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A new synthesis of 2-aryl/alkylbenzofurans by visible light stimulated intermolecular Sonogashira coupling and cyclization reaction in water

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ABSTRACT

A visible light induced rapid one pot intermolecular Sonogashira coupling and 5-*endo*-dig cyclization in water of *ortho*-halophenols and terminal alkynes catalyzed by [Pd] have been developed to furnish 2-aryl/alkyl benzofurans in good yields *sans* Ru or Ir complexes or any other additives.

2-Arylbenzofurans are important naturally occurring oxygen heterocycles known for their various biological activities[1] and a number of benzofuran core units containing natural products are available in nature.[2] For example, pterofuran,[3] isopterofuran,[4] vignafuran,[5] 6-demethylvignafuran[6] and so forth are of interest, as several have been recognized as antifungal phytoalexins. Hence, these molecules, for a long time, are attractive target for the synthesis by organic chemists and various methodologies[7] have been developed ever since the synthesis of 2-phenylbenzofuran was first reported by Dilthey and Quint[8] in 1931 and later on by Yates[9] in 1952.

Palladium catalyzed Sonogashira reaction[10] of terminal alkynes and 2-iodo/bromo phenols followed by cyclization reaction has later become a popular strategy for the synthesis of 2-alkyl/arylbenzofurans. A variety of reaction conditions have been used for this purpose, such as, $Pd(PPh_3)_2Cl_2$/CuI in THF,[11] $Pd(PPh_3)_2Cl_2$/CuI in Et_3N,[12] $FeCl_3$ in toluene under refluxing condition,[13] $Pd(PPh_3)_2Cl_2$/CuI in DMF,[14] and also from 2-chlorophenol.[15]

On the other hand, palladium catalyzed Sonogashira reactions in water[16] under thermal condition or under UV light[17] and by using a Ru/bipyridine complex as energy transfer agent under visible light[18] have been reported. Application of this reaction for the synthesis of substituted benzofurans is also available in the literature.[19] However, most of these reactions need prolonged reaction time or phase transfer catalyst, or external additives.

Sunlight is clean, abundantly available, and most importantly, environmentally friendly in all respects. In overall solar spectrum visible light (390–750 nm) accounts for 43%. As such, any natural reaction *in vivo* efficiently utilizes solar energy and converts it into chemical energy. As many organic compounds do not absorb visible light efficiently, visible-light photoredox catalysts such as ruthenium or iridium polypyridyl complexes have been employed to propel energy from visible light into organic molecules for C–C bond-formation.[20–22] Moreover, the use of light accelerates certain reactions in organic synthesis. Such photochemical activation of substrate without additional reagents very often minimizes the formation of byproducts; and for this reason, photochemical reactions occupy an interesting position in the realm of green chemistry. These concepts have been successfully employed in many organic syntheses employing visible light or sunlight or UV light, for example, Suzuki–Miyaura and Stille-type coupling reactions,[23] Nazarov cyclization,[24] Wittig reaction,[25,26] Heck reaction[27] etc. and excellent reviews[28,29] on photochemical reactions have been published.

We have been carrying out the synthesis of benzofurans[30,31] for over a period of time and recently, we have reported an efficient methodology for the synthesis of title compounds by intramolecular photochemical Wittig reaction,[26a] (Eq. 1, Fig. 1). Our enduring interest in this arena has led us to devise a visible light induced palladium catalyzed, copper-free Sonogashira reaction in water for the synthesis of 2-aryl/alkylbenzofurans in an environmentally friendly condition (Eq. 2, Fig. 1).

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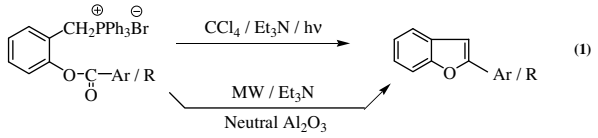
Previous work:



This study:

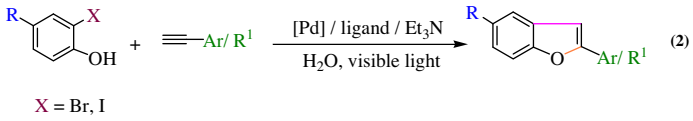
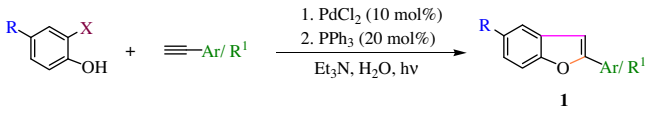


Figure 1. Visible light catalyzed synthesis of 2-aryl/alkyl benzofurans.



