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Cu-catalyzed coupling-cyclization in PEG 400 under ultrasound: a highly selective and greener approach towards isocoumarins†

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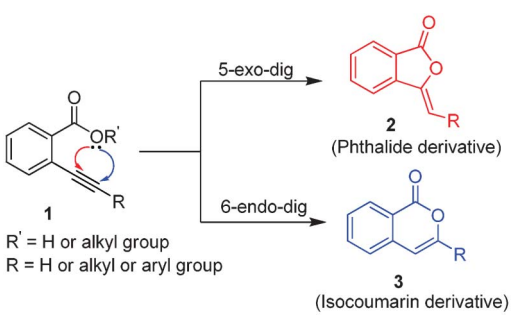
The combination of CuI–K_2CO_3-PEG 400 facilitated the coupling-cyclization of *o*-iodobenzoic acid with terminal alkynes under ultrasound, affording a greener and practical approach towards 3-substituted isocoumarins with remarkable regioselectivity. This inexpensive and Pd and ligand free methodology gave rise to various isocoumarins of potential pharmacological interest.

The development of highly selective, inexpensive and safer chemical methods not only considered as important initiatives in green and sustainable chemistry but also is one of the prime goals of chemical and pharmaceutical industries. Thus, not surprisingly enormous efforts have been devoted by organic/synthetic chemists in this direction.

Isocoumarins are an important class of naturally occurring lactones with innumerable pharmacological properties including antifungal, antitumor, antiallergenic, antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and immunomodulatory activities.[1] As a consequence, synthesis of naturally occurring and biologically active isocoumarins has been an active area of research for the past 20 years. A significant number of diverse methodologies have been reported,[2] the most explored one being the transition metal catalyzed intramolecular cyclization of internal alkynes with proximal carboxylate group. This type of cyclization is generally promoted by a variety of transition metal catalysts based on Pd, Zn, Rh, Hg, Ag, Au, Cu, Ru or Ir.[3,4] However, the Pd-catalysed Sonogashira type coupling followed by cyclization is the widely used method among them. Notably, the intramolecular ring closure of the alkynoic acids/esters (**1**) can give rise to a mixture of products resulting from 5-*exo-dig* (a phthalide *i.e.* **2**) and 6-*endo-dig* cyclization (an isocoumarin *i.e.* **3**) (Scheme 1). In several cases, the 5-*exo-dig* cyclization product *i.e.* the phthalide was obtained as a major product.[5] The formation of phthalide derivatives were largely avoided by using $Pd(PPh_3)_4$–$ZnCl_2$ catalytic system in DMF[6] or Pd/C–CuI in ethanol,[7] where the isocoumarin derivatives were obtained as the major products. These methodologies however involved the use of expensive and toxic palladium catalysts or harmful organic solvents. Thus the search for inexpensive, efficient and safer catalyst/solvent was of particular interest.[8] Accordingly, copper has emerged as an effective and complementary metal towards the synthesis of isocoumarin. Earlier in 1963, Stephens and Castro claimed isocoumarin synthesis *via* the coupling of *o*-iodobenzoic acid with stoichiometric amount of alkynylcopper (I) species in pyridine.[9] While in the later stage the isolated products were characterized as phthalides, since then, much effort has been devoted to develop synthetic route to isocoumarins that would require copper in catalytic quantity. Miura *et al.* developed a Cu(I)-catalyzed synthesis of 3-phenyl isocoumarin in 19% yield *via* the reaction of *o*-iodobenzoic acid and phenylacetylene using triphenyl phosphine as a ligand, K_2CO_3 as a base and DMF as a solvent at 120 °C for 24 h.[10] Later, Wang *et al.* performed the reaction under microwave irradiation which reduced the reaction time with increase in isocoumarin yield (86%).[11] A ligand-free copper mediated isocoumarin synthesis in DMF was also attempted, where a mixture of desired isocoumarin and the corresponding



Scheme 1 Intramolecular ring closure of the alkynoic acid/ester **1**.

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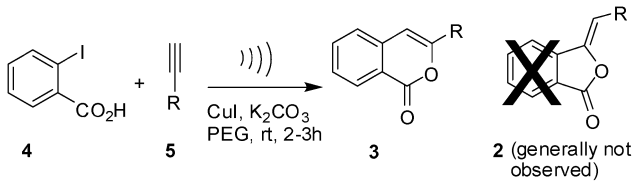
† Electronic supplementary information (ESI) available: Experimental Procedures, spectral data and copies of NMR for all new compounds. See DOI: 10.1039/c3ra40969d

