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A green approach for the regio- and stereo-selective syntheses of (*Z*)-3-methyleneisoindoline-1-ones in aqueous medium

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ABSTRACT

A high yielding novel methodology was developed for the regio- and stereo-selective syntheses of (*Z*)-3-methyleneisoindoline-1-ones from substituted 2-phenylethynyl benzamides, generated in situ from 2-(phenylcarbamoyl)phenyl-1-*H*-imidazole-1-sulfonates and corresponding alkyne by Cu-free Sonogashira cross-coupling–5-exo-dig-cyclization in aqueous medium under sonication. The compound could easily be purified by recrystallization from EtOAc without column chromatography.

Non-conventional chemistry appears to put forward important possibilities in the arsenal of environmentally friendly synthetic methods,[1] particularly in connection with the emerging concept of 'Green Chemistry'. Among the different technologies, the application of water as solvent in organic syntheses and in homogeneous transition-metal catalyzed reactions has been progressively growing.[2,3] Also, in recent time, interest is growing for the syntheses of biologically important compounds using sonochemical processes.[4] Therefore, syntheses of pharmacophores in aqueous environment under sonication are a useful alternative.

3-Methyleneisoindolin-1-one is a biologically significant scaffold and is present in a number of natural products and pharmacologically interesting compounds like aristolactam alkaloids,[5] fumaridine,[6] lennoxamine,[7] AKS 186,[8] pictonamine,[9] pazinaclone.[10] Few isoindolinone derivatives also have potent metabotropic glutamate receptor-1 antagonist activity,[11] anti-viral,[12] anti-leukemic,[13] and anti-hypertensive[14] activities. It is also a key intermediate in the total synthesis of lennoxamine. The varied biological activities of isoindolinone derivatives, have attracted the attention of organic chemists, and a number of synthetic methodologies have been developed.[15–23] However, these methods have drawbacks[24,25] like low yield, requirement of long reaction time, use of phase transfer catalyst, hazardous chemicals or external additives.

Palladium(II) salts, having bidentate N,N- or N,P-ligands in the presence of amines and copper(I) have been established to be efficient catalysts for these heteroannulation reactions. Copper-free Sonogashira cross coupling reactions,[25a,26,27] using a combination of a phosphine ligand or an amine with *tetra*-butyl ammonium salts as activator under strict anhydrous reaction conditions served as suitable alternative. We investigated a fast, efficient yet simple and green protocol in aqueous medium where domino Sonogashira-5-endo-dig-cyclization reaction was applied for the complete regio- and stereo-selective synthesis of (*Z*)-3-methyleneisoindolin-1-one. Generally aryl or alkenyl halides are used as an electrophilic partner in the Sonogashira reaction. However, oxygen based electrophiles, owing to their high stability and easy accessibility through functional group interconversion from readily available hydroxylated compounds, have attracted attention in recent times. Our method allows the domino Sonogashira-cyclization of oxygenated electrophilic compounds (**7a**) and terminal alkynes in water under sonication using GUAPHOS (**1**) as ligand (Fig. 1). This methodology not only eliminates the use of copper, high reaction temperature or use of toxic solvents but also do not require any involvement of quaternary ammonium salts as activator. A library of (*Z*)-3-methyleneisoindolin-1-ones could thus be synthesized in high yield and in short reaction time. The uniqueness of this methodology lies in its environment-friendly operation, short reaction time, and excellent yield.

Systematic studies of the reaction conditions in DMF in the presence of different palladium catalysts with copper(I) iodide as co-catalyst and various organic or inorganic bases had been carried out earlier with poor to moderate yield.[23b] Therefore, there is ample scope for the development of new methodologies. We