a : R = H, X = I/Br, Ar = C_6H_5 **b :** R = CH_3, X = Br, Ar = C_6H_5

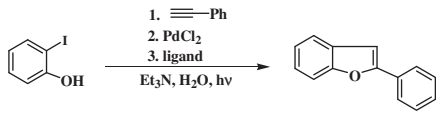
c : R = Cl, X = Br, Ar = C_6H_5 **d :** R = H, X = I, Ar = (*p*-OCH_3)C_6H_5

e : R = CH_3, X = Br, Ar = (*p*-OCH_3)C_6H_5 **f :** R = Cl, X = Br, Ar = (*p*-OCH_3)C_6H_5

g : R = H, X = I, Ar = (*p*-Cl)C_6H_5 **h :** R = Cl, X = Br, R^1 = C_6H_{13}

Scheme 1. Visible light catalyzed Sonogashira coupling and cyclization reaction of *ortho*-halophenols and terminal alkynes in water.

Table 1
Optimization of reaction condition



Entry	$PdCl_2$ (mol %)	Ligand (mol %)	Time (min)	Yield[a] (%)
1	2	PPh_3, 5	60	9
2	2	PPh_3, 5	60	12
3	5	PPh_3, 10	120	33
4	10	PPh_3, 20	60	43
5	10	PPh_3, 20	90	54
6	**10**	**PPh_3, 20**	**105**	**63**
7	10	PPh_3, 20	120	62
8	10	[b]dba, 20	105	0
9	10	[b]opd, 20	105	0

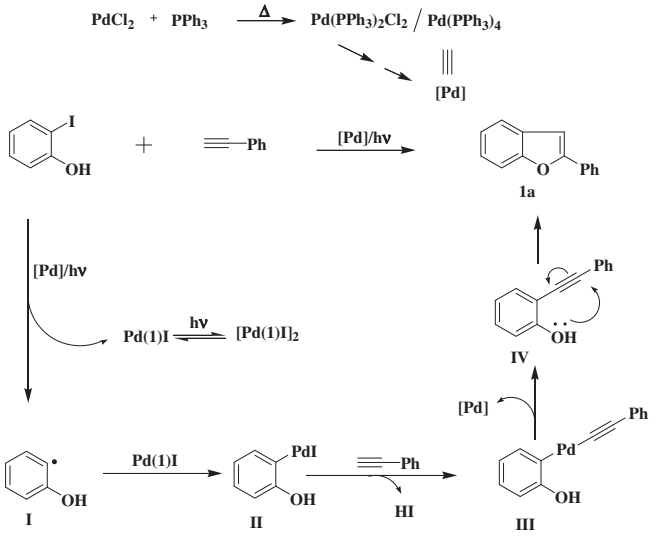
Bold value indicates the optimized condition for reaction.
[a] Isolated yield after column chromatographic separation over silica gel.
[b] dba: Dibenzylidene acetone; opd: *ortho*-phenylenediamine.

The present procedure for the synthesis of 2-substituted benzofurans (1) consists of photo-irradiation of substituted *ortho*-iodo/bromophenols and terminal alkynes in the presence of palladium chloride, triphenyl phosphine and triethyl amine in water and after subsequent work-up, the products are obtained in reasonably good yields (49–77%) by chromatography over silica gel in a highly pure state. The reaction proceeds through two consecutive steps: the Sonogashira coupling reaction mediated by $PdCl_2$ and PPh_3 as a ligand, followed by 5-*endo*-dig cyclization to give the products (Scheme 1).

In order to optimize the reaction condition, we carried out the reaction under visible light by varying the amount of $PdCl_2$, ligand, base and also the reaction time using *ortho*-iodophenol and phenyl acetylene (Table 1). For example, when dibenzylidene acetone or *ortho*-phenylenediamine was used as a ligand in place of triphenylphosphine at various mole percent (mol %), the reaction failed to produce benzofuran. Addition of cuprous chloride as a co-catalyst also did not improve the yield of the product and 1,4-diphenyl-but-1,3-diyne was obtained by coupling of phenyl acetylene itself. The optimum reaction condition requires the use of palladium chloride (10 mol %) and triphenylphosphine (20 mol %) in conjunction with triethylamine (4 mmol) for *ortho*-iodophenol and phenyl acetylene each 1 mmol (Table 1, entry 6). It is presumed that triethyl amine (in excess) acts not only as a base but also as a co-solvent to help the organic substrates to disperse in water.

