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DEVELOPMENT IN SONOGASHIRA COUPLING: CONSTRUCTION OF INDOLE AND BENZO[b]FURAN RING SYSTEMS CATALYZED BY Pd-Cu AND BASIC IONIC LIQUID [DBU]Ac

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ABSTRACT

An efficient $Pd(OAc)_2$, CuI catalyzed Sonogashira coupling of 2-iodophenols/anilines with phenyl acetylene to Benzo[b]furans/indoles is described. This protocol can be used to synthesize a variety of title compounds in good to excellent yields. This method can tolerate a variety of functional groups and does not require the use of expensive additives.

Key words: *Benzo[b]furans; Indoles; Sonogashira coupling; [DBU]Ac*

INTRODUCTION

Indoles are prevalent in many compounds and natural products that have important biological properties. Due to structural diversity and biological activity, it is not surprising that the indole nucleus is an important feature in many therapeutic agents [1]. Benzo[b]furan derivatives are of considerable interest because of their occurrence in a wide range of natural substances and medicinally active compounds [2]. These include inhibition of protein phosphatase1B [3], 5-HT2 and 5-HT3 antagonist activity [4], inhibition of 5-Lipoxygenase (5-LO) [5], and anti-fungal properties [6]. Pharmaceutically, these properties are relevant in the treatment for cancer, cardiovascular disease, type 2 diabetes, migraines, dementia, and anxiety. [5]

The Sonogashira reaction of aryl halides with terminal alkynes is an important tool in the synthesis of organic intermediates, which are mostly encountered within natural products, pharmaceutical intermediates, and molecular materials [7]. This reaction was first reported and catalyzed by $(Ph_3P)_2PdCl_2$ together with CuI as co-catalyst in 1975 [8]. The synthesis of indoles and benzo[b]furans via Sonogashira reaction is generally carried out in two steps *viz.* the palladium copper catalyzed Sonogashira cross coupling between 2-amino/hydroxyl aryl halide and alkyne followed by cyclization of the resulting 2-alkynylanilines/2-alkynylphenols.

In our laboratory, efforts are being made to explore the applications of ionic liquid as the solvent and catalysts in organic synthesis [9-19]. Various basic catalysts have been employed for Sonogashira coupling up till now, these include piperidine [20], DBU [21], Et_3N [22], Bu_4NOAc [23] TBAF [24], and Cs_2CO_3 [25]. Perusal of literature reveals that no report is found for basic ionic liquid mediated Sonogashira reaction. Thus finding a scope for the development of new protocol for preparation of benzo[b]furans and indoles, palladium catalyzed Sonogashira coupling in [DBU]Ac as a basic ionic liquid is attempted in current publication. This attempt has provided a more general, convenient and versatile synthetic approach for the targeted compounds.

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Experimental

All experiments were carried out under anhydrous conditions and an atmosphere of dry nitrogen. All the chemicals were purchased from Sigma-Aldrich and used without further purification. Melting points were determined using $\mu ThermoCal_{10}$ (Analab Scientific Pvt. Ltd.) melting point apparatus and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck silica plates. Column chromatography was performed using Merck silica gel (60-120 mesh size) and n-hexane as the eluent. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz instruments using TMS as the internal standard. Mass spectra were recorded on Shimadzu LCMS 2010 mass spectrometer. Elemental analysis was performed on Perkin Elmer PE 2400 elemental analyzer.

General Procedure for Synthesis of Indoles and Benzo[b]furans

Under nitrogen, a mixture of 2-iodophenol/2-iodoaniline (2.28 mmol), [DBU]Ac (50 mol%), CuI (10 mg), and $Pd(OAc)_2$ (10 mg) was dissolved in toluene (5 mL), and phenylacetylene (2.96 mmol) was added dropwise with stirring into the reaction. The reaction system was stirred at reflux and progress was monitored by TLC. Upon completion, the mixture was extracted with EtOAc (3 x 15 mL). The extract was washed with brine (2 x 15 mL) and dried over Na_2SO_4. After evaporation, the residue was purified via column chromatography on silica gel using n-hexane as the eluent to afford pure product.

