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Graphical Abstract

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Pd/C-mediated synthesis of (*Z*)-3-alkylidene phthalides of potential pharmacological interest

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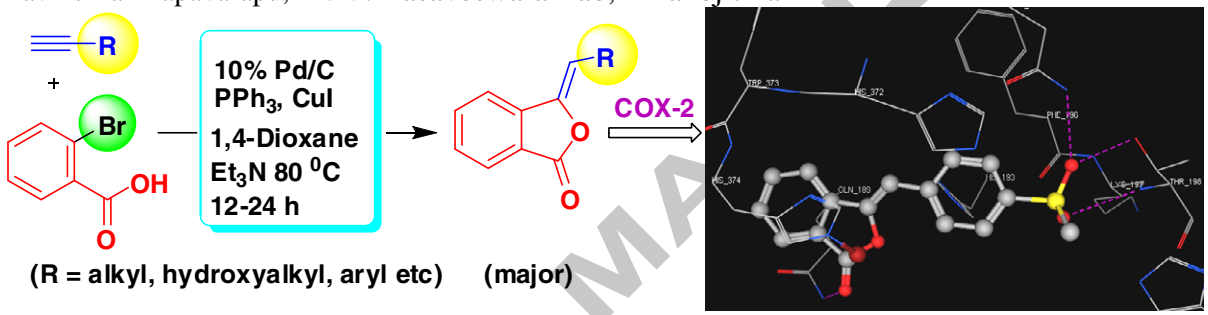

(R = alkyl, hydroxyalkyl, aryl etc) (major)

R = -$C_6H_4SO_2CH_3$

Pd/C-mediated synthesis of (*Z*)-3-alkylidenephthalides of potential pharmacological interest

D. Rambabu,[a] G. Pavan Kumar,[b] Barange Deepak Kumar,[c] Ravikumar Kapavarapu,[d] M. V. Basaveswara Rao,[e,*] Manojit Pal[a,*]

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Abstract: The coupling of *o*-bromobenzoic acid with terminal alkynes using 10%Pd/C-Et_3N-CuI-PPh_3 as a catalyst system leads to the synthesis of (*Z*)-3-alkylidenephthalides as the major product along with the traces of isocoumarin when the reaction was performed in 1,4-dioxane. The methodology afforded a range of compounds including (*Z*)-3-(4-(methylsulfonyl) benzylidene)isobenzofuran-1(3*H*)-one of potential pharmacological interest.

Keywords: Alkynes, Pd/C, coupling, 3-alkylidenephthalides.

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Phthalides (e.g. **A**, Fig 1) are an interesting class of oxygen heterocycles that possess a furan-2-(5*H*)-one framework and often found to be integral part of many natural products including

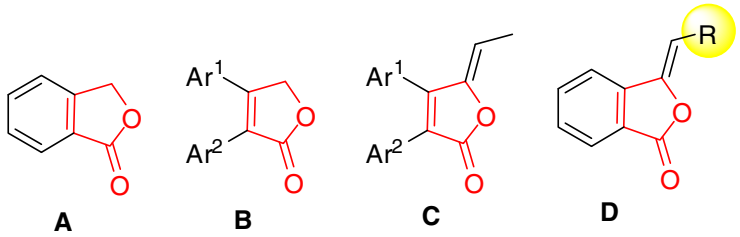
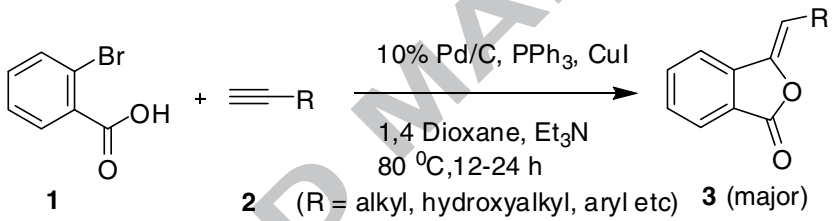


Fig. 1. Phthalide (**A**), 3,4-diarylfuran-2(5*H*)-ones (**B**), 5-alkylidenefuranone (**C**) and 3-alkylidenephthalides (**D**).

biologically active compounds.[1a] The 3,4-diarylfuran-2(5*H*)-ones (**B**, Fig 1) on the other hand have attracted particular interest in the discovery and development of anti-inflammatory agents targeting cyclooxygenase-2 (COX-2)[1b-d] e.g. rofecoxib or Vioxx® (**B**, Fig 1; when Ar^1 = $C_6H_4SO_2CH_3$-*p* & Ar^2 = C_6H_5). In pursuance of identification of furan-2-(5*H*)-one based inhibitors[2] of cyclooxygenase (COX) e.g. 5-alkylidenefuranone[2c] **C** (Fig. 1) we became interested to construct a library of small molecules based on 3-alkylidenephthalide **D** (Fig.1) for their *in vitro* evaluation against COX. We therefore required a direct and convenient synthetic route to **D**.

