodegeneration, Harvard NeuroDiscovery Center, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne Street, Cambridge, MA 02139, USA

ARTICLE INFO

Article history:
Received 20 July 2011
Revised 9 August 2011
Accepted 11 August 2011
Available online 19 August 2011

Keywords:
Isoindoline
Domino reaction
Cycloisomerization
Sonogashira coupling
Microwave

ABSTRACT

An efficient microwave assisted one-pot synthesis of substituted 3-(phenylmethylene)isoindolin-1-ones is reported via a copper-free Sonogashira coupling and a regioselective 5-exo-*dig* cycloisomerization. This domino reaction was also extended to other related heterocycles.

Considerable attention has been devoted to heterocyclic ring formation by intramolecular annulations of carboxylic acids,[1] esters,[2] ketones,[3] alcohols,[4] amines[5] and amides[6] to alkynes. In particular, various synthetic methods for the preparation of substituted 3-(phenylmethylene)isoindolin-1-ones and related systems have been developed[7] due to their presence in a wide variety of bioactive natural products, such as fumaridine[8] and lennoxamine.[9] This structural motif is also found in a number of molecules demonstrating interesting pharmaceutical properties, such as the local anesthetic **A**[10] and the AChE inhibitor **B**[11] (Fig. 1).

Included among the various strategies for preparing 3-(arylmethylene)isoindolin-1-ones are different metal-catalyzed reactions, such as Heck–Suzuki–Miyaura domino reactions involving ynamides and arylboronic acids,[12] Sonogashira coupling-carbonylation–hydroamination one-pot reactions of dihalides,[13] intramolecular Heck reactions of enamides,[14] and one-pot elimination–cyclization-Suzuki coupling of *o*-[gem-dihalovinyl]benzamides and arylboronic acids.[15] Recently, Ma and coworkers reported an Ullman coupling-heteroannulation of 2-bromobenzamides and terminal alkynes.[16] Herein, we report the development of a microwave assisted Sonogashira coupling/5-exo-*dig* cycloisomerization domino reaction for the synthesis of 3-(phenylmethylene)isoindolin-1-ones and related heterocycles.

In order to investigate the feasibility of a copper-free Sonogashira coupling-cycloisomerization domino strategy, different reaction variables such as Pd source, ligand, base and solvent were investigated using microwave (MW) heating at 120 °C for 30 min.[17] As indicated in Table 1, the reaction was performed on 2-bromobenzamide **1**, and phenylacetylene in DMF. The choice of

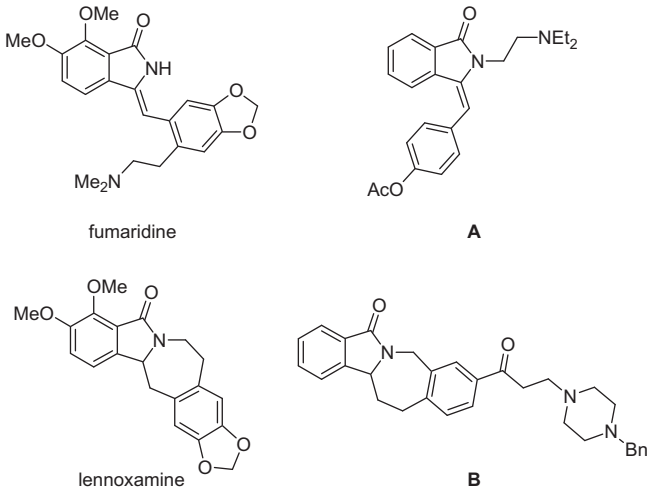

Figure 1. Structure of natural products and biologically active compounds containing isoindolinones.

* Corresponding author. Tel.: +1 617 768 8640; fax: +1 617 768 8606.
E-mail address: gcuny@rics.bwh.harvard.edu (G.D. Cuny).

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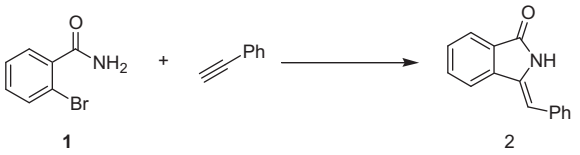
doi:10.1016/j.tetlet.2011.08.070

Table 1
Optimization of the reaction conditions



1 2

Entry	[Pd]	Ligand	Base	Solvent	Yield[a] (%)
1	$Pd(OAc)_2$	BINAP	DBU	DMF	39
2	$Pd_2(dba)_3$	BINAP	DBU	DMF	12
3	$PdCl_2(PPh_3)_2$	BINAP	DBU	DMF	15
4	$Pd(PPh_3)_4$	BINAP	DBU	DMF	23
5	$PdCl_2(MeCN)_2$	BINAP	DBU	DMF	89
6	$PdCl_2(MeCN)_2$	XantPhos	DBU	DMF	75
7	$PdCl_2(MeCN)_2$	dppf	DBU	DMF	41
8	$PdCl_2(MeCN)_2$	XPhos	DBU	DMF	30
9	$PdCl_2(MeCN)_2$	PPh_3	DBU	DMF	68
10	$PdCl_2(MeCN)_2$	—	DBU	DMF	16
11	$PdCl_2(MeCN)_2$	BINAP	Cs_2CO_3	DMF	49
12	$PdCl_2(MeCN)_2$	BINAP	K_2CO_3	DMF	38
13	$PdCl_2(MeCN)_2$	BINAP	NEt_3	DMF	0
14	$PdCl_2(MeCN)_2$	BINAP	NaOtBu	DMF	0
15	$PdCl_2(MeCN)_2$	BINAP	DBU	dioxane	0
16	$PdCl_2(MeCN)_2$	BINAP	DBU	*i*-PrOH	0
17	$PdCl_2(MeCN)_2$	BINAP	DBU	Toluene	24
18	$PdCl_2(MeCN)_2$	BINAP	DBU	MeCN	51

Reaction conditions: 2-bromobenzamide (0.5 mmol), phenylacetylene (0.75 mmol), [Pd] (5 mol %), Ligand (5–10 mol %), Base (1 mmol), DMF (2 mL), MW 120 °C, 30 min.
[a] Isolated yield.