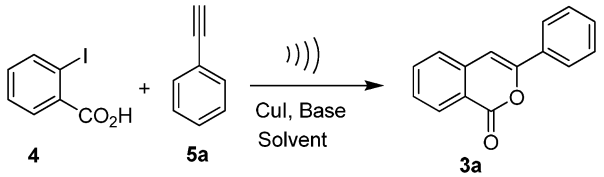


Scheme 2 Cu-mediated synthesis of isocoumarin in PEG 400.

phthalide was obtained.[12] Additionally, though the use of expensive and toxic Pd-catalysts and organic ligands was avoided in these reactions, the use of hazardous organic solvent as a reaction medium and lack of selectivity (*i.e.* the formation of substantial amount of phthalide along with isocoumarin) has made this method less attractive. This prompted us to develop an alternative, highly selective, inexpensive and safer method to address some of these concerns. Herein, we report for the first time the use of polyethylene glycol 400 (PEG 400) as a solvent in an environment friendly, efficient, palladium and ligand-free, Cu-mediated regioselective synthesis of isocoumarins. Because of its high boiling, non-hazardous and polar nature the use of PEG as a solvent in organic reactions is advantageous. Indeed, due to its easy recovery (from the reaction mixture) and recyclability, PEG has been used as a solvent in several organometallic reactions including Cu-mediated Sonogashira, Heck and Suzuki–Miyaura coupling.[13] The ultrasound mediated reactions on the other hand have become increasingly popular and widely used methodologies in organic synthesis.[14] The present methodology involved Cu-catalyzed coupling-cyclization of *o*-iodobenzoic acid with various terminal alkynes under ultrasound in the presence of K_2CO_3 in PEG 400, leading to a range of isocoumarin derivatives as sole or major products (Scheme 2).

Initially, the coupling of *o*-iodobenzoic acid (**4**) and phenyl acetylene (**5a**) was performed in water in the presence of 10 mol% CuI and K_2CO_3 (entry 1, Table 1) when no progress was observed after 72 h of sonication (using SONOREX SUPER RK 510H model producing irradiation of 40 kHz). The increase of catalyst loading (entry 2 and 3, Table 1) or the use of 1 : 1 water-PEG 400 did not afford any product (entry 4, Table 1). Finally, the use of only PEG 400 gave the desired isocoumarin **3a** in 45% yield (entry 5, Table 1). The increase of catalyst loading improved the product yield and decreased the reaction time (entry 6, Table 1) whereas further increase in the catalyst amount (50 mol%) did not improve the product yield (entry 7, Table 1). Notably the reaction did not proceed in the absence of ultrasound (entry 8, Table 1). The use of other bases *e.g.* Cs_2CO_3 and K_3PO_4 decreased the product yield (entry 9 and 10, Table 1). Nevertheless, the 6-*endo-dig* cyclization product (*i.e.* isocoumarin **3a**) was isolated as the sole product in all these cases and the formation of phthalide was not observed. In order to test the recyclability of the used PEG, the aqueous mixture of PEG collected after usual workup was distilled at 50 °C under vacuum [until the water content of residual PEG reached ~1% (by Karl Fischer method)]. The recovered PEG was reused for the reaction of **4** and **5a** under the condition of entry 6, Table 1 when **3a** was isolated in 75% yield after 6 h.

Table 1 The optimization of coupling of *o*-iodobenzoic acid (**4**) with phenyl acetylene (**5a**)[a]



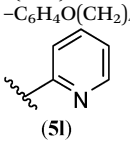
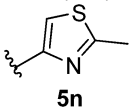
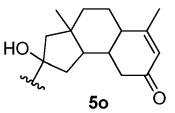
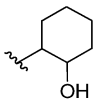
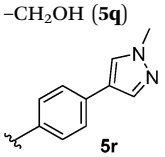
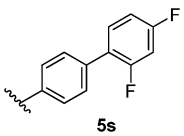
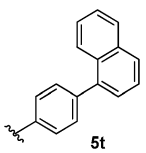
Entry	CuI (mol%)	Base	Solvent	Time (h)	Yield[b] (%)
1	10	K_2CO_3	H_2O	72	0
2	20	K_2CO_3	H_2O	65	0
3	50	K_2CO_3	H_2O	70	0
4	20	K_2CO_3	H_2O : PEG (1 : 1)	72	0
5	10	K_2CO_3	PEG	24	45
6	20	K_2CO_3	PEG	3	80
7	50	K_2CO_3	PEG	3	80
8	20	K_2CO_3	PEG	48	0[c]
9	20	Cs_2CO_3	PEG	4	69
10	20	K_3PO_4	PEG	4	66

[a] All the reactions were carried out by using 2-iodobenzoic acid (**4**, 1.0 mmol), phenyl acetylene (**5a**, 1.0 mmol), base (2.0 mmol), and CuI in a solvent (5.0 mL) at room temp (25 °C) in a sonicator under nitrogen. [b] Isolated yield. [c] Reaction was carried out in the absence of ultrasound.

