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Research Article

An Expedient Protocol to the Synthesis of Benzo(b)furans by Palladium Induced Heterocyclization of Corresponding 2-Allylphenols Containing Electron Rich and Electron Capturing Substituents in the Arene Ring

Kiran Rao, Ruchi Tyagi, Navjeet Kaur, and D. Kishore

Department of Chemistry, Banasthali University, Banasthali 304022, India

Correspondence should be addressed to Navjeet Kaur; nvjithaans@gmail.com

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A facile and rapid accessibility to the libraries containing several mono, and disubstituted benzo(b)furan derivatives substituted with a variety of electron rich and electron capturing groups on 2, 4, 5, 6, and 7 positions of its nucleus has been explored using the $PdCl_2(CH_3CN)_2$ catalyzed heterocyclization of the corresponding 2-allylphenols to afford **2(a–m)** in good yield and high purity.

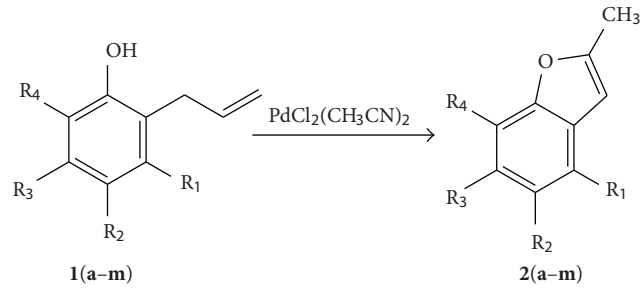
1. Introduction

The development of methods of general applicability empowered with the capacity to provide high yield of the target molecules is a crucial step in the synthesis of molecular libraries of potentially useful medicinal agents [1–3]. Ever since, Koch et al. [4] carried out a quantitative analysis of physiologically active natural product scaffolds and showed that ones with two or three rings were most often found in active natural products; the interest in the various facet of the chemistry of small molecules has expanded exponentially thereafter.

Natural products continue to be a very important source in the discovery of newer drugs and newer physiologically active materials [5]. On account of benzo(b)-furan ring system featuring in a large number of naturally occurring biologically active scaffolds [6] and in potentially useful pharmaceutical formulations, this nucleus has been recognized as a "*privileged structure*" in the design and the development of molecular probes for biological evaluations. For example, a number of benzo(b)furan derivatives have been investigated for their application as estrogen receptor (ER) ligands [7], H_3 receptor antagonists selective ligands for the dopamine D_3 receptor [8], and metalloproteinase-13-inhibitors

In addition, some 2-pyridinone derivatives of benzo(b)-furans have been identified [9] to be potent and selective nonnucleoside inhibitors of HIV-1 reverse transcriptase [10]. Another derivative namely; 2-[4-(benzofuran-2-yl)carbonyl]-piperazin-1-yl-3-propyl pyridine [11], has been demonstrated to be endowed with good anti-HIV activity. Their seemingly limitless structural features coupled with their novel biological applications [12] have provided enormous inspiration for the development of new reactions and new methodologies for their synthesis. Most of the approaches for the formation of furan ring from arene derivatives involved the dehydration of o-hydroxybenzyl ketones under acidic conditions [13], base mediated decarboxylation of o-acylphenoxyacetic acids or esters [14], cyclofragmentation of oxiranes [15] (available from the corresponding o-hydroxybenzophenones), dehydrative cyclization of phenoxyalkyl ketones [16], palladium(II) catalyzed cyclization of aryl acetylenes [17], o-alkenyl or o-alkynyl phenols [18, 19], or deprotection of benzyl ethers under basic conditions [20]. However, most of these methods require strong acidic or basic conditions, which make them less applicable to the

substrates containing acid and base sensitive groups. Coupled with this, most often they require such materials which are not easily accessible. Consideration of these factors has led the heterocyclization of 2-allylphenols with organopalladium reagent to emerge as a most valid and acceptable alternative to other known methods, in providing a facile one pot synthesis of benzo(b)furan derivatives under mild conditions [18]. As 2-allylphenols can be prepared easily by the Claisen rearrangement of the corresponding allylphenyl ethers [21], the palladium induced heterocyclisation of these provides a method of general applicability to the benzo(b)furan synthesis. Though the scope and utility of this methodology has been demonstrated [18] earlier in synthesis but its versatility to the synthesis of benzo(b)furan derivatives containing a wide array of electron releasing and electron-withdrawing substituents in the arene ring has not been fully explored (see Scheme 1).