Procedure for the Synthesis of [DBU]Ac Ionic Liquid [12]

Aliquot of acetic acid (1 equiv.) was added over a period of 15 min to DBU (1 equiv.) by maintaining the temperature below 5 °C in an ice bath under ultrasound. The reaction mixture was exposed to ultrasound for an additional period of 15 min at ambient temperature. The oily residue obtained was dried in vacuum at 60 °C for 1 h to afford [DBU][Ac] as a light yellow, viscous liquid.

Spectral Data of Synthesized Compounds (3a-n)

2-phenyl-1H-indole (**3a**): ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 7.16-7.69 (m, 9H), 8.39 (brs, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 98.6, 111.2, 120.1, 120.6, 124.9, 127.8, 129.1, 132.3, 136.4, 137.8; ESI-MS: m/z: 194.2 (M+H)+

2-cyclopropyl-1H-indole (**3b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99-1.05 (m, 4H), 2.12-2.20 (m, 1H), 6.35 (s, 1H), 7.21-7.47 (m, 4H), 7.9 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 16.2, 102.3, 114.9, 121.3, 121.5, 122.1, 132.6, 136.8, 143.7; ESI-MS: m/z: 158.1 (M+H)+

2-cyclohexyl-1H-indole (**3c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-3.05 (m, 11H), 6.48 (s, 1H), 7.26-7.62 (m, 4H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.7, 26.1, 35.2, 104.2, 112.8, 119.7, 120.4, 120.8, 127.8, 135.4, 137.8; ESI-MS: m/z: 200.1 (M+H)+

2-(pyridin-2-yl)-1H-indole (**3d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-8.1 (m, 9H), 8.5 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.5, 110.2, 117.3, 118.7, 119.5, 123.9, 125.1, 129.8, 133.6, 135.8, 136.7, 148.9, 150.8; ESI-MS: m/z: 195.3 (M+H)+

2-hexyl-1H-indole (**3e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.31-1.41 (m, 6H), 1.68-2.75 (m, 4H), 6.24 (s, 1H), 7.04-7.52 (m, 4H), 7.88 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.8, 30.8, 31.2, 31.9, 99.8, 112.4, 119.7, 120.1, 121.2, 128.3, 135.8, 136.7; ESI-MS: m/z: 202.1 (M+H)+

2-butyl-1H-indole (**3f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J=7.5 Hz, 3H), 1.27-1.35 (m, 2H), 1.55-1.61(m, 2H), 2.60 (t, J=7.5 Hz, 2H), 6.15 (s, 1H), 6.97-7.43 (m, 4H), 7.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 22.5, 27.6, 30.7, 101.6, 108.7, 119.6, 120.2, 121.3, 128.7, 135.8, 138.0; ESI-MS: m/z: 174.5 (M+H)+

2-propyl-1H-indole (**3g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 3H), 1.68-1.76 (m, 2H), 2.75 (t, J = 7.6 Hz, 2H), 6.24 (s, 1H), 7.13-7.70 (m, 4H), 7.86 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.6, 29.8, 98.6, 111.3, 116.8, 119.8, 120.1, 120.9, 129.7, 137.6; ESI-MS: m/z: 160.5 (M+H)+

2-phenylbenzofuran (**3h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.34-7.90 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.6, 112.4, 121.8, 124.7, 125.8, 126.4, 128.0, 129.8, 131.4, 133.2, 155.1, 155.8; ; ESI-MS: m/z: 195.5 (M+H)+

2-cyclopropylbenzofuran (**3i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99-1.04 (m, 4H), 2.01-2.08 (m, 1H), 6.37 (s, 1H), 7.15-7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 14.3, 98.6, 115.7, 124.4, 126.3, 127.8, 135.8, 158.9, 162.7; ESI-MS: m/z: 319.8 (M+H)+

2-cyclohexylbenzofuran **(3j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-2.90 (m, 11H), 6.42 (s, 1H), 7.20-7.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.6, 29.6, 39.8, 102.5, 112.4, 122.2, 123.4, 124.4, 130.5, 153.9, 162.1; ESI-MS: m/z: 200.9 (M+H)+