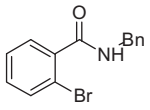
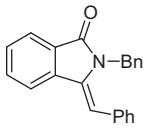
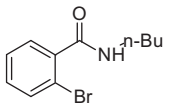
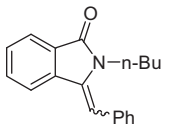
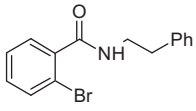
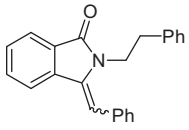
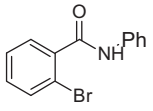
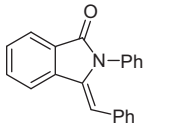
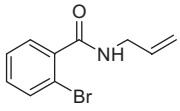
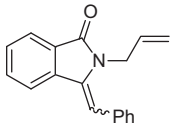
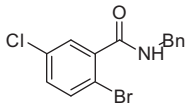
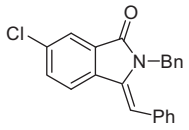
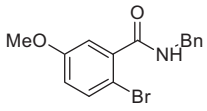
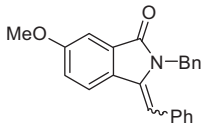
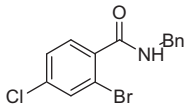
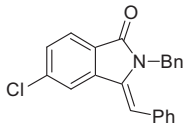
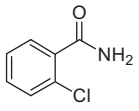
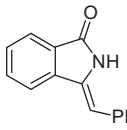
catalyst (Pd source and ligand) was critical for the reaction. The combination of $PdCl_2(MeCN)_2$ and BINAP was found to be the optimal catalyst for the reaction by furnishing (*Z*)-isomer **2** in 89% yield (Table 1, entry 5). The yields decreased dramatically when $Pd(OAc)_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ were used (entries 1–4). Further investigation revealed that the reaction was also dependent on the presence and choice of ligand. For example, lower yields were observed when Xantphos, dppf, Xphos, and PPh_3 were used (entries 6–9) or in the absence of a ligand (entry 10).

Next, the base and solvent were further investigated. Replacing DBU with K_2CO_3 or Cs_2CO_3 (entries 11 and 12) resulted in poorer yields, whereas no desired product was isolated in the presence of NEt_3 or NaO*t*-Bu (entries 13 and 14). Performing the reaction in a variety of other solvents also proved detrimental. For example, no reactions were observed in either 1,4-dioxane or *i*-PrOH, and significant decreases in yields were observed in toluene and acetonitrile, due to the lack of solubility of **1** (entries 15–18).

Finally, the influences of temperature and heating source on the reaction were examined. Reducing the reaction temperature to 80 or 100 °C resulted in decreased yields of 31% and 45%, respectively. In addition, the desired product was obtained in only 13% yield using conventional heating at 120 °C for 30 min. The yield could be improved to 80% when the conventional heating was extended to 24 h. Overall, the optimized reactions conditions were: 2-bromobenzamide **1** (1 equiv), phenylacetylene (1.5 equiv), $PdCl_2(MeCN)_2$ (5 mol %), BINAP (5 mol %), DBU (2 equiv) in DMF under microwave irradiation at 120 °C for 30 min.

With the optimized conditions identified, the scope of this palladium-catalyzed reaction was extended to a series of 2-halobenzamides **3** (Table 2). A wide range of N-substituents were tolerated, including benzyl, allyl, phenyl, and alkyl groups (entries 1–5). Furthermore, this one-pot reaction was highly stereoselective, and gave the *Z*-isomer as the main product. These results are consistent with a based-mediated cyclization process. As

Table 2
Substrate scope of the reaction[a]

Entry	Amide	Product	Yield[b] (%)
1	 **3a**	 **4a**	87
2	 **3b**	 **4b**	94[c]
3	 **3c**	 **4c**	93[d]
4	 **3d**	 **4d**	89
5	 **3e**	 **4e**	63[e]
6	 **3f**	 **4f**	73
7	 **3g**	 **4g**	53[f]
8	 **3h**	 **4h**	51
9	 **3i**	 **2**	42[g]

[a] Reaction conditions: **3a–i** (0.5 mmol), phenylacetylene (0.75 mmol), $PdCl_2(MeCN)_2$ (5 mol %), BINAP (5 mol %), DBU (1 mmol), DMF (2 mL), MW 120 °C, 30 min.
[b] Isolated yield.
[c] Ratio *Z*:*E* = 88:12.
[d] Ratio *Z*:*E* = 93:7.
[e] Ratio *Z*:*E* = 80:20.
[f] 140 °C, ratio *Z*:*E* = 82:18.
[g] 140 °C.