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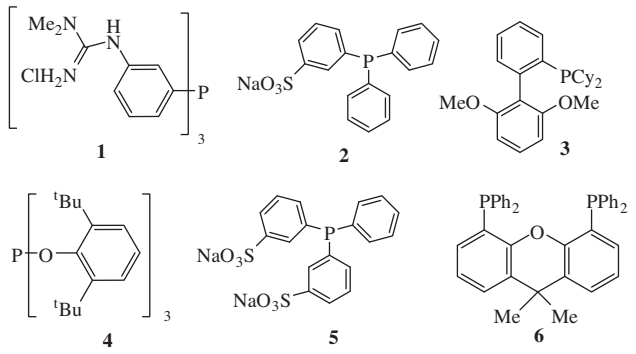


Figure 1. Ligands used in the study.

envisaged using substituted benzamides (**7a–7e**) to endow different acetylenes (**8a–8g**) that could subsequently be used in a one-pot, two-step synthesis of 3-methyleneisoindoline-1-ones. We used **7a** and phenylethyne **8a** as model reactants and investigated the feasibility of the copper-free Sonogashira coupling–cycloisomerization domino strategy under sonication in aqueous medium at 50 °C using $PdCl_2$ as only catalyst (Scheme 1).

The effect of different ligands[28] was first investigated (Table 1). Ligand **1** appeared to be the most efficient when employed in 3.0 mol % affording excellent yield of the product. However, among the ligands, SPhos ligand **3** as well as ligand **2** and **5** were efficient as they produce a notable yield of 86%, 71% and 76%, respectively (Table 1, entry 7, 6, and 9). The use of sterically hindered phosphate ligand **4**, bidentate phosphate derived ligand **6** led to lower yields (Table 1, entry 8 and 10). The effect of different bases, viz. DBU, Et_3N, NaOAc, KO^{t}Bu, (iPr)$_2$EtN, piperidine, and Cs_2CO_3 was also investigated (Table 2). (iPr)$_2$EtN appeared to be the most effective when employed in 2.0 mol equiv affording the product in maximum yield (Table 2, entry 7). It was concluded that organic bases were better in comparison to inorganic bases. The effect of external additives (e.g., NaCl, NaBr, etc.) was also investigated. However, no significant change in yield was noticed (data not shown). It is worth mentioning that use of other Pd-catalysts [$PdCl_2$(phosphine)$_2$, palladium(II) bathophenanthroline, Pd-C], under the same reaction conditions gave poor to moderate yield.

To explore the scope and generality of this approach, reactions with various aryl or aliphatic alkynes were attempted (Table 3). The Sonogashira-5-exo-dig cyclomerization domino process was found to be completely regio- and stereo-selective (only Z-isomer was obtained in all cases) and products were obtained in high yield in all cases. The reaction was best performed with **7a** which gave maximum yield of 94% with phenyl acetylene (Table 3, entry 1). Another major advantage of this method is that no dimerized products, normally produced as side products during heteroannulation reaction, were formed. The reaction was performed in aqueous medium and the ligands used in this study were soluble in water.

Table 1
Effect of different ligands for the synthesis of **9a**

Entry[a]	Ligands	Amount (mol %)	Time (h)	Yield[b] (%)
1	1	1.5	1	69
2	1	2.0	1	74
3	1	2.5	1	80
4	**1**	**3.0**	**1**	**94**
5	1	3.5	1	91
6	2	3.0	1	71
7	3	3.0	1	86
8	4	3.0	1	20
9	5	3.0	1	76
10	6	3.0	1	41

The bold values signify the best yields/results obtained.
[a] Reactions were performed using **7a** (10 mmol), alkyne **8a** (10 mmol), $PdCl_2$ (2 mol %), (iPr)$_2$EtN (20 mmol) as base in water under sonication (50 °C) for 1 h. Products were characterized by spectroscopic and analytical techniques.
[b] Isolated yield (some losses during filtration were unavoidable in certain cases).