2-(benzofuran-2-yl)pyridine (**3k**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 7.13-8.58 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.3, 111.5, 117.8, 121.5, 123.6, 124.5, 125.9, 128.4, 138.6, 148.2, 149.1, 149.9, 156.8; ESI-MS: m/z: 196.7 (M+H)+

2-hexylbenzofuran (**3l**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-0.92 (m, 3H), 1.22-1.45 (m, 6H), 1.74-2.76 (m, 4H), 6.36 (s, 1H), 7.14-7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 25.2, 30.1, 31.2, 32.4, 100.5, 112.5, 115.2, 120.6, 127.3, 128.3, 135.9, 138.4; ESI-MS: m/z: 203.5 (M+H)+

2-butylbenzofuran (**3m**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J=7.5 Hz, 3H), 1.25-1.35 (m, 2H), 1.55-1.61(m, 2H), 2.56 (t, J=7.5 Hz, 2H), 6.15 (s, 1H), 7.04-7.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 21.7, 27.6, 32.1, 102.2, 111.3, 122.1, 123.6, 124.9, 130.1, 156.1, 160.2; ESI-MS: m/z: 175.4 (M+H)+

2-propylbenzofuran (**3n**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J = 7.6 Hz, 3H), 1.65-1.76 (m, 2H), 2.78 (t, J = 7.6 Hz, 2H), 6.24 (s, 1H), 7.28-7.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.1, 23.4, 100.6, 110.4, 121.9, 122.5, 130.1, 129.4, 142.6, 156.8; ESI-MS: m/z: 161.3 (M+H)+

RESULTS AND DISCUSSION

o-iodo phenol **1** and phenyl acetylene **2** were chosen as the building blocks for the model reaction. The first objective of the study was to optimize the mol ratio of the [DBU]Ac in the model reaction. The results are summarized in Table 1.

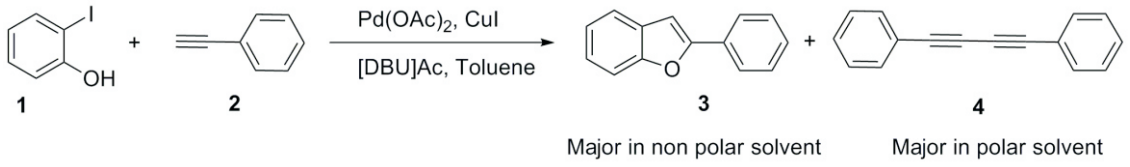
Table 1: The effect of different amounts of [DBU]Ac on the reaction of o-iodo phenol and phenyl acetylene.[a]

Entry	[DBU]Ac (mol %)	Time (min)[b]	Yield[c]
1	20	90	65
2	30	80	70
3	40	75	72
4	**50**	**60**	**80**
5	60	60	80

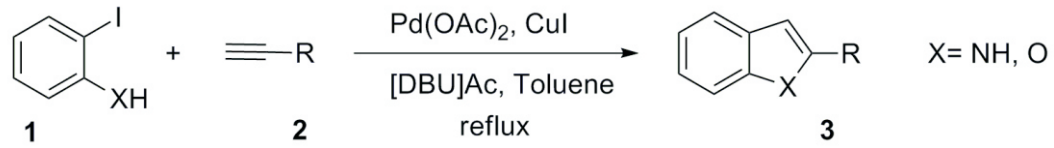
[a]o-iodophenol (2.28 mmol), phenyl acetylene (2.96 mmol), $Pd(OAc)_2$ (10 mg), CuI (10 mg) and toluene (5 mL). [b]time required to complete the reaction as indicated by TLC. [c]isolated yield.

As shown in Table 1, when 50 mol % of IL was taken for the synthesis, best result was achieved in terms of yield as well as time (entry 4, Table 1). Reaction was completed in 60 min with 80 % yield. $Pd(OAc)_2$ and CuI were necessary to complete this transformation. Use of 50 mol % IL is found to be sufficient to accelerate the reaction forward; increase in the equivalent of IL beyond this level did not improve the conversion. We also tested the same transformation in absence of CuI but the reaction did not proceed to forward direction.