Among the numerous methods known for the synthesis of 3-alkylidenephthalides as major or minor products, the use of *o*-halobenzoic acids and terminal alkynes has been explored as the key starting materials.[3] All these methodologies usually consist of two separate steps: e.g. (i) a Sonogashira type reaction followed by (ii) an intramolecular cyclization mediated by metal complexes,[4–6] bases,[7] or halogens.[8] The first one-pot synthesis of 3-alkylidenephthalides following this coupling-cyclization strategy was reported by Castro[9] *et al*. way back in 1966. The methodology however involved the use of a stoichiometric amount of copper acetylide, large volume of environmentally harmful pyridine and elevated temperature. Thus, a catalytic method was developed by Kundu *et al* in 1993 which involved the use of $PdCl_2(PPh_3)_2$–CuI as a catalyst system and the methodology showed greater selectivity towards phthalides.[10] In 2007, Zhou *et al* reported the synthesis of phthalides *via* Pd/CNTs-catalyzed reaction of terminal alkynes and *o*-iodobenzoic acid under copper and ligand-free conditions.[11] Subsequently, Li *et al* reported the synthesis of phthalides *via* regioselective cyclization of *o*-alkynyl benzaldehydes in the presence of sodium chlorite under environmentally friendly oxidative conditions.[12] All these methods

generally involved the use of expensive starting material (e.g. *o*-iodobenzoic acid) or Pd-catalyst or ligands. In 2005, during our studies on the Pd/C mediated synthesis of isocoumarins[4f] we observed that the use of Pd/C-CuI-PPh_3 as a catalyst system in the presence of Et_3N in 1,4-dioxane afforded 3-alkylidenephthalides as a major product instead of isocoumarin. In continuation of that study, we have examined the coupling of commercially available and inexpensive *o*-bromobenzoic acid (in place of *o*-iodobenzoic acid) with terminal alkynes under Pd/C-Cu catalysis in 1,4-dioxane. Once again, we observed that the reaction showed better selectivity towards phthalide. This prompted us to develop a Pd/C mediated general method for the synthesis of (*Z*)-3-alkylidenephthalides. Herein, we report our preliminary results. To the best of our knowledge, a similar one-pot and regioselective synthesis of (*Z*)-3-alkylidenephthalides (**3**) from *o*-bromobenzoic acid (**1**) and terminal alkynes (**2**) under Pd/C-Cu catalysis (Scheme 1) has not been reported earlier.

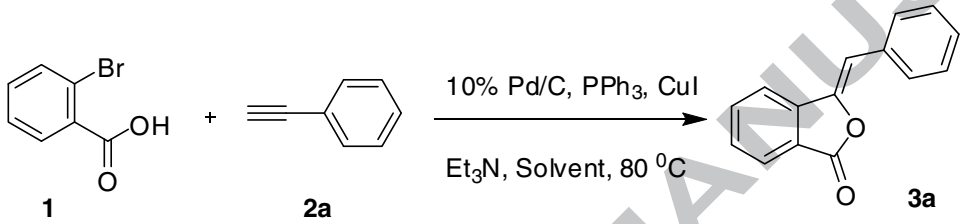


Scheme 1. Pd/C-Cu mediated synthesis of (*Z*)-3-alkylidenephthalides

To establish an optimum reaction condition for the Pd/C-Cu mediated synthesis of phthalides, we chose to examine the coupling reaction of *o*-bromobenzoic acid (**1**) with phenyl acetylene (**2a**) in the presence of 10% Pd/C (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv), and Et_3N (5 equiv) under various conditions. The results obtained are summarized in Table 1. The reaction was initially carried out in 1,4-dioxane for 12 h when the desired product i.e. (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one (**3a**) was isolated in 65% yield (entry 1, Table 1) along with a trace amount of 3-phenyl isocoumain. The increase of reaction time did not improve the product yield further (entry 2, Table 1). The reaction was performed in the presence of 0.03 equiv of 10% Pd/C. The use of lower or higher quantity of Pd/C did not improve the product yield (entries 3 and 4, Table 1) whereas its omission decreased the product yield significantly (entry 5, Table 1). The omission of CuI or PPh_3 or Et_3N also decreased the yield of **3a** (entries 6-8, Table 1). The use of other solvents such as EtOH and DMF was examined and found to afford

