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Assembly of Substituted 3-Methyleneisoindolin-1-ones via a CuI/L-Proline-Catalyzed Domino Reaction Process of 2-Bromobenzamides and Terminal Alkynes

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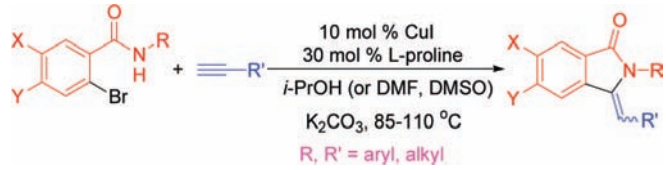
ABSTRACT



CuI/L-proline catalyzed coupling of 2-bromobenzamides and terminal alkynes in *i*-PrOH (or DMF and DMSO) at 85−110 °C and subsequent additive cyclization produces substituted 3-methyleneisoindolin-1-ones. Variation of N-substituents, aromatic ring, and methylene part is possible by using suitable starting materials.

The 3-methyleneisoindolin-1-one is a core structure of numerous natural products or designed pharmaceutical molecules.[1] These compounds include fumaridine (Figure 1) that was extracted from vegetable sources,[1a] compound **1** that has local anesthetic activity superior to that of procaine,[1b] compound **2** that exhibited sedative activity,[1h] and muscaric receptor ligand **3**.[1f] In addition, 3-methyleneisoindolin-1-ones have been found to be useful intermediates for the total synthesis of alkaloids such as lennoxamine.[2]

The classical methods to 3-methyleneisoindolin-1-ones are based on using phthalimides as starting materials, which undergo Wittig reaction[3] or addition of organometallic reagents and subsequent dehydration[2a,4] to give the target molecules. This approach suffers from poor regioselectivity in the cases of unsymmetrical substrates. To avoid this problem, a new method based on condensation of phosphorylated 4-alkoxy-

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(1) (a) Blaskó, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105. (b) Laboratori Baldacci S. p. A. JP 59046268, *Chem. Abstr.* **1984**, *101*, 54922. (c) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060. (d) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1999**, *47*, 529. (e) Chia, Y.-C.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. *J. Nat. Prod.* **2000**, *63*, 1160. (f) Botero Cid, H. M.; Tränkle, C.; Baumann, K.; Pick, R.; Mies-Klomfass, E.; Kostenis, E.; Mohr, K.; Holzgrabe, U. *J. Med. Chem.* **2000**, *43*, 2155. (g) Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557. (h) Hulin, B.; Parker, J. C.; Piotrowski, D. W. US2005234065. (i) Toyooka, K.; Kanamitsu, N.; Yoshimura, M.; Kuriyama, H.; Tamura, T. WO2004048332.

(2) (a) Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707. (b) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2004**, *69*, 4527. (c) Rys, V.; Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *Tetrahedron* **2005**, *61*, 665. (d) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 767. (e) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2007**, *5*, 1466.

(3) Flitsch, W.; Peters, H. *Tetrahedron Lett.* **1969**, *10*, 1161.

(4) (a) Griesbeck, A. G.; Warzecha, K.-D.; Neudörfl, J.-M.; Görner, H. *Synlett* **2004**, *13*, 2347. (b) Bousquet, T.; Fleury, J.-F.; Daïch, A.; Netchitaïlo, P. *Tetrahedron* **2006**, *62*, 706.

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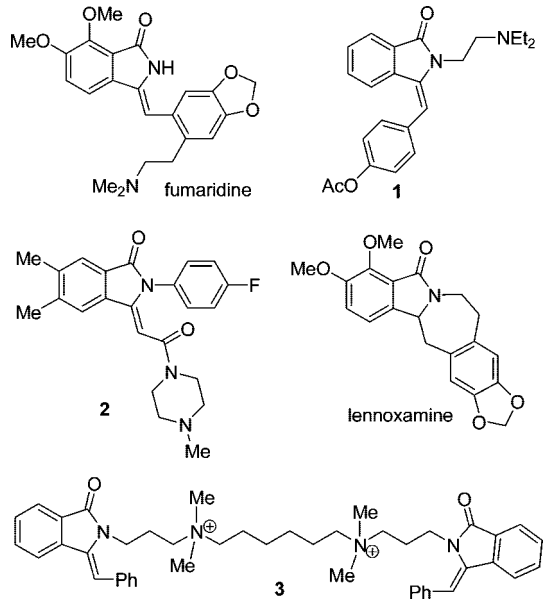


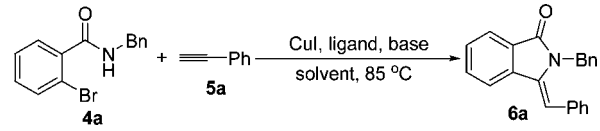
Figure 1. Structures of some biologically important 3-methyleneisoindolin-1-ones and their derivatives.

