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A simple access to *N*-(un)substituted isoquinolin-1(2*H*)-ones: unusual formation of regioisomeric isoquinolin-1(4*H*)-ones†

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A ligand/additive/Pd-free Cu-mediated coupling/cyclization strategy afforded the first practical, one-pot and general approach towards synthesis of *N*-(un)substituted isoquinolin-1(2*H*)-ones. Both the catalyst and the solvent used are recyclable. The use of the Cu reagent in excess led to the unusual formation of regioisomeric and uncommon isoquinolin-1(4*H*)-ones.

While the transition metal-catalyzed addition of an N–H bond across the C–C triple bond affords various N-heterocycles,[1] several of these methods suffer from limitations, *e.g.*, the lack of generality and regioselectivity, the use of expensive or toxic catalysts, ligands/additives and solvents, complicated operational procedures, *etc.* Thus, development of simple, green and sustainable methodologies is in high demand.

In view of the widespread occurrences of isoquinolin-1(2*H*)-one frameworks in natural products[2,3] (Fig. 1) and many bioactive compounds[4] a range of synthetic methods[5] have been reported including the transition metal-catalyzed reactions.[5a–j] Since the intramolecular cyclization of 2-alkynylbenzamides (generally obtained *via* an additional step, *e.g.*, Sonogashira coupling) appeared as a potential strategy for the direct synthesis of isoquinolin-1(2*H*)-ones, hence considerable efforts have been devoted in this direction. Various conditions employed for this cyclization include the use of a base,[6] an electrophile,[7] or a transition-metal catalyst.[6,8] However, the lack of regioselectivity due to the 5-*exo vs.* 6-*endo* cyclization and chemoselectivity due to the nucleophilicity of both the O- and N-atoms of the amide moieties (involved in these cyclizations) often afforded a mixture of products in several cases (Scheme 1). While a chemoselective synthesis of isoquinolin-1(2*H*)-ones has been achieved *via* Pd-catalyzed cyclization of *N*-alkoxy-*o*-alkynylbenzamides,[9] the methodology involved the use of 20 mol% of an expensive Pd-catalyst along with the large excess (500 mol%) of *p*-benzoquinone. Additionally, this 2-step methodology is not suitable for the preparation of *N*-unsubstituted isoquinolin-1(2*H*)-ones. Herein we report the first Cu-mediated single-step coupling/cyclization of 2-iodobenzamide derivatives (**1**) with terminal alkynes (**2**) leading to a green and general approach towards *N*-(un)substituted isoquinolin-1(2*H*)-ones (**3**) (Scheme 2) with remarkable chemo- and regioselectivities.[10] We also

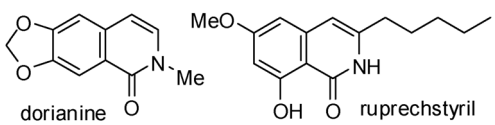
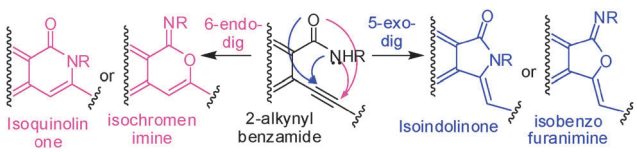
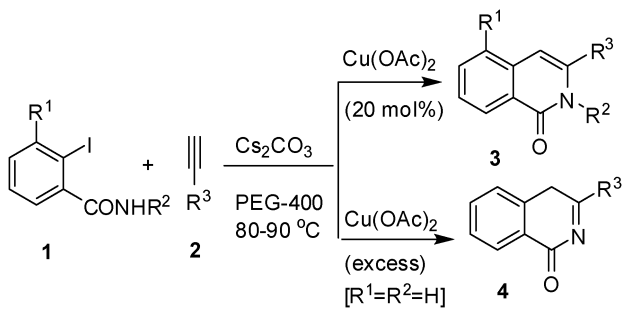


Fig. 1 Natural products containing the isoquinolin-1(2*H*)-one core.



Scheme 1 Intramolecular cyclization of 2-alkynyl benzamide.



Scheme 2 Cu-mediated synthesis of isoquinolin-1(2*H*)-ones and isoquinolin-1(4*H*)-ones.