1(a–m) **2(a–m)**

Scheme 1: R_1, R_2, R_3, and R_4=H, Br, Cl, Me, NO_2, OMe, COOMe, COOEt, CHO represent arene ring substituents.

2. Experimental

All the melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 infrared. ^{1}H-NMR spectra were recorded in $CDCl_3$ (DMSO-d_6) on model **AC-300F (Brucker)** spectrophotometer. The mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. Microanalytical results were obtained from NCL Pune (India). The reactions were monitored by TLC on silica gel G plates and the spots were detected by exposing the plates to UV radiations at 254 nm.

The 2-allylphenols [22] were prepared from the Claisen rearrangement of the corresponding allylphenyl ethers. Substituted phenols required in the synthesis were obtained from commercial sources.

2.1. Preparation of Dichlorobis(acetonitrile)palladium(II) Complex. Anhydrous palladium(II) chloride was suspended in dry acetonitrile and the resulting dark brown slurry was stirred for 12 h at 25°C, which produced an orange slurry. Filteration followed by drying gave virtually a quantitative yield of the complex.

2.1.1. Stoichiometric Cyclization: General Procedure. Preparation of 5-Bromo-2-methyl Benzo(b)furan (2a). The $PdCl_2(CH_3CN)_2$ (260 mg, 1 mmol, 1 equiv.) was placed in a 100 mL two necked flask fitted with a stopcock, stir bar, and serum cap. The flask was flushed with nitrogen and a constant pressure of nitrogen was maintained throughout the reaction. THF (15 mL) was added to the complex via syringe and allowed to stir for 5–10 min. 2-Allyl-4-bromophenol (1a) (213 mg, 1 mmol, 1 equiv.) was taken in THF (5.0 mL) and added to the slurry of complex via a syringe. The mixture was stirred for 1.5–2 h. Et_3N (100 μL.) with syringe was added to this solution. After stirring for an additional 1.0 h, a second equivalent of 100 μL. of Et_3N was added. Finally, a third equivalent of 100 μL. Et_3N was added after further 1 h stirring. The mixture was then allowed to stir for 2 h and then filtered. The resulting solution was concentrated on a rotatory evaporator. The product was purified by recrystallization with hexane to give 5-bromo-2-methylbenzo(b)furan **(2a)**. Similarly other benzo(b)furans **2(b–m)** were prepared.

2.1.2. Catalytic Cyclization. The yields of the substituted benzo(b)furans were found to be lower in case of stoichiometric cyclization and moreover, it required one mole equivalent (the stoichiometric amount) of fairly expensive palladium chloride reagent. Thus, the Pd induced cyclisation of 2-allyl phenols was carried out under catalytic conditions, which gave acceptable yields of the products.

Preparation of 5-Bromo-2-methyl Benzo(b)furan (2a). General procedure. In a 100 mL two necked flask fitted with a stopcock, serum cap and stir bar were placed $PdCl_2(CH_3CN)_2$ (25 mg, 0.01 mmol), p-benzoquinone (108 mg, 1 mmol), and LiCl (420 mg, 10 mmol). The flask was flushed with nitrogen and a constant pressure of nitrogen was maintained throughout the reaction. THF (15 mL) was then added and the mixture was stirred for 3–5 min. The 2-allyl-4-bromophenol, **(1a)** (213 mg, 1 mmol) in THF (5.0 mL) was added to the flask via a syringe and the solution was refluxed for 18 h. The THF was removed on rotatory evaporator and the residue was taken up in ether (25 mL) and stirred for 20 min with a small amount of decolorizing carbon. The product was purified by recrystallization from hexane to give 5-bromo-2-methyl benzofuran **(2a)**. Similarly other benzofurans 2(b-m) were prepared. Reaction conditions **2(a–m)** obtained under stoichiometric and catalytic conditions are summarized in Table 1.