We then examined the reaction of **5a** with *o*-bromo and *o*-chloro benzoic acid separately. While **3a** was isolated in poor yield (~10%) in the first case the reaction did not proceed in the second case. We also examined the reaction of methyl-2-iodobenzoate (**6**) with **5a** under the same reaction conditions (entry 6, Table 1), which gave the *o*-alkynyl benzoate ester **7** instead of **3a** [even after a long reaction time (72 h) or increasing the catalyst amount up to 50 mol%] indicating that unlike the $-CO_2H$, the ester group of **7** was unable to participate in the cyclization step under the conditions employed (Scheme 3).

The generality of the present PEG based methodology was examined by coupling **4** with various terminal alkynes under the optimized reaction conditions. The nature of terminal alkynes used was varied from aromatic (**5a–e**, **5l**, **5n**, **5r**, **5s**, **5t**) to cyclic (**5o**, **5p**) or acyclic (**5f–h**, **5i–k**, **5m** and **5q**) aliphatics. The reaction proceeded well with all these alkynes employed affording the desired product **3** in moderate to good yields within 2–3 h (Table 2). The reaction also proceeded well when a substituted 2-iodobenzoic acid *e.g.* 2-iodo-3-methoxybenzoic acid was treated with **5a** affording the desired 5-methoxy-3-phenyl-1*H*-isochromen-1-one in 77% yield after 3 h. Notably the reaction of 2-iodo-5-nitrobenzoic acid with **5a** afforded the uncyclized product *i.e.* 5-nitro-2-(phenylethynyl)benzoic acid instead of desired isocoumarin. While in most of the cases isocoumarin was isolated as the only product, traces (>5%) of regioisomeric phthalide was isolated when alkynes **5f–h** were employed. In some of the cases the unreacted starting material **4** was recovered reducing isocoumarin yields to 60–65%. All the compounds synthesized were characterized by ^1H and ^{13}C NMR, IR, and HRMS spectra. The formation of isocoumarin ring was confirmed by the appearance of an absorption band at ~1750 cm^{-1} (for C=O) in IR, a singlet at

Table 2 Synthesis of isocoumarins (**3**) *via* Cu-mediated coupling-cyclization strategy in PEG 400 under ultrasound (Scheme 2)[a]

Entry	Alkyne (**5**), R=	Products (**3**)	Time (h)	Yield[b] (%)
1	Ph (**5a**)	**3a**	3	80
2	$-C_6H_4Br$-*p* (**5b**)	**3b**	2	65
3	$-C_6H_4NH_2$-*p* (**5c**)	**3c**	2.5	60
4	$-C_6H_4CH_3$-*p* (**5d**)	**3d**	2.5	60
5	$-C_6H_4Br$-*o* (**5e**)	**3e**	3	80
6	$-(CH_2)_3CH_3$ (**5f**)	**3f**	2	75
7	$-(CH_2)_4CH_3$ (**5g**)	**3g**	3	60
8	$-(CH_2)_5CH_3$ (**5h**)	**3h**	2.5	80
9	$-(CH_2)_2CH_2Cl$ (**5i**)	**3i**	3	70
10	$-(CH_2)_3CH_2OH$ (**5j**)	**3j**	2.5	80
11	$-C_6H_4O(CH_2)_4CH_3$-*p* (**5k**)	**3k**	3	65
12	 (**5l**)	**3l**	3	80
	(**5l**)			
13	$-C_6H_4(CH_2)_4CH_3$-*p* (**5m**)	**3m**	2	65
14	 **5n**	**3n**	2	80
15	 **5o**	**3o**	2	80
16	 **5p**	**3p**	2	80
17	$-CH_2OH$ (**5q**)	**3q**	2	85
18	 **5r**	**3r**	3	80
19	 **5s**	**3s**	3	70
20	 **5t**	**3t**	3	85

[a] All the reactions were carried out by using **4** (1.0 mmol), an appropriate terminal alkyne (**5**, 1.0 mmol), K_2CO_3 (2.0 mmol), and CuI (20 mol%) in PEG (5.0 mL) at room temp (25 °C) in a sonicator under nitrogen. [b] Isolated yield.

~6.80–6.20 ppm (for CH=C) in ^{1}H NMR and a quaternary carbon at ~167.0 ppm (C=O) in the ^{13}C NMR spectra.