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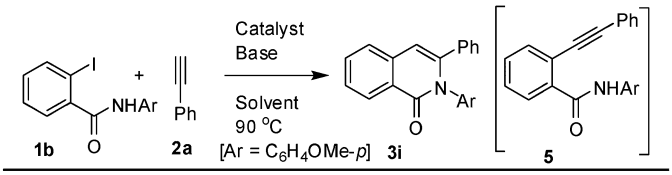
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, copies of spectra. See DOI: 10.1039/c4cc01580k

Table 1 Effect of reaction conditions on the coupling of **1b** with **2a**[a]



Entry	Catalyst	Base	Time (h)	Yield[b] (%)
1	CuCl	Cs_2CO_3	72	0
2	CuBr	Cs_2CO_3	65	0
3	CuI	Cs_2CO_3	70	80[c]
4	$Cu(OAc)_2$	Cs_2CO_3	2	82 (79, 75, 73)[d]
5	$Cu(OAc)_2$	Cs_2CO_3	4	72[e]
6	$Cu(OAc)_2$	Cs_2CO_3	12	50[f]
7	$Cu(OAc)_2{\cdot}2H_2O$	Cs_2CO_3	12	19
8	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	12	33
9	$Cu(OAc)_2$	Na_2CO_3	6	12
10	$Cu(OAc)_2$	K_2CO_3	8	30

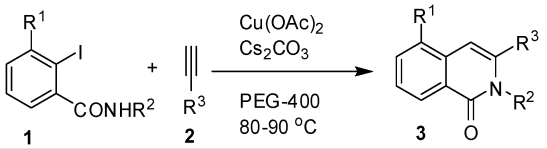
[a] All the reactions were carried out by using 2-iodobenzamide **1b** (1.0 mmol), phenyl acetylene **2a** (1.0 mmol), a base (2.0 mmol), and a catalyst (0.2 mmol) in PEG-400 (5.0 mL) at 80–90 °C under nitrogen. [b] Isolated yields. [c] Yield of compound **5**. [d] Yields after recovery and reuse of the catalyst after the 1st (2.2 h), 2nd (2.4 h) and 3rd (2.5 h) recycle, respectively. [e] 0.1 mmol of the catalyst was used. [f] 0.05 mmol of the catalyst was used.

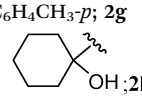
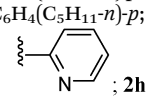
report the unusual formation of regioisomeric isoquinolin-1(4*H*)-ones (**4**) in the presence of excess of the same Cu reagent (Scheme 2).

To establish the optimized reaction conditions the coupling of 2-iodo-*N*-(4-methoxyphenyl)benzamide (**1b**) with phenyl acetylene (**2a**) was performed in the presence of a range of Cu catalysts and Cs_2CO_3 in PEG-400. Due to its polar nature, nontoxic properties and high boiling point the PEG has several advantages over the other conventional organic solvents.

Moreover, it is less expensive and recyclable. Initially, the use of CuCl and CuBr was found to be ineffective (entries 1 and 2, Table 1) whereas CuI afforded the uncyclized intermediate **5** (entry 3, Table 1). The use of anhydrous $Cu(OAc)_2$ however afforded the expected isoquinolin-1(2*H*)-one **3i** (entry 4, Table 1) within 2 h. All these reactions were carried out using 20 mol% of the catalyst. While the reaction proceeded in the presence of 10 or 5 mol% of catalysts (entries 5 and 6, Table 1), the product yield was decreased significantly in these cases. The product yield was also decreased when $Cu(OAc)_2{\cdot}2H_2O$ or $Cu(OAc)_2{\cdot}H_2O$ was used (entries 7 and 8, Table 1). The use of other bases such as Na_2CO_3 or K_2CO_3 (entries 9 and 10, Table 1) was examined but found to be less effective. The use of other solvents, *e.g.*, acetonitrile, 1,4-dioxane, DMF, DMSO and 1 : 1 PEG-H_2O was also found to be less effective. The recyclability of both $Cu(OAc)_2$ and PEG-400 was examined. The catalyst was recovered by filtration (after diluting the reaction mixture with EtOAc) followed by drying and then recycled three times (entry 4, Table 1) without affecting the product yield significantly. Similarly, the PEG-400 recovered (by diluting the filtrate with cold water, collecting the aqueous layer and

Table 2 Cu-mediated synthesis of isoquinolin-1(2*H*)-ones (**3**)[a]