the corresponding isocoumarin as a major product (entries 9 and 10, Table 1). To test the recyclability of Pd/C used, the catalyst was recovered and reused for additional three runs (after completion of the first reaction the Pd/C was filtered off, washed with water, acetone and EtOAc, dried at 100 °C and reused in the next run along with fresh CuI and PPh_3 in every repeated run) when the product **3a** was isolated in 62, 59 and 55% yield respectively. Since best result for the synthesis of phthalide was achieved by using 1,4-dioxane as a solvent all the subsequent studies were carried out using this solvent.

Table 1. Effect of reaction conditions on Pd/C-mediated coupling-cyclization of *o*-bromobenzoic acid (**1**) with phenyl acetylene (**2a**).[a]



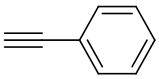
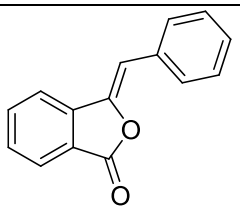
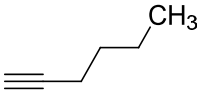
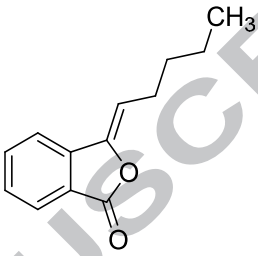
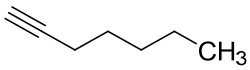
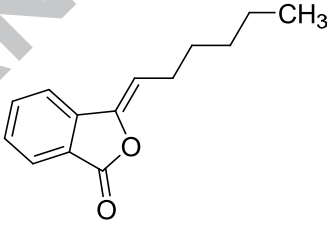
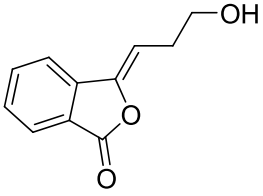
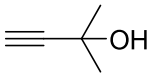
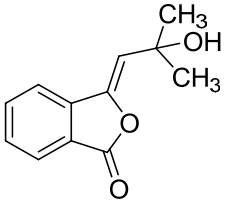
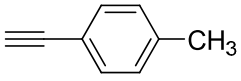
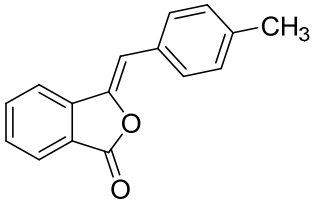
Entry	Solvent	10% Pd/C	Time (h)	%Yield[b]
1	1,4-Dioxane	0.03	12	65
2	1,4-Dioxane	0.03	24	67
3	1,4-Dioxane	0.01	12	44
4	1,4-Dioxane	0.05	12	63
5	1,4-Dioxane	--	12	29[c]
6	1,4-Dioxane	0.03	12	12[d]
7	1,4-Dioxane	0.03	12	27[e]
8	1,4-Dioxane	0.03	12	0[f]
9	EtOH	0.03	12	10[g]
10	DMF	0.03	12	11[g]

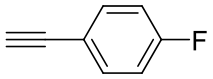
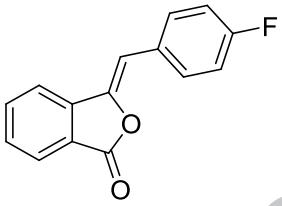
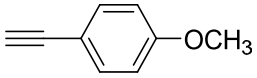
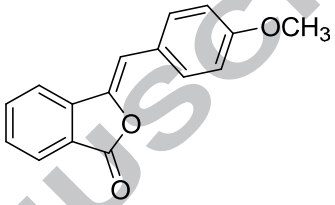
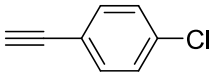
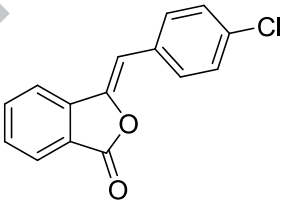
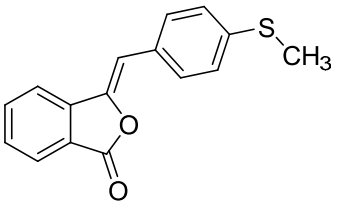
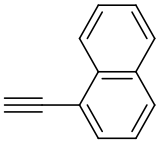
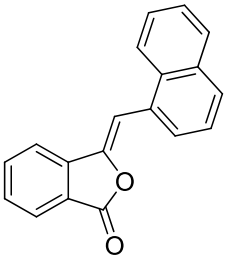
[a]All the reactions were carried out by using **1** (1.49 mmol), **2** (0.28 mmol), 10% Pd/C (0.044 mmol), PPh_3 (0.17 mmol), CuI (0.088 mmol), and Et_3N (7.45 mmol) under a nitrogen atmosphere.
[b]Isolated yields.