5-Bromo-2-methyl Benzofuran (2a). Yield 76%, m.p. 502°C, IR (KBr) cm^{-1}: 3015, 2922, 1625, 1287, 590; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.66 [1H, s], 7.36 [1H, J = 7.8 Hz, d], 7.31 [1H, J = 7.7 Hz, d], 6.24 [1H, s], 2.16 [3H, s]; MS: m/z: 211 [M$^+$], analysis: Calcd./found for C_9H_7OBr: C, 51.19/51.38; H, 3.34/3.32.

7-Bromo-2-methyl Benzofuran (2b). Yield 74%, b.p. 553°C, IR (KBr) cm^{-1}: 3010, 2925, 1637, 1273, 585; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.43 [1H, J = 8.0 Hz, d], 7.36 [1H, J = 7.8 Hz, d], 7.02 [1H, J = 7.5 Hz, t], 6.28 [1H, s], 2.14 [3H, s]; MS: m/z: 211 [M$^+$], analysis: Calcd./found for C_9H_7OBr: C, 51.19/51.35; H, 3.34/3.32.

Table 1: Reactions' conditions[a] used for the Pd(II) induced cyclisation of the 2-allylphenols to benzo(b) furans.

	Stoichiometric cyclization (A)	Catalytic cyclization (B)
$PdCl_2(CH_3CN)$	1.0 equiv.	0.1 equiv.
Triethylamine	3.0 equiv.	—
Benzoquinone	—	1.0 equiv.
Lithium chloride	—	1.0 equiv.
Solvent	THF	THF

[a] The reactions were run in THF at 0.05 M.

5-Chloro-2-methyl Benzofuran (2c). Yield 69%, m.p. 473°C, IR (KBr) cm^{-1}: 3017, 2920, 1628, 1281, 738; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.50 [1H, s], 7.38 [1H, J = 7.9 Hz, d], 7.20 [1H, J = 7.7 Hz, d], 6.21 [1H, s], 2.16 [3H, s]; MS: m/z: 166 [M^+]; 168 [M^++2], analysis: Calcd./found for C_9H_7OCl: C, 64.80/64.59; H, 4.23/4.25.

2,5-Dimethyl Benzofuran (2d). Yield 71%, m.p. 42°C, IR (KBr) cm^{-1}: 3014, 2918, 1624, 1284, 2955; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 [1H, J = 7.7 Hz, d], 7.26 [1H, s], 6.72 [1H, J = 7.6 Hz, d], 6.18 [1H, s], 2.32 [3H, s], 2.15 [3H, s]; MS: m/z: 146 [M^+], analysis: Calcd./found for $C_{10}H_{10}O$: C, 82.15/82.31; H, 6.90/6.88.

2-Methyl-5-nitro Benzofuran (2e). Yield 58%, m.p. 102°C, IR (KBr) cm^{-1}: 3022, 2915, 1630, 1280, 1360; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.42 [1H, s], 8.12 [1H, J = 8.4 Hz, d], 7.68 [1H, J = 8.1 Hz, d], 6.17 [1H, s], 2.17 [3H, s]; MS: m/z: 177 [M^+], analysis: Calcd./found for $C_9H_7O_3N$: C, 60.99/61.12; H, 3.98/4.00.

2,4-Dimethyl Benzofuran (2f). Yield 78%, m.p. 102°C, IR (KBr) cm^{-1}: 3020, 2936, 1625, 1274; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.23 [1H, J = 7.7 Hz, d], 7.09 [1H, J = 7.2 Hz, t], 6.94 [1H, J = 7.6 Hz, d], 6.21 [1H, s], 2.31 [3H, s], 2.11 [3H, s]; MS: m/z: 146 [M^+], analysis: Calcd./found for $C_{10}H_{10}O$: C, 82.15/82.31; H, 6.90/6.92.

2,7-Dimethyl Benzofuran (2g). Yield 74%, m.p. 42°C, IR (KBr) cm^{-1}: 3011, 2922, 1635, 1272, 2952; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29 [1H, J = 7.8 Hz, d], 7.04 [1H, J = 7.5 Hz, t], 6.86 [1H, J = 7.6 Hz, d], 6.19 [1H, s], 2.29 [3H, s], 2.13 [3H, s]; MS: m/z: 146 [M^+], analysis: Calcd./found for $C_{10}H_{10}O$: C, 82.15/82.31; H, 6.90/6.87.