isoindolinones and aldehydes was developed. However, this method required additional steps to prepare phosphorylated reagents.[2b,5] The lack of an efficient approach to 3-methyleneisoindolin-1-ones has stimulated intensive studies for assembly of these heterocycles via metal-catalyzed reactions.[6] The successful examples include a Sonogashira reaction of 2-iodobenzamides with terminal alkynes followed by NaOEt-mediated cyclization,[6c] Heck−Suzuki−Miyaura domino reactions involving ynamides,[6d] and a Sonogashira reaction−carbonylation−hydroamination of 2-bromoiodobenzene.[6f] Among them, Kundu's method is quite attractive because both 2-halobenzamides and terminal alkynes are conveniently available.[6c] In Kundu's report, $(Ph_3P)_2PdCl_2$ and CuI were utilized for promoting the cross-coupling reaction, leading to a mixture of open-chain condensation products and heteroannulation products in most cases.[6c] The pure 3-methyleneisoindolin-1-ones had to be obtained by treatment of the mixture with NaOEt. In addition, when aliphatic alkynes were employed a mixture of 3-methyleneisoindolin-1-ones and isoquinolinones was formed.[6c] These shortcomings limited its application in organic synthesis.

In connection with our project to develop new heterocycle synthesis via amino acid-promoted Ullmann-type reactions,[7−9] we became interested in using CuI/amino acid to catalyze the coupling reaction of 2-bromobenzamides and terminal alkynes.[8e,10] We were pleased to find after the reaction that substituted 3-methyleneisoindolin-1-ones were isolated exclusively. Both aromatic and aliphatic alkynes are compatible with this process, thereby giving an inexpensive, diverse, and convenient approach to assemble these heterocycles. Herein, we disclose our results.

As indicated in Table 1, we initiated our studies by conducting a coupling reaction of *N*-benzyl-2-bromobenzamide with phenylacetylene. It was found that under the catalysis of CuI/L-proline and heating at 85 °C for 24 h in DMF, 3-methyleneisoindolin-1-one **6a** was isolated as a single product in 85% yield (entry 1). Similar results were observed when the solvent was changed to *i*-PrOH and DMSO (entries 2 and 3). However, poor yields were obtained if the reaction was carried out in dioxane or toluene (entries 4 and 5). Switching base to K_3PO_4 and Cs_2CO_3 had little influence to this reaction (entries 6 and 7). Further investigation revealed that ligand is essential for this process, as evident from the unsatisfactory yields that were observed when *N*,*N*-dimethylglycine, pipecolinic acid, 2-picolinic acid, ethyl 2-cyclohexanonecarboxylate, and *N*,*N*-dimethylethylenediamine were used (entries 8−12) and the fact that no

Table 1. Coupling of *N*-Benzyl-2-bromobenzamide with Phenylacetylene under Different Conditions[a]



entry	ligand[b]	base	solvent	yield[c] (%)
1	A	K_2CO_3	DMF	85
2	A	K_2CO_3	*i*-PrOH	86
3	A	K_2CO_3	DMSO	83
4	A	K_2CO_3	dioxane	50
5	A	K_2CO_3	toluene	<10
6	A	K_3PO_4	*i*-PrOH	82
7	A	Cs_2CO_3	*i*-PrOH	82
8	B	K_2CO_3	*i*-PrOH	37
9	C	K_2CO_3	*i*-PrOH	70
10	D	K_2CO_3	*i*-PrOH	47
11	E	K_2CO_3	*i*-PrOH	17
12	F	K_2CO_3	*i*-PrOH	30
13	no	K_2CO_3	*i*-PrOH	0

[a] Reaction conditions: **4a** (1 mmol), **5a** (1.5 mmol), CuI (0.1 mmol), ligand (0.3 mmol), solvent (2 mL), 85 °C, 24 h. [b] Key: (A) L-proline; (B) *N*,*N*-dimethylglycine; (C) pipecolinic acid; (D) 2-picolinic acid; (E) ethyl 2-cyclohexanonecarboxylate; (F) *N*,*N*-dimethylethylenediamine. [c] Isolated yield.

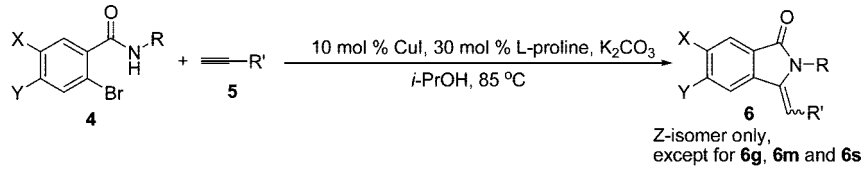
(5) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Synlett* **1997**, 1475.