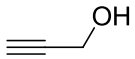
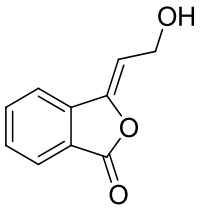
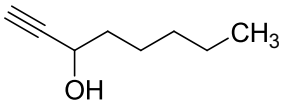
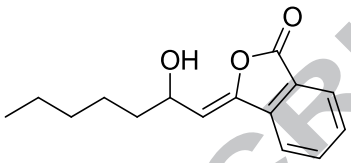
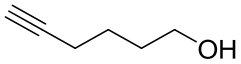
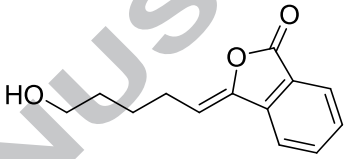
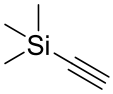
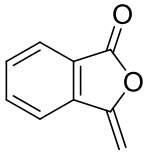
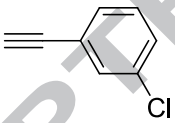
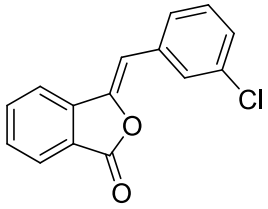
[c]The reaction was carried out without Pd/C.
[d]The reaction was carried out without CuI.
[e]The reaction was carried out without PPh_3.
[f]The reaction was carried out without Et_3N.
[g]3-Phenyl isocoumarin was isolated as a major product.

To investigate the scope and generality of the present Pd/C-Cu mediated coupling-cyclization reaction leading to phthalide, a range of commercially available terminal alkynes (**2**) were coupled with *o*-bromobenzoic acid (**1**) under the optimized reaction conditions[13a] presented in entry 1 of Table 1. The results are summarized in Table 2. A variety of phthalides containing alkylidene, hydroxyalkylidene and arylidene substituents at C-3 were prepared in moderate to good yields by using this methodology. The yields were generally good when aryl (entries 1 and 6-10, Table 2) or highly substituted alkyl acetylene (entry 5, Table 2) were employed. The other terminal alkynes except the trimethylsilyl acetylene (**2o**) provided the desired products in acceptable yields. In the case of **2o**, the product isolated was found to be a desilylated one e.g. **3o** (entry 15, Table 2) as indicated by the NMR data (Fig. 2). While phthalides were isolated as major products in all these cases, the formation 10-20% of corresponding isocoumarins was also observed depending on the nature of terminal alkynes used. The dimerization of terminal alkynes as a side reaction was also observed in some of the cases. We also tested the coupling reaction of the terminal alkyne **2a** with a highly substituted bromobenzoic acid e.g. 2,3-bis(benzyloxy)-5-bromoterephthalic acid prepared according to a similar procedure described in the literature.[13b] However, the reaction did not afford the desired phthalide[13c] and debrominated product of the bromobenzoic acid used was isolated. Notably, its iodo analogue afforded the corresponding phthalide when treated with propargyl alcohol in the presence of $(PPh_3)_4Pd$, $ZnCl_2$ and Et_3N.[13b] The use of relatively less substituted bromobenzoic acid e.g. 2-bromo-5-methoxybenzoic acid afforded the desired product i.e. (*Z*)-3-benzylidene-6-methoxyisobenzofuran-1(3*H*)-one (51% yield) on coupling with terminal alkyne **2a.** Based on the spectral data of the compounds synthesized[14] and comparing them with that reported in the literature[4a] all the compounds synthesized were found to possess the exocyclic double bond *with Z*-geometry. Thus the present approach to 3-alkylidenephthalides appears to be a regio and stereoselective process.