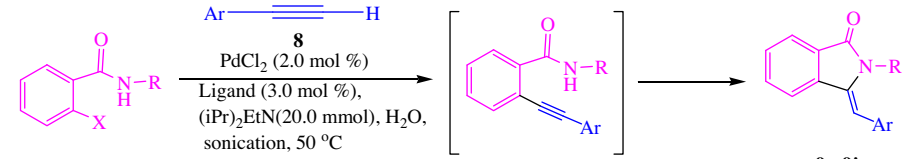
Table 2
Effect of different bases for the synthesis of **9a**

Entry[a]	Base	Amount (mol equiv)	Time (h)	Yield[b] (%)
1	Na_2CO_3	2.0	1	34
2	Cs_2CO_3	2.0	1	43
3	NaOAc	2.0	1	56
4	Et_3N	2.0	1	82
5	DBU	2.0	1	84
6	DMAP	2.0	1	81
7	**(iPr)$_2$EtN**	**2.0**	**1**	**94**
8	(iPr)$_2$EtN	2.5	1	92

The bold values signify the best yields/results obtained.
[a] Reactions were performed using **7a** (10 mmol), alkyne **8a** (10 mmol), $PdCl_2$ (2 mol %), ligand **1** (3.0 mol %), in water under sonication (50 °C) for 1 h. Products were characterized by spectroscopic and analytical techniques.
[b] Isolated yield (some losses during filtration were unavoidable in certain cases).

Hence, compounds can be easily extracted with EtOAc and purified by recrystallization and no column chromatography was required.

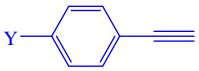
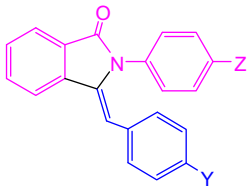
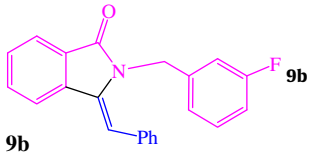
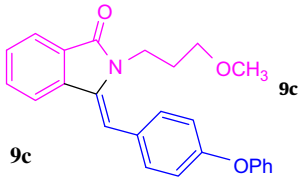
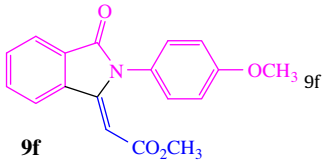
The one-pot reaction thus developed was found to be completely regio- and stereo-selective and only Z-isomer was obtained. Neither the 6-membered ring via 6-endo-dig cyclization mode nor products with E-stereo chemistry were obtained. In the ^{1}H NMR the olefinic proton (C-4 proton) appeared in the up field (δ_H <7 ppm) due to the absence of the deshielding effect of the benzene ring, indicating the Z-stereochemistry of the exo-cyclic double bond. The chemical shift (δ_H) of the vinylic proton for Z-isomer of **9a** and **9i** has earlier been reported in the range 6.8 ppm,[23b,d,e] where as for E-isomer the signal appears at relatively lower field.[30] The NMR of the synthesized compounds confirmed formation of only Z-stereoisomer. Finally, single crystal X-ray analysis of product **9a** (CCDC 911875) confirmed the stereochemistry and structure of (*Z*)-3-benzylidene-*N*-(4-phenyl)isoindolin-1-one (**9a**) simultaneously (Supplementary data).



7a R = Ph, X = OSO_2imidazol-1-yl
7bR = Ph, X = I
7c R = Ph, X = Br
7d R =*m*-F-benzyl, X = OSO_2imidazol-1-yl
7e R = $(CH_2)_3OCH_3$, X = OSO_2imidazol-1-yl

Scheme 1. One-pot Sonogashira cross-coupling and subsequent intramolecular cyclization to generate 3-methyleisoindoline-1-ones in aqueous medium under sonication.

Table 3
Reactions of **7a–e** with terminal alkynes (**8a–g**) leading to isoindolinones (**9a–j**) in aqueous medium under sonication

Entry[a]	Amide	Acetylene	Product	Yield[b] (%)	Ref.
					