We have demonstrated that the combination of CuI–K_2CO_3-PEG 400 can facilitate the coupling-cyclization of *o*-iodobenzoic acid with terminal alkynes under ultrasound affording a greener and practical approach towards 3-substituted isocoumarins with remarkable regioselectivity. This inexpensive and Pd and ligand free methodology gave rise to various isocoumarins of potential pharmacological interest. For example, compounds **3b**, **3d** and **3e** are known to inhibit thymidine phosphorylase[15] whereas **3b** and **3e** are known to possess antimicrobial activities.[16] The compound **3g** showed promising antibiotic activities comparable to the standard antibiotics.[17] Moreover, hydrogenation of **3g** in the presence of 10%Pd/C in MeOH at room temperature for 12 h afforded the dihydroisocoumarin **8** (see ESI†) that showed antibacterial activities *in vitro* (Fig. 1).[17]

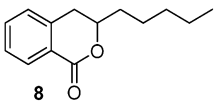

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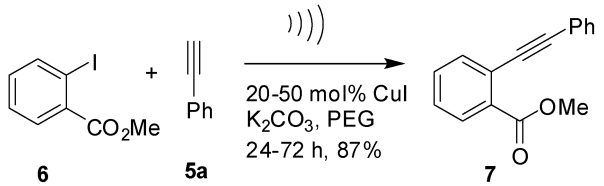
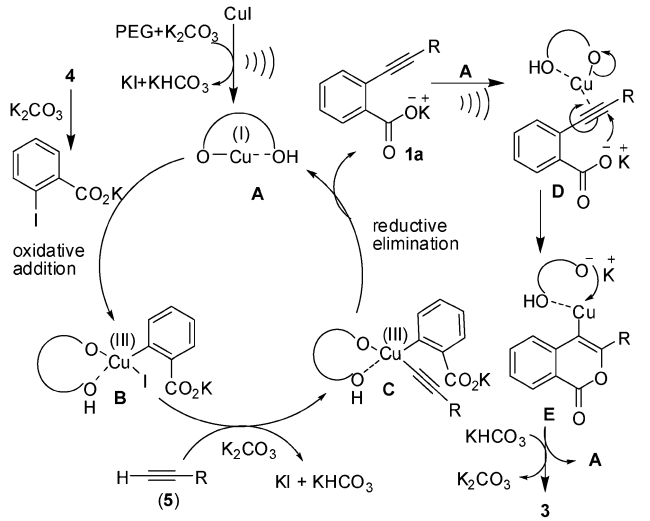
Fig. 1 Dihydroisocoumarin **8** as an antibacterial agent.

Based on the results of Table 1 and the fact that PEG plays the role of a ligand in several Cu-mediated coupling reactions[13a,c] a probable mechanism for the present synthesis of isocoumarin is shown in Scheme 4. Thus, PEG appeared to play the pivotal role as a solvent and also as a ligand in the present reaction. Initially, a Cu(I) complex (**A**) formed *via* the interaction of CuI with PEG[13c,18] under ultrasound, underwent oxidative addition with *o*-iodobenzoic acid to afford the arene-Cu(III) species **B**. Subsequently, the alkyne **5** reacts with **B** in the presence of K_2CO_3 leading to the arene-Cu(III)-alkyne species **C**, which on reductive elimination furnished the *o*-alkynyl benzoate salt (**1a**) with the regeneration of active Cu(I) catalyst **A**. The *o*-alkynyl benzoate salt (**1a**) then underwent intramolecular ring closure in the presence of **A** in a regioselective manner to give the desired isocoumarin **3**. The participation of Cu(III) complex **B** or **C** which could catalyze the cyclization of **1a** to afford a 4-aryl or 4-alkynyl isocoumarin derivative, was ruled out as these products were not detected in the reaction mixture. It seems that the cyclization of **1a** therefore was aided by the combined effect of bulky catalytic species **A**, ultrasound and $KHCO_3$ (generated *in situ*). Though the specific reasons for the enhanced selectivity was not clearly understood, the formation of a five-membered ring from **D** could lead to the more steric crowding than that in **E** perhaps account for somewhat different *i.e.* better regioselectivity observed in the present case compared to that reported earlier.[12] Nevertheless, the



Scheme 3 Cu-mediated coupling of methyl-2-iodobenzoate (**6**) with phenyl acetylene (**5a**).



Scheme 4 Proposed mechanism for the Cu-mediated coupling-cyclization of **4** with **5** in PEG under ultrasound.

combination of CuI–K_2CO_3-PEG400 and ultrasound emerged as a newer option for isocoumarin synthesis.

In summary, PEG400 has been identified as an efficient, non-hazardous and reusable solvent for the synthesis of 3-substituted isocoumarins *via* a Cu-mediated coupling-cyclization of *o*-iodobenzoic acid with terminal alkynes under ultrasound. Except few cases the reaction showed remarkable regioselectivity towards the formation of isocoumarin over phthalide. The present palladium and ligand free methodology does not require the use of expensive or toxic catalyst, reagents or solvents and therefore represents a useful and safer alternative to the existing methods. The methodology may find wide usage in constructing diversity based isocoumarin library for chemical and medicinal applications.

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