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Graphical Abstract

Pd-free Sonogashira Coupling: One pot synthesis of Phthalide *via domino* Sonogashira coupling and 5-*exo-dig* cyclization

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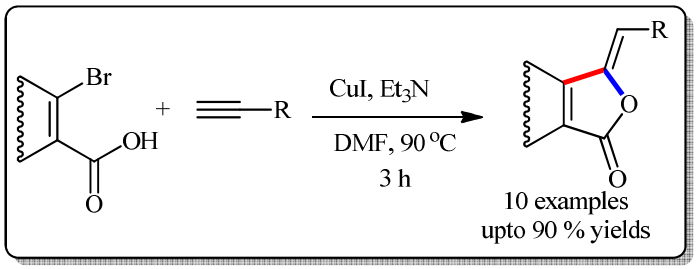

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Pd-free Sonogashira Coupling: One pot Synthesis of Phthalide *via domino* Sonogashira Coupling and 5-*exo-dig* Cyclization

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Phthalides have been synthesized exclusively in one pot *via* Pd-free Sonogashira coupling. A Cu-catalyzed domino Sonogashira coupling and 5-*exo-dig* cyclization between suitable substituted *ortho*-bromobenzoic acids and terminal alkynes afforded phthalides in good yields under mild reaction condition.

Phthalides are the core structural subunit of enormous drug candidates.[1] Though, many phthalide derivatives are used as clinical medicine, two most important marketed drugs are antiarthritic agent talniflumate[2] and the immunosuppressant drug mycophenolate mofetil.[3] Particularly C3-substituted phthalides are exemplified by the natural products cytosporone **E** (**1**)[4], fuscinarin (**2**)[5], cryphonectric acid (**3**)[6] (Fig.1) and important intermediate in synthesis of complex natural products.[7]
Therefore, owing to their pharmacological importance and synthetic utility in organic synthesis development of efficient and economic method of preparation is of considerable interest for last few decades.

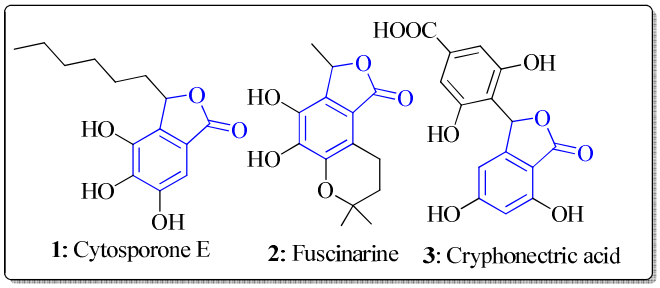
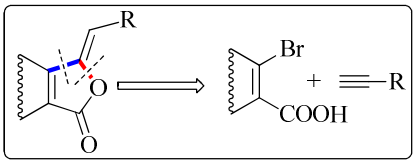


Fig 1: Bioactive phthalide derivatives

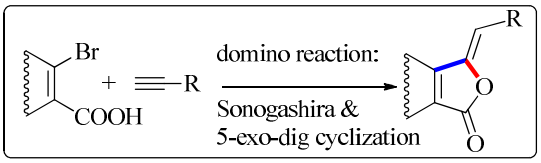
A number of methods for the synthesis of 3-substituted phthalide have been developed, most of them involved the cyclization of *ortho*-substituted arylaldehydes[8] or C3-alkylation of phthalides.[9] Recently, several transition-metal mediated syntheses of phthalide such as, Ru-catalysed cross-dehydrogenative coupling[10] and and Ru- or Rh-catalyzed intramolecular hydroacylation[11] have been reported.

In literature there are few reactions involving Pd-free Sonogashira coupling for the synthesis of heterocycles and carbocycles. We envisaged that *regio*-selectively 3-substituted phthalides could be obtained by *domino* Sonogashira coupling and 5-*exo-dig* cyclization (Scheme 1).



Scheme 1: Retro-synthetic analysis

Consequently, in this report we have described an interesting method for one-pot synthesis of 3-substituted phthalides exclusively starting from *o*-bromobenzoic acid and terminal alkyne (Scheme 2).



Scheme 2: Synthesis of phthalides

The precursor 2-bromobenzoic acids were prepared in moderate to good yields *via* Pinnick oxidation[12] from the corresponding aldehydes. We started the investigation of the *domino* process with simple 2-bromobenzoic acid (1mmol) and phenylacetylene (0.1 mmol) (Table 1). While screening with different Cu-salt, we identified CuI (10 mmol %) as a convenient and inexpensive catalyst that is more effective over the other. DMF gave the better yields of the product compared to other solvents. Addition of ligands (such as, 1, 10-phenanthroline) did not have marked effect on the reaction yields (Table 1, entry 6). Amine base triethylamine have prominent

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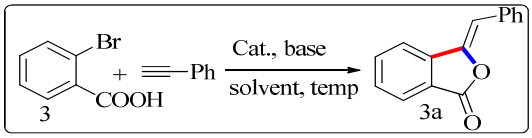
effect on reaction among the organic and inorganic bases. Some increment of the product yields was resulted with elevation of temperature from 60 °C to 80 °C (Table 1, entry 7). Further elevation temperature to 100 °C did not affect the yields of the reaction.