Table 2. Pd/C-mediated preparation of (*Z*)-3-alkylidenephthalides.[a]

Entry	Substrate **(2)**	Time (h)	Products[b] **(3)**	% yield[c]
1	 **2a**	12	 **3a**	65
2	 **2b**	20	 **3b**	66
3	 **2c**	18	 **3c**	50
4	 **2d**	22	 **3d**	55
5	 **2e**	24	 **3e**	74
6	 **2f**	12		65

			3f	
7	 **2g**	12	 **3g**	72
8	 **2h**	12	 **3h**	73
9	 **2i**	12	 **3i**	70
10	 **1j**	14	 **3j**	72
11	 **2k**	14	 **3k**	67

12	 **2l**	22	 **3l**	58
13	 **2m**	18	 **3m**	65
14	 **2n**	18	 **3n**	68
15	 **2o**	12	 **3o**	37
16	 **2p**	14	 **3p**	72

[a]All the reactions were carried out by using **1** (1.49 mmol), **2** (0.28 mmol), 10% Pd/C (0.044 mmol), PPh_3 (0.17 mmol), CuI (0.088 mmol), and Et_3N (7.45 mmol) under a nitrogen atmosphere at 80 ^oC for 12-24 h.
[b]Identified by ^{1}HNMR, IR, mass.
[c]Isolated yield.