Entry	Iodoamide (**1**); R^1 & R^2 =	Alkyne (**2**); R^3 =	Time (h)	Product (**3**)	Yield[b] (%)
1	H & $-C_6H_3Me_2$-*m*,*m*; **1a**	$-C_6H_5$; **2a**	3	**3a**	81
2	**1a**	$-C_6H_4(C_5H_{11}$-*n*)-*p*; **2b**	3	**3b**	76
3	**1a**	$-C_6H_{13}$-*n*; **2c**	3	**3c**	68
4	**1a**	$-(CH_2)_2CH_2Cl$; **2d**	4	**3d**	71
5	**1a**	$-C_6H_4Br$-*p*; **2e**	4	**3e**	83
6	**1a**	$-C_6H_4(OC_5H_{11}$-*n*)-*p*; **2f**	4	**3f**	79
7	**1a**	$-C_6H_4CH_3$-*p*; **2g**	4	**3g**	75
8	**1a**	 ; **2h**	4	**3h**	68
9	H & $-C_6H_4OMe$-*p*; **1b**	$-C_6H_5$; **2a**	3	**3i**	82
10	**1b**	$-C_6H_4(C_5H_{11})$-*p*; **2b**	3	**3j**	77
11	**1b**	$-C_6H_{13}$-*n*; **2c**	3	**3k**	75
12	**1b**	$-C_6H_4Br$-*p*; **2e**	3	**3l**	82
13	**1b**	$-C_6H_4(OC_5H_{11}$-*n*)-*p*; **2f**	4	**3m**	79
14	**1b**	$-C_6H_4Me$-*p*; **2g**	4	**3n**	73
15	H & $-C_6H_5$; **1c**	$-C_6H_4(C_5H_{11}$-*n*)-*p*; **2b**	3	**3o**	56
16	Cl & $-C_6H_4OMe$-*p*; **1d**	$-C_6H_4(C_5H_{11}$-*n*)-*p*; **2b**	3	**3p**	63
17	OMe & $-C_6H_4OMe$-*p*; **1e**	$-C_6H_4(C_5H_{11}$-*n*)-*p*; **2b**	3	**3q**	73
18	H & H; **1f**	 ; **2h**	3	**3r**	93
19	**1f**	$-C_6H_4Me$-*p*; **2g**	3	**3s**	84
20	**1f**	$-C_6H_4(C_5H_{11}$-*n*)-*p*; **2b**	3	**3t**	87
21	**1f**	**2e**	3	**3u**	83

[a] All the reactions were carried out by using **1** (1.0 mmol), terminal **2** (1.0 mmol), Cs_2CO_3 (2.0 mmol), and anhyd $Cu(OAc)_2$ (0.2 mmol) in PEG-400 (5.0 mL) at 80–90 °C under nitrogen. [b] Isolated yields.

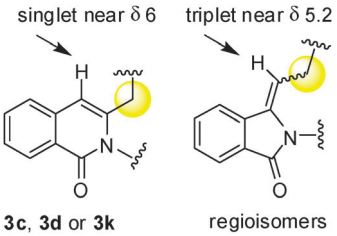


Fig. 2 Appearance of olefinic protons of **3c**, **3d** and **3k** in ^{1}H NMR.

distilling off the contaminated water under vacuum) was recycled three times affording product **3i** in 80, 78 and 76% yields, respectively. Overall, the combination of 20 mol% of anhydrous $Cu(OAc)_2$ and 2 equiv. of Cs_2CO_3 in PEG-400 was found to be optimum and used to expand the generality and scope of this methodology further.

A variety of isoquinolin-1(2*H*)-ones (**3**) were synthesized by using this Pd-free Cu-mediated method (Table 2). Both *N*-substituted (**3a–q**) and unsubstituted derivatives (**3r–u**) were obtained in a single step without involving any N-deprotection step[5i,9] for compounds **3r–u**. All the synthesized isoquinolin-1(2*H*)-ones (**3**) were characterized by using NMR, IR, and HRMS spectra.[11] For example, compounds **3c**, **3d** and **3k** contain a $–CH_2–$ group next to the double bond of the heterocyclyl ring (Fig. 2). In the case of the endocyclic double bond (6-membered ring), the olefinic proton does not couple with the protons of the $–CH_2–$ group and therefore appears as a singlet near δ 6.0. However, in the case of the exocyclic double bond (5-membered ring), the vinylic hydrogen being next to the $–CH_2–$ group is known to couple with these protons to give a triplet near δ 5.2, as observed by Kundu *et al.*[6] This was not observed in the case of **3c**, **3d** and **3k**. Additionally, the gHMBC (gradient heteronuclear multiple bond coherence) NMR study[11] of **3i** (Fig. 3) shows that its olefinic proton has a cross peak with an aromatic C–H (appearing near 130 ppm) in addition to two other cross peaks with aromatic quaternary carbons. This is not possible in the case of the corresponding regioisomeric isoindolin-1-one derivative as its olefinic proton would show three cross peaks with three aromatic quaternary carbons. Nevertheless, compound **3u** was further functionalized *via* a Suzuki coupling with naphthalen-2-ylboronic acid to give 3-(4-(naphthalen-2-yl)phenyl)isoquinolin-1(2*H*)-one (**6**) in 80% yield (see ESI†).