(6) (a) Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. (b) Wu, M.-J.; Chang, L.-J.; Wei, L.-M.; Lin, C.-F. *Tetrahedron* **1999**, *55*, 13193. (c) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777. (d) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (f) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281. (g) Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361.

(7) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.

(8) (a) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115. (b) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (c) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (d) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291. (e) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844. (f) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (g) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (h) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761. (i) Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159. (j) Guo, L.; Li, B.; Huang, W.; Pei, G.; Ma, D. *Synlett* **2008**, 1833.

Table 2. Synthesis of Substituted 3-Methyleneisoindolin-1-ones via a Domino Coupling/Additive Cyclization Process from 2-Bromobenzamides and Terminal Alkynes[a]



entry	X	Y	R	R′	time (h)	product	yield[b] (%)
1	H	H	Bn	4-MeC_6H_4	24	**6b**	78
2	H	H	Bn	4-$MeOC_6H_4$	36	**6c**	81
3	H	H	Bn	3-FC_6H_4	24	**6d**	80
4	H	H	Bn	$BnOCH_2$	36	**6e**	74
5	H	H	Bn	*n*-C_5H_{11}	24	**6f**	55[c]
6	H	NO_2	Bn	Ph	48	**6g**	57[d]
7	H	OMe	Bn	Ph	24	**6h**	78
8	Cl	H	Bn	Ph	36	**6i**	70
9	H	H	4-$ClC_6H_4CH_2$	Ph	48	**6j**	90
10	H	H	4-$MeOC_6H_4CH_2$	Ph	48	**6k**	88
11	H	H	allyl	Ph	48	**6l**	88
12	H	NO_2	allyl	Ph	36	**6m**	61[d,e]
13	H	OMe	allyl	Ph	36	**6n**	93
14	H	H	C_6H_5	Ph	36	**6o**	92
15	H	H	H	Ph	36	**6p**	70
16	H	H	*n*-C_4H_9	Ph	48	**6q**	83
17	H	H	$TBSO(CH_2)_2$	Ph	48	**6r**	82
18	H	H	$Et_2N(CH_2)_2$	4-HOC_6H_4	48	**6s**	58[f,g,h]

[a] Reaction conditions: aryl bromide (0.5 mmol), 1-alkyne (0.75 mmol), CuI (0.05 mmol), L-proline (0.15 mmol), *i*-PrOH (1 mL), 85 °C. [b] Isolated yield. [c] The reaction was carried out in DMSO at 100 °C. [d] A mixture of *E*- and *Z*-isomers was determined in a ratio of 5:1. [e] The reaction was carried out in DMSO at 85 °C. [f] The reaction was carried out in DMF at 100 °C. [g] 4-Ethynylphenyl acetate was used as a coupling partner. [h] A mixture of *E*- and *Z*-isomers was determined in a ratio of 14:1.

desired product was isolated in the absence of a ligand (entry 13). Based on these results, we chose L-proline as the ligand, K_2CO_3 as the base, and *i*-PrOH as the solvent in the subsequent studies.

The reaction scope and limitations were then examined under the optimized conditions, and the results are summarized in Table 2. Some functionalized arylacetylenes also worked well, giving the corresponding products in good yields (entries 1−3). Gratifyingly, when aliphatic alkynes were employed, only 3-methyleneisoindolin-1-ones **6e** and **6f** were isolated (entries 4 and 5). This result indicated that the CuI-mediated additive cyclization of the amide moiety to the triple bond took place in a 5-*exo* manner exclusively, which is different with base or Lewis acid-mediated additive cyclization (both 5-*exo* and 6-*endo* attacks were observed).[6c] In cases of 1-heptyne as a substrates, the reaction was sluggish at 85 °C, and good conversion was obtained by increasing the reaction temperature and using DMSO as a solvent (entry 5). This result illustrated that aliphatic alkynes are less reactive substrates for this transformation.

We next explored the possibility of changing the substituents at the aromatic ring of aryl bromides and were pleased to find that both electron-rich and electron-deficient aryl bromides were compatible with these conditions (entries 6−8). It seemed that electron-rich aryl bromides are more reactive than electron-deficient ones, as longer reaction times were required for nitro- and chloro-substituted aryl bromides.