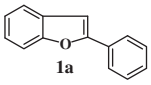
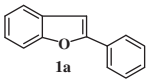
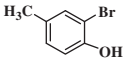
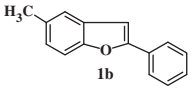
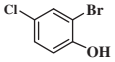
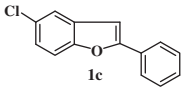
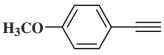
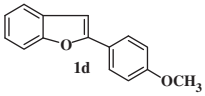
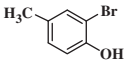
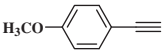
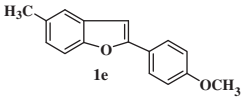
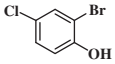
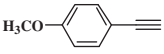
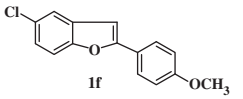
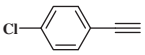
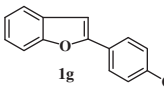
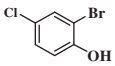
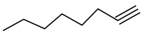
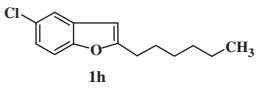
These experimental observations indicate that the catalytic amount of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ is generated in the reaction mixture when PPh_3 and $PdCl_2$ are preheated at the beginning. Once Sonogashira process commences, the reaction may proceed through Pd(0) via a radical path under light (Scheme 2), thereby shortening the reaction time. Mechanistically, it may be proposed that in the first step, *ortho*-iodophenol reacts with Pd(0) under photo irradiation to afford aryl radical (**I**) and Pd(1)I via one electron transfer[32] that further couples with Pd(1)I to give aryl palladium intermediate (**II**); and gives the coupling product (**IV**) through an intermediate (**III**). In this pathway, a rather unfamiliar Pd(1)I-type species may be involved that may exist in equilibrium with PdI dimer[17,33] under photochemical condition.[34] Finally the intramolecular cyclization of **IV** gives 2-phenylbenzofuran (**1a**).

When this optimized reaction condition was applied to substituted *ortho*-iodo/bromophenols and different terminal aliphatic



Scheme 2. Plausible mechanism for the synthesis of 2-aryl/alkylbenzofurans.

Table 2
Results of visible light catalyzed Sonogashira coupling and cyclization reaction of *ortho*-halophenols and terminal alkynes

Entry	Halophenol	Alkyne	2-Aryl/alkylbenzofurans[a]	Yield[b] (%)
1			 **1a**	63
2			 **1a**	57
3			 **1b**	49
4			 **1c**	63
5			 **1d**	71
6			 **1e**	53
7			 **1f**	58
8			 **1g**	51
9			 **1h**	77

[a] All products were characterized by their satisfactory spectral data and also by comparison with the literature data (vide Supplementary data).
[b] Yield refers to combined amounts of first and second crops of crystallized products obtained after chromatography (for 1 h: only chromatographically separated yield as it is liquid).

or aromatic alkynes, 2-substituted benzofurans were formed in very good yield (Table 2) and the reaction smoothly occurred in both cases.

In conclusion, we have developed a rapid, visible light induced one pot two reactions (Sonogashira and 5-*endo*-dig cyclization) for the synthesis of 2-alkyl/arylbenzofurans in an environmentally friendly nature's solvent like water. The present methodology[35] is an improvement over existing ones in terms of efficiency and time of reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.078.

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35. Method: Palladium chloride (17.7 mg, 10 mol %), triphenylphosphine (52.4 mg, 20 mol %) distilled water (25 mL) were taken in an Erlenmeyer flask and heated on water bath for 10 min followed by cooling at room temperature. Afterwards, 2-halophenols and terminal alkynes were added followed by addition of triethylamine (400 mg, 4 mmol). The reaction mixture was irradiated with a 150 W tungsten lamp (Philips India Ltd) for 1 h and 45 min. After the reaction was complete (monitored by TLC), the product was isolated, by Et_2O (20 mL) and purified by column chromatography on silica gel (2% ethyl acetate in light petrol, 60–80 °C) and crystallized further from appropriate solvents. 2-(*n*-Hexyl)-5-chloro-benzofuran (1 h): Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, 22 °C) δ 7.43 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.15 (dd, J = 8.8, 2.0, 2.5 Hz, 1H), 6.32, (s, 1H), 2.75 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.32 (m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 22 °C) δ 161.5, 153.1, 130.5, 128.2, 123.2, 119.9, 111.7, 101.6, 31.6, 29.0, 28.6, 27.6, 22.7, 14.1 ppm. HRMS (ESI) m/z $[M+H]^+$, calcd. for $C_{14}H_{17}ClO$ 237.1047; found 237.2703.