During our studies on the coupling of 2-iodobenzamide (**1f**) with a terminal alkyne we observed formation of a different product exclusively when the reaction was performed in the presence of excess of $Cu(OAc)_2$. This new product characterized as a regioisomeric isoquinolin-1(4*H*)-one derivative prompted us to examine this reaction further. Thus, six derivatives[12a] (**4**)

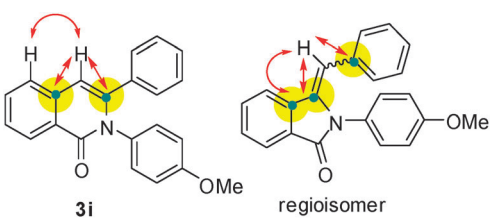
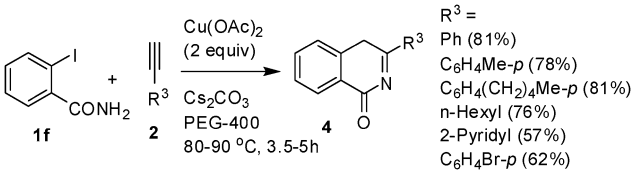


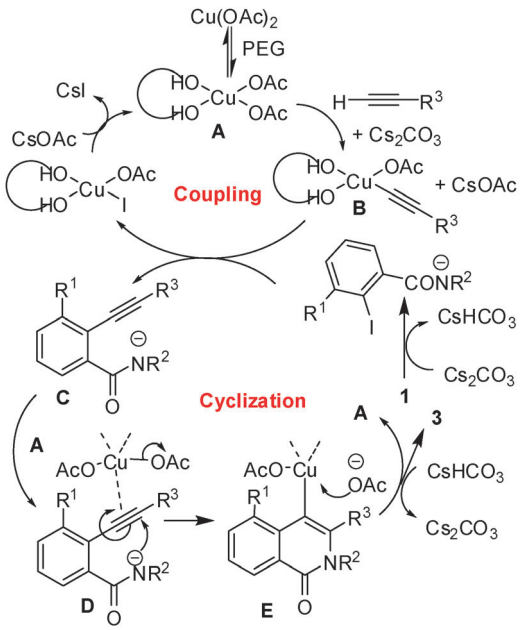
Fig. 3 Cross peaks shown by the olefinic proton of **3i** in the gHMBC NMR study (see ESI†).



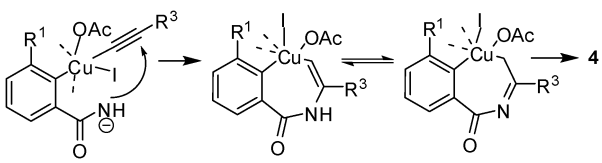
Scheme 3 Synthesis of isoquinolin-1(4*H*)-ones (**4**).

were prepared by reacting **1f** with **2** in the presence of 2.0 equiv. of $Cu(OAc)_2$ (Scheme 3). Notably, as a class these compounds are not common in the literature.[12b]

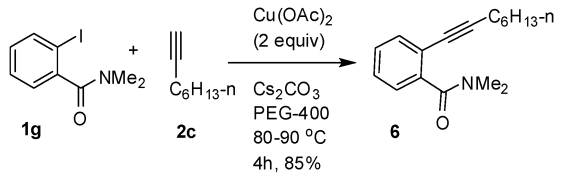
The proposed reaction mechanism (Scheme 4) leading to **3** involved the generation of an active catalyst **A** [*via* the interaction of $Cu(OAc)_2$ with PEG] that facilitated the formation of **C** *via* **B** with the regeneration of **A** (the coupling step).[13] The intramolecular cyclization of **C**[14] was then facilitated by **A** to afford **3** with the regeneration of **A** (the cyclization step). The 5-*exo*-dig cyclization[10] was not favored perhaps due to the possible steric crowding between the bulky Cu species and R^3 in the corresponding 5-membered ring intermediate. Though not clearly understood, the formation of **4** could be due to the intramolecular addition of an amide anion to the alkyne during the coupling reaction (Scheme 5). In a separate study, the 2-iodo-*N*,*N*-dimethylbenzamide (**1g**) was coupled with alkyne **2c** (Scheme 6) under the conditions given in Scheme 3 when the product was trapped as a normal Sonogashira product **6** indicating that the reaction might be