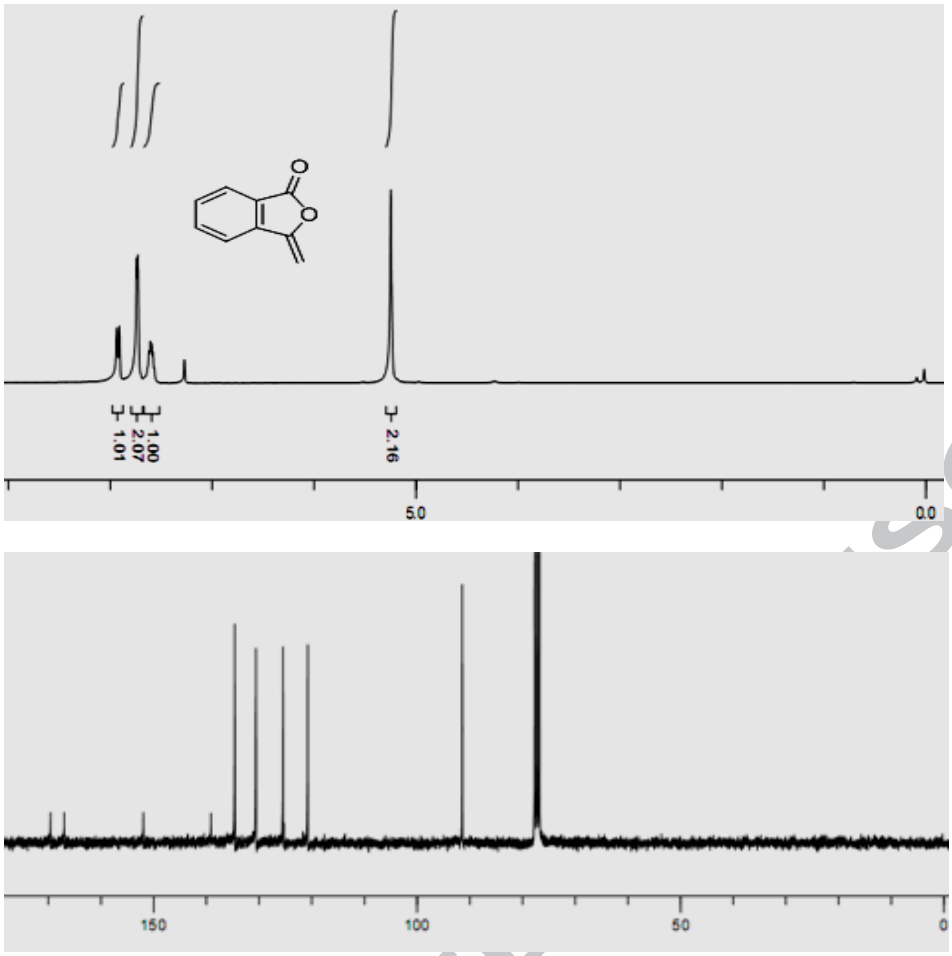
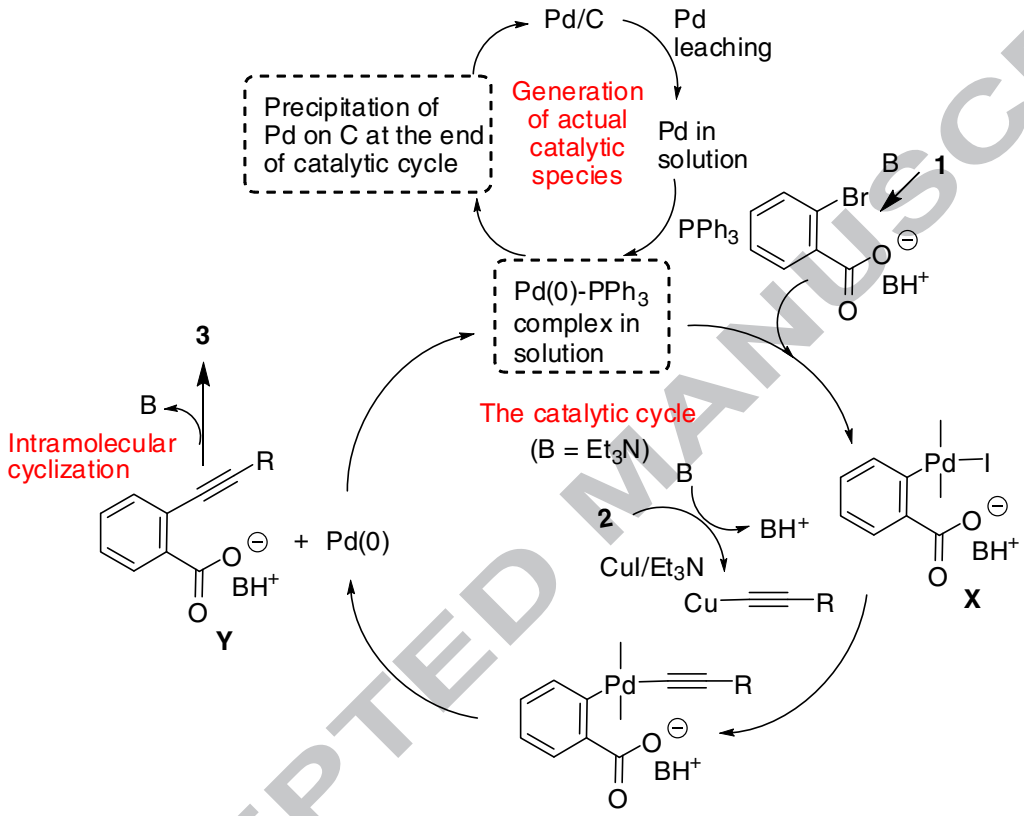


Fig. 2. ^{1}H and ^{13}CNMR spectra of compound **3o** in $CDCl_3$.

A plausible mechanism for the present Pd/C-Cu mediated synthesis of phthalides *via* coupling-cyclization strategy is shown in Scheme 2. The reaction appears to proceed *via in situ* generation of 2-(1-alknyl)benzoic acid from the coupling of *o*-bromobenzoic acid (**1**) with a terminal alkyne (**2**) in the presence of 10% Pd/C, PPh_3 and CuI, which in turn undergoes *5-endo-dig* cyclization that gives the five membered (Z)-3-alkylidenephthalides. Initially, a minor portion of the bound palladium (Pd/C) generates an active Pd(0) species via a Pd leaching process into the solution.[15] On interactions with phosphine ligands the leached Pd affords a dissolved Pd(0)–PPh_3 complex which being the active species actually catalyzes the C–C bond forming reaction in solution. It is evident that the catalytic cycle therefore works in solution rather than on the surface. An oxidative addition of the active Pd(0) species with triethylammonium salt of *o*-bromobenzoic acid **1** gives the organo-Pd(II) species **X**. The reaction then follows (i) trans organometallation of **X** with copper acetylide generated *in situ* from CuI and terminal alkyne followed by (ii)

reductive elimination of Pd(0) to give the 2-(1-alknyl)benzoic acid salt **Y** and then (iii) Et_3NH^+ (conjugate acid) mediated 5-*exo-dig* ring closure of **Y** in an intramolecular fashion[4a,7a] to give the five-membered ring product (**3**). At the end of the reaction re-precipitation of Pd occurs on the surface of the charcoal. It is worthy to note that the *6-endo-dig* cyclization leading to isocoumarin is more favored when **1** was reacted with terminal alkynes in ethanol.[4f]