Table 1: Optimization of reaction conditions for the *domino* process[b]



Entry	Catalyst	Base	Solvent	Temp.(°C)	Time (h)	Yield (%)[c]
1	CuI	Et_3N	DMF	60	3	75
2	CuBr	Et_3N	DMF	60	3	45
3	CuCl	Et_3N	DMF	60	3	30
4	$Cu(OTf)_2$	Et_3N	DMF	60	3	25
5	$Cu(OAc)_2$	Et_3N	DMF	60	3	0
6	CuI	Et_3N	DMF	60	3	74*
7	**CuI**	**Et_3N**	**DMF**	**80**	**3**	**90**
8	CuI	Et_3N	DMF	80	5	65
9	CuI	Et_3N	DMA	80	3	65
10	CuI	Et_3N	DMSO	80	3	53
11	CuI	NaOAc	DMF	80	3	50
12	CuI	Na_2CO_3	DMF	80	3	41
13	CuI	K_2CO_3	DMF	80	3	44
14	CuI	Et_3N	DMF	100	3	90

[b]Reaction conditions: *o*-bromobenzoic acids (1 mmol), phenylacetylene (0.1 mmol), base (3.0 mmol), Cu-salt (10 mol %), solvent (3 mL). [c]Isolated yield. *With 1,10-phenanthroline ligand.

We found that prolonged reaction time did not give better conversion of phthalides. Optimal conditions for the domino reaction were finalized to be CuI (10 mol %), Et_3N (3.0 mmol), DMF (3mL), 80 °C, 3 h.

Exclusive formation of the phthalide was unambiguously confirmed by the single crystal structure analysis of the product formed with an *exo*-cyclic double. CCDC of the compound **3a** is 1000643 and ORTEP of the compound is shown in Fig 2.

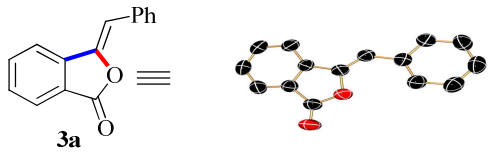
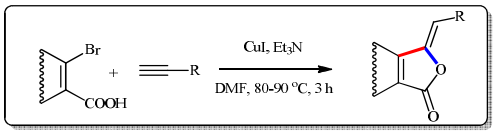


Fig 2: The X-ray crystal structure of compound **3a**

The scope and generality of the reaction was demonstrated by synthesizing a number of structurally diverse phthalide derivatives with varying substituents (Table 2). Results described in the Table 2 shows that our synthetic protocol has a wide range functional group tolerance, including amine, alkyl, halogens, methoxy and primary alcoholic OH. Influence of the electron-donating and withdrawing functional groups on both the coupling partner is quite clear from the results in Table 2. Electron withdrawing group such as F and pyridyl ring in combination with COOH in the 2-bromobenzoic acid part increase the reactivity of the C-Br bond producing good yields of phthalides (**3b**, **3l**). In contrast, electron-donating group methyl, methoxy, ^{t}Bu in both acids and alkyne part decrease the reactivity of alkyne moiety as well as C-Br bond resulting lower yields of phthalides (**3c**, **3d**, **3f**). A steric factor may be operating in the *o*-chloro substituent and the bulky aryl group in the alkyne part which afforded quite lower amount the phthalide formation (**3g**, **3i**, **3j**).

Table 2: Synthesis of phthalide derivatives[d,†]