1	**7a**	**8a** Y = H	**9a** Y = H, Z = H	94	23b
2	**7b**	**8a**	**9a**	92	23b
3	**7c**	**8a**	**9a**	90	23b
4	**7d**	**8a**	 **9b**	79	29
5	**7e**	**8b** Y = OPh	 **9c**	78	–
6	**7a**	**8c** y = C_5H_{11}	**9d** Y = C_5H_{11}, Z = OCH_3	91	–
7	**7a**	**8d** Y = OPh	**9e** Y = OPh, Z = OCH_3	92	–
8	**7a**	**8e** 	 9f	68	–
9	**7a**	**8f** Y = NO_2	**9g** Y = NO_2, Z = OCH_3	91	–
10	**7a**	**8a**	**9h** Y = H, Z = F	93	29
11	**7a**	**8a**	**9i** Y = H, Z = CH_3	94	23b
12	**7a**	**8g** Y = OCH_3	**9j** Y = OCH_3, Z = H	92	23b

[a] Reactions were performed using **7a–e** (10 mmol), alkynes **8a–g** (10–20 mmol), $PdCl_2$ (2 mol %), ligand **1** (3.0 mol %), $(iPr)_2EtN$ (20 mmol), water, under sonication (50 °C) for 1 h. Products were characterized by spectroscopic and analytical techniques.
[b] Isolated yield (some losses during filtration were unavoidable in certain cases).

In summary, we have demonstrated a Cu-free domino Sonogashira-cyclization reaction of aryl imidazol-1-yl-sulphonates with aryl and alkyl substituted terminal alkynes using H_2O as only solvent for the synthesis of the isoindolinone[31,32] scaffold. The green reaction conditions (aqueous medium under sonication activation), ease of product separation, and excellent yields of products, made this protocol a useful one for the preparation of oxindoles.

Acknowledgments

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Supplementary data

^1H and ^{13}C NMR spectra of all new compounds associated with this article can be found in the online version. Crystallographic data in CIF format are available free of charge via the Internet at CCDC 911875. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.004.

References and notes

1. Cintas, P.; Luche, J. L. *Green Chem.* **1999**, *1*, 115.
2. (a) Anastas, P.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998; (b) Polshettiwar, V.; Varma, R. S. *J. Org. Chem.* **2007**, *72*, 7420.
3. Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174.
4. (a) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109; (b) Kardos, N.; Luche, J. L. *Carbohydr. Res.* **2001**, *332*, 115.
5. Chang, Z.-L.; Zhu, D.-Y. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1978; Vol. 31, p 29.
6. Blasko, G.; Guha, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105.
7. Cordell, G. A. In *The Alkaloids: Chemistry and Pharmacology*; Academic: San Diego, 1998; Vol. 50,
8. Achinami, K.; Ashizawa, N.; Kobayashi, F.; Jpn Patent JP 03, 1991, 133, 955.
9. Valencia, E.; Fajardo, V.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993.
10. Wada, T.; Fukuda, N. *Psychopharmacology* **1991**, *103*, 314.
11. Ito, S.; Hirata, Y.; Nagatomi, Y.; Satoh, A.; Suzuki, G.; Kimura, T.; Satow, A.; Maehara, S.; Hikichi, H.; Hata, M.; Ohta, H.; Kawamoto, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5310.
12. Clercq, E. D. *J. Med. Chem.* **1995**, *38*, 2491.
13. Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J. G. *Tetrahedron Lett.* **1997**, *38*, 521.
14. Ferland, J. M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361.
15. Gabriel, S. *Berichte* **1985**, *18*, 3470.
16. Ang, W. S.; Halton, B. B. *Aust. J. Chem.* **1971**, *24*, 851.

17. Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313.
18. Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335.
19. (a) Mali, R. S.; Yeola, S. *Synthesis* **1986**, 755; (b) Epsztajn, J.; Grzelak, R.; Jozwiak, A. *Synthesis* **1996**, 1212.
20. (a) Weidner-Wells, M. A.; Oda, K.; Mazzochi, P. H. *Tetrahedron* **1997**, *53*, 3475; (b) Griesbeck, A. G.; Hirt, J.; Kramer, W.; Dallakian, P. *Tetrahedron* **1998**, *54*, 3169.
21. Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485.
22. (a) Yamamoto, I.; Tabo, Y.; Gotoh, H. *Tetrahedron Lett.* **1971**, *12*, 2295; (b) Dominh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P., Jr. *J. Org. Chem.* **1977**, *42*, 4217; (c) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063; (d) Rowe, F. M.; McFadyen, W. T.; Peters, A. T. *J. Chem. Soc.* **1947**, 468; (e) Takeuchi; Eguchi, S. *J. Chem. Soc., Perkin Trans.* **1989**, *1*, 2149.
23. (a) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508; (b) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777; (c) Wilkinson, G.; Stone, F. G. A.; Abel, E. W., 1st ed. In *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1982; Vol. 1,; (d) Kundu, N G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, *55*, 12361; (e) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435.
24. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
25. (a) Yi, C. Y.; Hua, R. M. *J. Org. Chem.* **2006**, *71*, 2535; (b) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191.
26. Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.
27. (a) Mino, T.; Shirae, Y.; Saito, T.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2006**, *71*, 9499; (b) Dang, D.; Zheng, Y.; Bai, Y.; Guo, X.; Ma, P.; Niu, J. *Cryst. Growth Des.* **2012**, *12*, 3856; (c) Genin, E.; Amengual, R.; Michelet, V.; Savignac, M.; Jutand, A.; Neuville, L.; Gene, J. P. *Adv. Synth. Catal.* **2004**, *346*, 1733.
28. (a) Hessler, A.; Stelzer, O.; Dibowski, H.; Worm, K.; Schmidtchen, F. P. *J. Org. Chem.* **1997**, *62*, 2362; (b) Herd, O.; Hessler, A.; Langhans, K. P.; Stelzer, O. *J. Organomet. Chem.* **1994**, *475*, 99; (c) Roshchin, I. A.; Bumagin, A. N.; Beletskaya, I. *Tetrahedron Lett.* **1995**, *36*, 125; (d) Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, *36*, 3111; (e) Civicos, J. F.; Alonso, D. A.; Najera, C. *Adv. Synth. Catal.* **2013**, *355*, 203.
29. Zhang, L.; Zhang, Y.; Wang, X.; Shen, J. *Molecules* **2013**, *18*, 654.
30. Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.* **1975**, *28*, 2499.
31. *General procedure for the preparation of (Z)-3-methyleneisoindoline-1-ones (**9a–9j**)*: A mixture of amide (**7a**–**7e**, 10 mmol) and alkyne [**8a** (10 mmol), **8b** (12 mmol), **8c** (10 mmol), **8d** (10 mmol), **8e** (20 mmol), **8f** (15 mmol), **8g** (18 mmol)] in water (15 mL) was sonicated in an ultrasonic bath in the presence of $PdCl_2$ (2 mol %), ligand **1** (3.0 mol %) and $(i\text{Pr})_2\text{EtN}$ (20 mmol) for 1 h at 50 °C. The compounds were then extracted with EtOAc (50 mL × 2) and washed thoroughly with water (20 mL × 3). It was then dried over anhydrous Na_2SO_4 and recrystalized (EtOAc). No chromatographic separation was required.
32. *Spectral data of (Z)-3-(4-phenoxybenzylidene)-2-(3-methoxypropyl)isoindolin-1-one (**9c**)*: ^{1}H NMR ($CDCl_3$; 300 MHz): δ = 1.48–1.57 (m, 2H), 3.05 (t, J = 6.45 Hz, 2H), 3.15 (s, 3H), 3.82 (t, J = 7.2 Hz, 2H), 6.74 (s, 1H), 7.04 (t, J = 7.5 Hz, 5H), 7.14 (t, J = 7.35, 1H), 7.30–7.39 (m, 3H), 7.48 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$; 75 MHz): δ = 28.16, 38.64, 58.37, 69.96, 105.94, 118.23, 119.07, 119.18, 123.17, 123.61, 128.21, 128.86, 129.42, 129.81, 130.96, 131.82, 134.54, 138.27, 156.84, 168.69 ppm; HRMS (ESI): m/z calcd for $C_{25}H_{23}NO_3$ $[M+Na]^+$ 408.1576; found: 408.1571.