Scheme 2. Probable mechanism of Pd/C-mediated synthesis of (*Z*)-3-alkylidenephthalides (**3**)

We have shown that (*Z*)-3-alkylidenephthalides can be accessed directly *via* a one-pot Pd/C-Cu mediated coupling of *o*-bromobenzoic acid with terminal alkynes in 1,4-dioxane. Some of these compounds showed biological activities[16] when tested *in vitro*[17] against the cyclooxygenase (COX) enzyme. The compound **3j** was converted to the corresponding sulfone derivative i.e. (Z)-3-(4-(methylsulfonyl)benzylidene)isobenzofuran-1(3*H*)-one (**4**) in the presence of oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in 1:2 acetone-$H_2O$ at room temperature in 87% yield. Notably, the methanesulfonyl group is usually known to confer optimal COX inhibitory activity when present at the C-4 position of an appropriate aryl ring.[18] Accordingly, the compound **4** showed 80% and

16% inhibition of COX-2 and COX-1 respectively, when tested at 10μM *in vitro* with the reference compound indomethacin showing 97 and 100% inhibiton of COX-2 & 1 at 10μM. The compound **4** also showed good interactions with COX-2 when docked into this protein *in silico* (see SI).[19] Overall, the COX inhibiting potential of the present class of phthalide has not been explored earlier and our preliminary studies indicate that 3-alkylidenephthalide can be a useful template for the identification of potential inhibitors of COX.

In conclusion, we have described Pd/C-Cu mediated general, one-pot and direct synthesis of (*Z*)-3-alkylidenephthalides *via* the coupling-cyclization reaction of *o*-bromobenzoic acid with a range of terminal alkynes under mild conditions. The scope and limitations of the methodology are presented. The methodology involved the use of readily available and relatively inexpensive starting metarial (*o*-bromobenzoic acid is cheaper than *o*-iodobenzoic acid) and catalyst [Pd/C is cheaper than $Pd(PPh_3)Cl_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$ etc.]. The methodology afforded a range of compounds including (*Z*)-3-(4-(methylsulfonyl)benzylidene)isobenzofuran-1(3*H*)-one of potential pharmacological interest. In spite of some demerits the described methodology permits an easy access to 3-alkylidenephthalides for synthetic and medicinal uses. Further application of this methodology for the synthesis of more complex molecules is under active investigation.

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13. (a) General procedure for the preparation of compound **3**: A mixture of **1** (1.49 mmol), 10% Pd/C (0.044 mmol), PPh_3 (0.17 mmol), CuI (0.088 mmol), and Et_3N (7.45 mmol) in 1,4-dioxane (5 mL) was stirred at 25 ^oC for 30 min under nitrogen atmosphere. The acetylenic compound **2** (0.28 mmol) was added slowly with stirring. The mixture was then stirred at 80 ^oC for 12-24 h. The mixture was then cooled to room temperature, diluted with ethylacetate (20 mL), and filtered through Celite. The filtrate was collected and concentrated. The residue was purified by column chromatography (petroleum ether/ ethylacetate) to afford the desired product. (b) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567. (c) We thank one of the reviewers for raising this concern.

14. Spectral data of selected compounds: (*Z*)-3-pentylideneisobenzofuran-1(3*H*)-one (**3b**)**:** ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.49 (4H, m), 5.63 (1H, t, *J* = 8.0 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 1.52-1.50 (2H, m), 1.42-1.40 (2H, m), 0.93 (3H, t); IR (KBr) ν_{max} 1716, 1656, 1055 cm^{-1}; EI-MS: m/z 203 (M+1, 100%); (*Z*)-3-hexylideneisobenzofuran-1(3*H*)-one (**3c**)**:** ^1H NMR (400 MHz, $CDCl_3$): δ 7.88–7.45 (4H, m), 5.64 (1H, t, *J* = 8.0 Hz), 2.47 (2H, q), 1.37-1.35 (2H, m), 1.34–1.30 (4H, m), 0.90 (3H, t); IR (KBr) ν_{max} 1717, 1656, 1050 cm^{-1}; EI-MS: m/z 216.9 (M+1, 100%); (*Z*)-3-(3-hydroxypropylidene) isobenzofuran -1(3*H*)-one (**3d**)**:** ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* = 7.6 Hz), 7.66–7.60 (1H, m), 7.57–7.50 (1H, m), 7.45–7.40 (1H, m), 7.30 (1H, d, *J* = 8.0 Hz), 6.36 (1H, s), 3.71 (2H, t, *J* = 6.4 Hz), 2.50 (2H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 154.7, 137.2, 134.3, 129.3, 128.5, 127.6, 125.0, 104.7, 66.5, 23.4; IR (KBr) ν_{max} 3395,