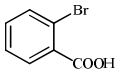
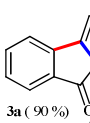
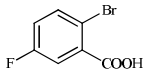
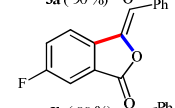
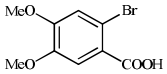
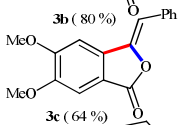
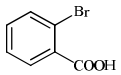
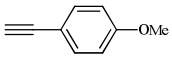
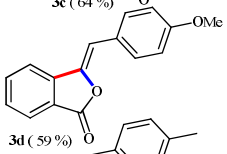
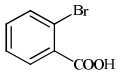
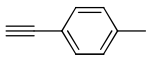
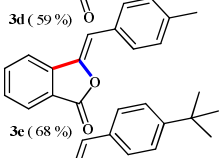
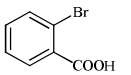
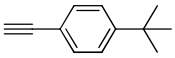
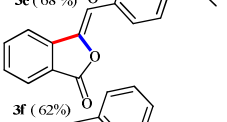
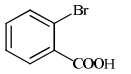
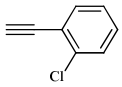
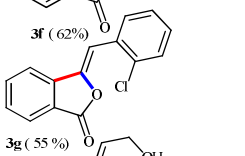
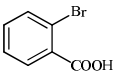
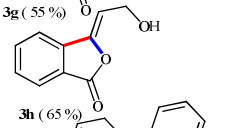
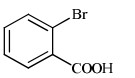
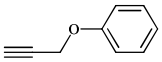
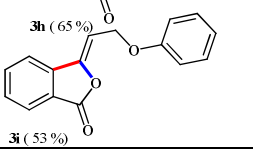
Entry	Substrate	Alkyne	Product (% yields)[e]
1			 **3a** (90 %)
2			 **3b** (80 %)
3			 **3c** (64 %)
4			 **3d** (59 %)
5			 **3e** (68 %)
6			 **3f** (62%)
7			 **3g** (55 %)
8			 **3h** (65 %)
9			 **3i** (53 %)

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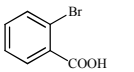
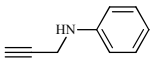
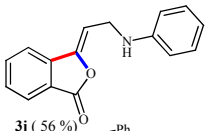
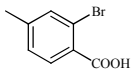
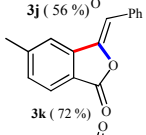
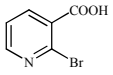
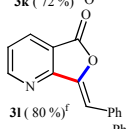
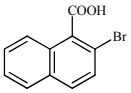
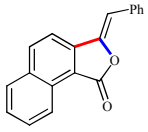
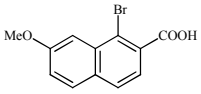
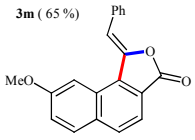
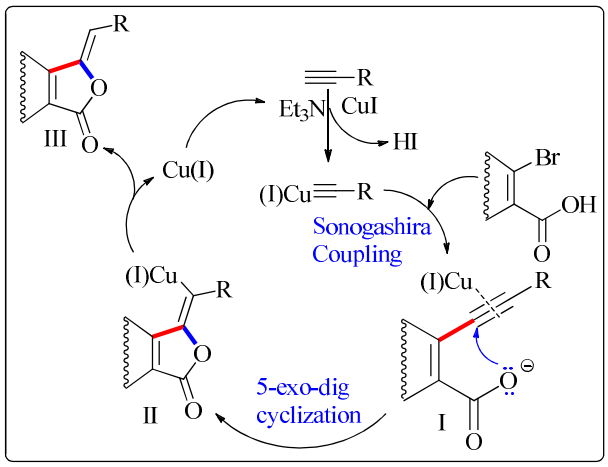
Table 2 : Continued.

Entry	Substrate	Alkyne	Products(% yields)[e]
10			 **3j** (56 %)
11			 **3k** (72 %)
12			 **3l** (80 %)[f]
14			 **3m** (65 %)
15			 **3n** (60 %)

[e]Reaction conditions: *o*-bromobenzoic acids (1 mmol), terminal alkyne (0.1 mmol), Et_3N (3.0 mmol), CuI (10 mol %), DMF (3 mL), 80 °C, 3 h. Isolated yield in parenthesis. [f]Isocumarin (10 %) was isolated.

We propose that the reaction proceeds *via* domino reaction of Cu-mediated Sonogashira coupling and intramolecular 5-*exo*-*dig* cyclization (Scheme 3). Firstly, CuI in presence of Et_3N base formed Cu-acetylide which undergoes a Sonogashira type coupling with the C-Br bond to afford the *o*-alkynylcarboxylate (**I**). Intramolecular attack of the carboxylate on the Cu(I) co-ordinated electrophilic *o*-alkyne moiety in a 5-*exo*-*dig* fashion to gave the intermediate **II**. The intermediate **II** finally produced our desired compound **III** and Cu(I) which enters into the catalytic cycle.



Scheme 3: Proposed reaction pathway

Conclusions

In conclusion, we have developed a very short and efficient methodology for the regio-selective synthesis of 3-substituted phthalide using very cheap starting materials and under mild reaction conditions. Our methodology is a very convenient one to be applied in the total synthesis of complex molecules of prevalent pharmacological values.