Further investigations demonstrated that a wide range of N-substituents were tolerated in this process, which include functionalized benzyl groups, allyl, phenyl, proton, and simple and functionalized alkyl groups (entries 9−18). These additional functional groups would allow further conversion to more useful heterocycles. For example, **6r** could be transformed into a known tetracyclic intermediate for alkaloid

(9) For related studies from other groups, see: (a) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. (b) Klapars, A.; Parris, S.; Andersom, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (c) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (d) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (e) Hu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (f) Martin, R.; Rodrı´guez, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (g) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (h) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749. (i) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737. (j) Bao, W.; Liu, Y.; Lv, X.; Qian, W. *Org. Lett.* **2008**, *10*, 3899. (k) Coste, A.; Toumi, M.; Wright, K.; Razafimahaleo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841. (l) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (m) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, *10*, 5285. (n) Hasegawa, K.; Kimura, N.; Arai, S.; Nishida, A. *J. Org. Chem.* **2008**, *73*, 6363. (o) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. (p) Li, Z.; Sun, H.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 3263. (q) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535. (r) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (s) Martins, A.; Lemouzy, S.; Lautens, M. *Org. Lett.* **2009**, *11*, 181.

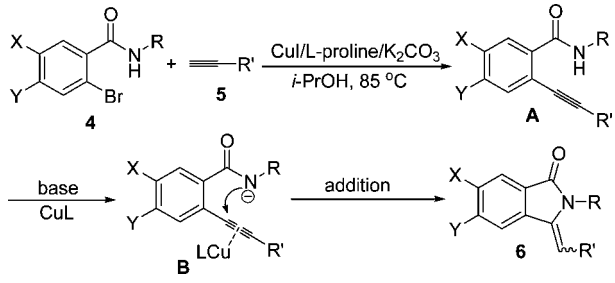
(10) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934.

synthesis,[4b] while acylation of **6s** would provide compound **1** that has local anesthetic activity superior to that of procaine.[1b]

For stereochemistry of the present transformation, it was found that in most cases only *Z*-isomers were determined. However, in cases of two nitro-substituted aryl bromides (entries 6 and 12) and *N*,*N*-diethylethylene-substituted aryl bromide (entry 18) as substrates, *E*-isomers were isolated as a major product. Their geometry was established via NOESY studies and comparison of the analytical data with the known compounds. The reason for this difference is not clear yet, but this result indicated that some substituents have strong influence to the transition state in additive cyclization step.

For reaction process, we envisaged that coupling of aryl bromides with 1-alkynes should occur first as indicated in Scheme 1. The coupling products **A** might undergo depro-

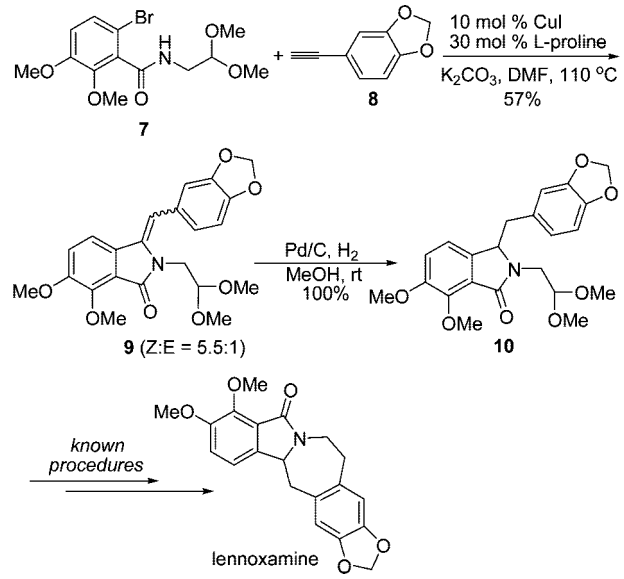
Scheme 1



tonation of the amide moiety and subsequent addition to C−C triple bond under the action of the copper complex (as intermediates **B**) to afford substituted 3-methyleneisoindolin-1-ones. Indeed, in some cases the simple Sonogashira reaction products **A** could be isolated if the reaction time was shortened.

To further illustrate the synthetic usage of the present method, we developed a formal synthesis of lennoxamine as depicted in Scheme 2. Aryl bromide **7** was prepared from 2,3-dimethoxybenzoic acid in two steps based on known procedure, which was coupled with 1-alkyne **8** under the catalysis of CuI/L-proline in DMF at 110 °C to afford heteroannulation product **9** in 57% yield as a mixture of *Z*- and *E*-isomers (about 5.5:1 determined by ^{1}H NMR). Upon hydrogenation, this mixture was transformed into isoindoli-

Scheme 2



none **10** in quantitative yield. This intermediate has been converted into lennoxamine in two steps by Cossy and coworkers.[2d]

In conclusion, we have developed a CuI/L-proline-catalyzed coupling/additive cyclization domino reaction process for assembling substituted 3-methyleneisoindolin-1-ones from 2-bromobenzamides and terminal alkynes. Variation of N-substituents, aromatic ring, and methylene part was proven possible. Thus, this process gives a straightforward access to substituted 3-methyleneisoindolin-1-ones and may find applications in the synthesis of complex natural products or designed bioactive compounds.

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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