2922, 1717, 1655, 1050 cm^{-1}; EI-MS: m/z 190.9 (M+1, 100%); 3-(2-Hydroxy-heptylidene)-3*H*-isobenzofuran-1-one (**3m**)**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* =7.6 Hz), 7.71–7.65 (2H, m), 7.55–7.52 (1H, m), 5.62 (1H, d, *J* = 8.3 Hz), 4.90-4.88 (1H, m), 1.92 (1H, br), 1.73–1.69 (2H, m), 1.62–1.58 (2H, m), 1.33–1.30 (4H, m), 0.86 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 145.3, 139.0, 134.4, 130.1, 125.2, 124.2, 120.1, 110.7, 66.8, 37.1, 31.5, 24.8, 22.4, 14.0; IR (KBr) ν_{max} 3415, 3055, 2930, 1787, 1685, 1470, 1275 cm^{-1}; EI-MS: m/z 247.0 (M+1, 100%); 3-(5-Hydroxy-pentylidene)-3*H*-isobenzofuran-1-one (**3n**)**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* = 7.7 Hz), 7.66–7.61 (1H, m), 7.43–7.41 (1H, m), 7.32 (1H, d, *J* = 7.6 Hz), 6.26 (1H, s), 3.64 (2H, t, *J* = 6.0 Hz), 2.83 (2H, t, *J* = 7.2 Hz), 1.67–1.56 (4H, m); ^{13}CNMR (100 MHz,$CDCl_3$): δ 164.0, 151.5, 137.4, 134.0, 129.3, 128.6, 127.8, 125.2, 103.6, 66.4, 34.0, 26.5, 23.0; IR (KBr) ν_{max} 3433, 2927, 1717, 1652, 1203, 1050 cm^{-1}; EI-MS: m/z 218.9 (M+1, 100%). 3-methylene-3*H*-isobenzofuran-1-one (**3o**)**:** ^{1}HNMR (400MHz, $CDCl_3$): δ 7.92 (1H, d, *J* = 8.0 Hz), 7.72 (2H, d, *J* = 4.0 Hz), 7.62-7.57 (m, 1H), 5.24 (2H, dd, *J* = 3.0, 6.2 Hz,); ^{13}CNMR(100MHz, $CDCl_3$): δ 166.8, 151.8, 139.0, 134.4, 130.4, 125.2, 125.1, 120.6, 91.2; IR (KBr) ν_{max} 2925, 1784, 1735, 1663, 1474, 1272, 1007, 955 cm^{-1}; EI-MS: m/z 147 (M+1, 100%).

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19. **The docking procedure**: The molecular docking simulation was performed with Chemical Computing Group's Molecular Operating Environment (MOE) software 2008.10 Version, "DOCK" application Module. The COX-2 protein (PDB code3LN1)

used as the receptor for docking studies was retrieved from PDB and protonated (addition of H atoms) with protonation 3D application in MOE. Connolly Molecular surface was generated around the ligand site of the protein, Gasteiger Partial charges was added to the protein and finally the energy was minimized to relieve bad crystallographic contacts. "Active site finder" function of the MOE software was used to denote potential docking pockets within the protein crystal structure. The compound **4** was placed in the active site pocket of the protein by the "Triangle Matcher" Method, which generates poses by aligning the ligand triplet of atoms with the triplet of alpha spheres in cavities of tight atomic packing and Dock scoring was done with London dG method and then finally retaining and scoring the best 10 poses of the molecule. The preparation of the Ligands for Docking Simulation involved the Energy minimization with Molecular Mechanics Force-field MMFF94x (Merck Molecular Force Field 94×) and then the molecule was subjected to conformational search in MOE using the Conformations Stochastic search module to find the lowest energy conformers.