7-Methoxy-2-methyl Benzofuran (2h). Yield 73%, m.p. 42°C, IR (KBr) cm^{-1}: 3017, 2922, 1631, 1265, 1271, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.08 [1H, J = 7.8 Hz, d], 7.03 [1H, J = 7.3 Hz, t], 6.71 [1H, J = 7.7 Hz, d], 6.14 [1H, s], 3.62 [3H, s], 2.11 [3H, s]; MS: m/z: 162 [M^+], analysis: Calcd./found for $C_{10}H_{10}O_2$: C, 74.16/74.34; H, 6.21/6.23.

Ethyl-2-methylbenzofuran-7-carboxylate (2i). Yield 74%, m.p. 65°C, IR (KBr) cm^{-1}: 3015, 2930, 1640, 1270, 1680, 1168, 1252, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.90 [1H, J = 8.2 Hz, d], 7.69 [1H, J = 8.0 Hz, d], 7.21 [1H, J=7.4 Hz, t], 6.21 [1H, s], 4.25 [2H, s], 1.21 [3H, s], 2.16 [3H, s]; MS: m/z: 204 [M^+], analysis: Calcd./found for $C_{12}H_{12}O_3$: C, 70.57/70.78; H, 5.92/5.94.

Methyl-2-methylbenzofuran-7-carboxylate (2j). Yield 74%, m.p. 107°C, IR (KBr) cm^{-1}: 3020, 2918, 1629, 1261, 1685, 1168, 1252, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 [1H, J = 7.9 Hz, d], 7.65 [1H, J = 7.7 Hz, d], 7.24 [1H, J = 7.1 Hz, t], 6.26 [1H, s], 3.71 [3H, s], 2.10 [3H, s]; MS: m/z: 190, analysis: Calcd./found for $C_{11}H_{10}O_3$: C, 69.44/69.65; H, 5.30/5.32.

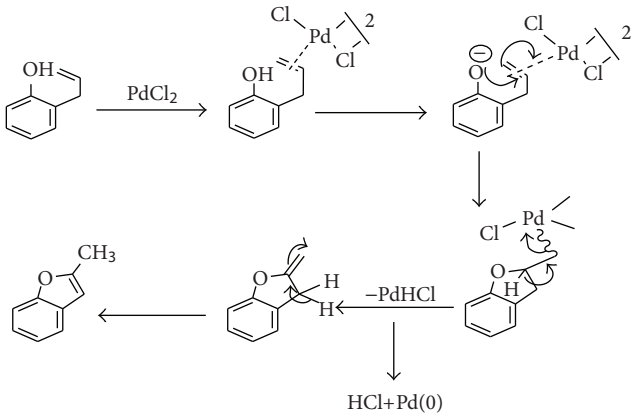
2-Methylbenzofuran-7-carbaldehyde (2k). Yield 72%, m.p. 96°C, IR (KBr) cm^{-1}: 3018, 2920, 1635, 1263, 1710; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.71 [1H, s], 7.71 [1H, J = 7.9 Hz, d], 7.68 [1H, J = 7.8 Hz, d], 7.31 [1H, J = 7.2 Hz, t], 6.21 [1H, s], 2.18 [3H, s]; MS: m/z: 160 [M^+], analysis: Calcd./found for $C_{10}H_8O_2$: C, 74.97/74.73; H, 5.26/5.24.

2,5,7-Trimethyl Benzofuran (2l). Yield 71%, m.p. 190°C, IR (KBr) cm^{-1}: 3010, 2915, 1638, 1270, 2950; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.09 [1H, s], 6.75 [1H, s], 6.24 [1H, s], 2.26 [3H, s], 2.24 [3H, s], 2.15 [3H, s]; MS: m/z: 160 [M^+], Analysis: Calcd./found for $C_{11}H_{12}O$: C, 82.45/82.71; H, 7.55/7.57.