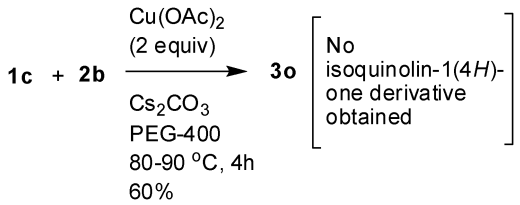
Scheme 4 Proposed reaction mechanism leading to compound **3**.



Scheme 5 Proposed reaction mechanism leading to compound **4**.



Scheme 6 Coupling of amide **1g** with alkyne **2c**.



Scheme 7 Coupling of amide **1c** with alkyne **2b** under the conditions given in Scheme 3.

following the pathway shown in Scheme 5.[15] Moreover, coupling of **1c** with **2b** under the same conditions afforded **3o** (Scheme 7) confirming the need for the $-CONH_2$ (with no substituent on NH_2) group to afford a product that belongs to the isoquinolin-1(4*H*)-one class **4**.[15] The observation that compound **3s** did not provide the corresponding isoquinolin-1(4*H*)-one derivative when treated with 2 equiv. of $Cu(OAc)_2$ (under the conditions given in Scheme 3) ruled out the possibility of formation of **4** *via* isomerization of **3**.[15]

In conclusion, Cu-mediated coupling/cyclization of 2-iodobenzamides with terminal alkynes in PEG afforded *N*-(un)substituted isoquinolin-1(2*H*)-ones instead of isoindolin-1-ones. The methodology is Pd-free and does not require the use of any expensive reactants, reagents or catalysts. Both the Cu-catalyst and the solvent are recyclable. We also report the unprecedented formation of regioisomeric isoquinolin-1(4*H*)-ones in the presence of excess of the Cu reagent.

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10 Notably, 5-membered ring products (isoindolin-1-ones) were obtained from microwave assisted coupling/cyclization of 2-bromobenzamides with arylacetylene, *e.g.* for Cu-free Pd-mediated method, see: (*a*) M. Hellal and G. D. Cuny, *Tetrahedron Lett.*, 2011, **52**, 5508; For Pd-free Cu-mediated method, see: (*b*) L. Zhang, Y. Zhang, X. Wang and J. Shen, *Molecules*, 2013, **18**, 654; For microwave and the Pd-free Cu-mediated method, see: (*c*) J. Pan, Z. Xu, R. Zeng and J. Zou, *Chin. J. Chem.*, 2013, **31**, 1022, DOI: 10.1002/cjoc.201300346. See also ; (*d*) H. Cao, L. McNamee and H. Alper, *Org. Lett.*, 2008, **10**, 5281; (*e*) L. Li, M. Wang, X. Zhang, Y. Jiang and D. Ma, *Org. Lett.*, 2009, **11**, 1309 and ref. 6.
11 For COSY, HSQC and HMBC spectra of **3i** and HSQC and HMBC spectra of **3a** see the ESI†.
12 (*a*) The appearance of a peak near 4.0–4.5 δ in the ^{1}H NMR spectra and 43.0–43.5 ppm in ^{13}C NMR spectra indicated the presence of a benzylic–CH_2– moiety in compound **4** (see ESI†). For HSQC and HMBC spectra of **4a** see the ESI†; (*b*) see: CSID: 10551086, http://www.chemspider.com/Chemical-Structure.10551086.html (accessed 13:54, Mar 1, 2014).
13 We propose a Cu(II)/Cu(IV) pathway for the conversion of **1** to **C** instead of the Cu(I)/Cu(III) mechanism (that though can not be ruled out completely, for a review, see: E. Perotto, G. P. M. van Klink, G. van Koten and J. G. de Vries, *Dalton Trans.*, 2010, **39**, 10338) as the second pathway is unable to explain the recovery and recyclability of the catalyst.
14 The intermediacy of **C** was further supported by the fact that alkyne **5** (1 mmol) upon treatment with $Cu(OAc)_2$ (20 mol%) and Cs_2CO_3 (2 mmol) in PEG-400 (5 mL) at 80–90 °C for 2 h afforded the cyclized product **3i** in 45% yield.
15 We thank one of the reviewers for his suggestion to perform this experiment.