Notes and references

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

†General procedure of the preparation of 3-substituted phthalides:

o-bromobenzoic acids (1mmol), terminal alkyne (0.1 mmol), Et_3N (3.0 mmol), CuI (10 mol %) and 3mL of DMF were taken in a 25 ml round bottomed flask in argon atmosphere. The mixture was heated to 80 °C temperature for 3 h. The completion of the reaction was monitored by TLC checking. After completion of the reaction mixture was cooled to room temperature and diluted with water. It was then extracted with ethyl acetate (3×50 ml). Combined organic layer was washed with brine and evaporated to dryness under reduced pressure. The desired phthalide was isolated by usual column chromatography with a mixture of ethyl acetate and petroleum ether (1:20) as eluent. Spectral data of the representative compound **3-benzylideneisobenzofuran-1(3H)-one (3a):** White Solid; mp: 84-86 °C; Yield: 90 %; ^{1}H NMR (200 MHz, $CDCl_3$) : 6.40 (1H, s), 7.29-7.44 (3H, m), 7.48-7.56 (1H, m), 7.66-7.76 (2H, m), 7.82-.792 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$): 107.2, 120.0, 123.4, 125.6, 128.5, 128.9 (2C), 129.8, 130.2 (2C), 133.2, 134.6, 140.7, 144.7, 167.2; Elemental Analysis: C: 81.07 %; H: 4.54%; Found: C: 81.00%; H: 4.49%; HRMS of $C_{15}H_{11}O_2^+$ [M+ H^+]: 223.0754; Observed : 223.0750.

1 (a) K. Knepper, R. E. Ziegert and S. T. Bräse, *Tetrahedron* 2004, ***60***, 8591–8603 and references therein. (b) T. V. Hung, B. A. Mooney, R. H. Prager and J. M. Tippett, *Aust. J. Chem.* 1981, ***34***, 383–395.

2 (a) Phthalidyl-2-(3'-trifluoromethylanilino)-pyridine-3-carboxylate and process for its preparation. Br. Pat. GB *1553171*, 1979; *Chem. Abstr.* 1980, ***93***, 8024. (b) H. Torriani, *Drugs Future* **1979**, *4*, 448–450. (c) *Ann. Drug Data Rep*. 1982, ***4***, 195-196.

3 (a) P. H. Nelson, C.-L. L. Gu, A. C. Allison, E. M. Eugui and W. A. Lee, U.S. Pat. **4**,*753*,935, 1988; *Chem. Abstr.* 1988, ***109***, 149226. (b) C. Robinson and J. Castaner, *Drugs Future* 1995, ***20***, 356–361.

4 S. F. Brady, M. M. Wagenaar, M. P. Singh, J. E.; Janso and J. Clardy, *Org. Lett.* 2000, ***2***, 4043–4046.

5 K. Yoganathan, C. Rossant, S. Ng, Y. Huang, M. S. Butler and A. D. Buss, *J. Nat. Prod.* 2003, ***66***, 1116–1117.

6 A. Arnone, G. Assante, G. Nasini, S. Strada and A. Vercesi, *J. Nat. Prod.* 2002, ***65***, 48–50.

7 (a) L. Patil, H. B. Borate, D. E. Ponde and V. H. Deshpande, *Tetrahedron* 2002, ***58***, 6615–6620. (b) D. Mal and P. Pahari, *Chem. Rev.* 2007, ***107***, 1893–1918. (c) R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.* 2014, ***114***, 6213–6284.

8 (a) J. H. Park, S. V.; Bhilare and S.W. Youn, *Org. Lett.*, 2011, ***13***, 2228–223. (b) J. Mangas-Sanchez, E. Busto, V. Gotor-Fernandez and V. Gotor, *Org. Lett.*, 2012, ***14***, 1444–1447. (c) D. C. Gerbino, D. Augner, N. Slavov and H. -G. Schmalz, *Org. Lett.*, 2012, ***14***, 2338–2341.

9 M. Singh and N. P. Argade, *J. Org. Chem.* 2010, ***75***, 3121–3124.

10 L. Ackermann and J. Pospech, *Org. Lett.* 2011, ***13***, 4153–4155.

View Article Online
DOI: 10.1039/C4RA07339G
Journal Name

11 (a) D. Phan, B. Kim and V. M. Dong, *J. Am. Chem. Soc.* 2009, ***131***, 15608–15609. (b) S. Omura, T. Fukuyama, Y. Murakami, H. Okamoto and I. Ryu, *Chem. Commun.* 2009, 6741–6743. See also: (c) M. C. Willis, *Angew. Chem., Int. Ed.* 2010, ***49***, 6026–6027.

12 B. S. Bal, W. E. Jr. Childers and H. W. Pinnick, *Tetrahedron* 1981, ***37***, 2091.