4,6-Dibromo-2-methyl Benzofuran (2m). Yield 66%, m.p. 66°C, IR (KBr) cm^{-1}: 3022, 2925, 1630, 1265, 5950; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.51 [1H, s], 7.47 [1H, s], 6.24 [1H, s], 2.14 [3H, s]; MS: m/z: 289 [M^+], Analysis: Calcd./found for $C_9H_6OBr_2$: C, 77.25/77.44; H, 2.33/2.35.

3. Results and Discussion

The applicability of the palladium induced cyclization procedure to the synthesis of benzo(b)furan derivatives from the corresponding 2-allylphenols has been examined in the present work via stoichiometric as well as catalytic cyclization routes. In the stoichiometric cyclization, 2-allylphenol is believed to interact with dichlorobis(benzonitrile)palladium(II) in presence of Et_3N to form the crude benzo(b)furan derivatives. It has been reported that the treatment of 2-allylphenol with Pd on charcoal at 500–800°C gives 2-methylbenzofuran. Compared to this, the present method which used the palladium induced heterocyclization of 2-allylphenols provided a very convenient synthetic entry to 2-substituted benzo(b)furans. The mechanism of formation of 2-substituted benzo(b)furans from the corresponding 2-allylphenols is outlined in Scheme 2 which is believed to involve the intramolecular oxypalladation of the substrate to give an intermediate (from palladium(II)chloride) followed by β-elimination of PdHCl species (where the hydrogen from the C-2 carbon is eliminated along with palladium). This elimination results an exo-methylenebenzo(b)furan species, which eventually isomerizes to the thermodynamically stable 2-methylsubstituted benzo(b)furans. Although the stoichiometric cyclization provided a simple and convenient synthetic entry into the benzo(b)furan nucleus under mild conditions but it suffered from the requirement of one mole equivalent (the stoichiometric amount) of fairly expensive palladium chloride



Scheme 2: Mechanism of formation of 2-substituted benzofuran derivatives.

reagent. Though the palladium is not consumed in the reaction and is reduced to metallic palladium but recycling of it requires either tedious reoxidation or costly "trading in" of $PdCl_2$ salt. For this reason, the application of catalytic cycle to carry out this process appeared to be less cumbersome, but it required to find a method to reoxidize Pd(0) to Pd(II) in the presence of 2-allylphenols and benzo(b)furans, both of which are readily oxidizable. In addition, the oxidizing agent should be such that it does not complex strongly to substrate or to Pd(II) species, if this happened, it would interfere with the cyclization process. Consideration of these factors prompted us to use p-benzoquinone as a suitable oxidizing agent in this process. The formation of compounds **2(a-m)** were unequivocally established on the basis of their microanalysis, IR, ^{1}HNMR, and MS spectral data, which were found to be in good agreement with the assigned structures. The IR spectrum of all the compounds on KBr pellet exhibited a sharp peak at 1287 cm^{-1} for the presence of C–O–C framework in the molecule. Along with this, disappearance of peak of phenolic OH group (3595 cm^{-1}) clearly indicated the formation of benzo(b)furan ring in **2a** from **1a**. A sharp and strong intensity peak at 590 cm^{-1} suggested the presence of monosubstituted furan ring in the molecule which was further substantiated by the appearance of a singlet for 3H at δ 2.17 in all the compounds **2(a-m)**. This was attributed to the presence of CH_3 group at 2-position in the molecule. The disappearance of singlet of one proton at δ 5.09 for phenolic OH observed in its precursor 1a, clearly indicated the formation of benzo(b)furan **2a** from **1a**. Similar spectral interpretations established the structures of other compounds.

4. Conclusion

Our results corroborate strongly to the earlier reports on heteroannulation using organopalladium reagents. It established that palladium induced cyclization protocol provided a very convenient synthetic entry to the benzo(b)furans from 2-allylphenols substituted with electron releasing and electron capturing groups in the arene moiety. The results indicate that cyclization proceeds with high yield and purity in substrates containing electron-releasing groups. However, the electron-capturing group such as the nitro group formed product in low yield. This result was expected in view of the electrophilic character of the organopalladium reagent. Our study substantiates to the catalytic protocol to score better over stoichiometric process in heteroannulations using palladium reagents.

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