Jaseer *et al* [26] have reported that when the reaction of o-iodophenol **1** and phenyl acetylene **2** was performed in polar solvent such as DMSO, DMF and acetonitrile afforded poor yield of the desired product **3**. The oxidative homo coupling of phenyl acetylene occurred to produce product **4** as the major product (Scheme 1). While in non-polar solvents such as 1, 4 - dioxane and toluene, the homo coupling product **4** was found to be reduced to 2-5 % of yield. Therefore all the experiments were carried out in toluene as the co-solvent in the present study. The obtained experimental results encouraged us to extend the scope of reaction to apply on a range of variously substituted 2-iodo phenols/amines and acetylenes (Scheme 2, Table 2).



Scheme 1 Model reaction condition



Scheme 2. General synthetic pathway for the synthesis of indoles and benzofurans

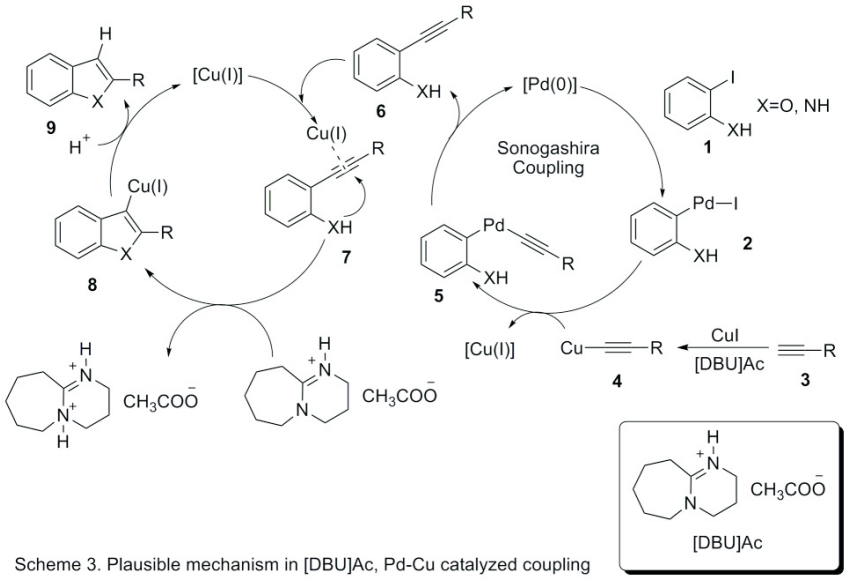
Table 2: Generalization of the protocol employing variously substituted 2-iodophenols/amines

Entry	X	R	Time (min)[a]	Yield (%)[b]
3a	-NH	$-C_6H_5$	90	85
3b	-NH	$-C_3H_5$	60	78
3c	-NH	$-C_6H_{11}$	105	84
3d	-NH	$-C_5H_4N$	120	82
3e	-NH	$-C_6H_{13}$	60	84
3f	-NH	$-C_4H_9$	60	78
3g	-NH	$-C_3H_7$	75	76
3h	O	$-C_6H_5$	60	80
3i	O	$-C_3H_5$	105	78
3j	O	$-C_6H_{11}$	75	82
3k	O	$-C_5H_4N$	105	75
3l	O	$-C_6H_{13}$	120	80
3m	O	$-C_4H_9$	75	78
3n	O	$-C_3H_7$	60	80

[a]time required to complete the reaction as indicated by TLC. [b]isolated yield.

Both aromatic and aliphatic acetylenes were well-tolerated. All the reactions were completed in 60-120 min. The percentage yield of all the synthesized indoles/benzofurans using conventional technique is shown in Table 2.

Plausible Reaction Mechanism in [DBU]Ac



Scheme 3. Plausible mechanism in [DBU]Ac, Pd-Cu catalyzed coupling

Oxidative addition of Pd (0) to 2-iodophenol/aniline **1** produces intermediate **2** in which Pd(0) is oxidized to Pd (+2). Simultaneously terminal proton of acetylene **3** gets abstracted by [DBU]Ac and insertion of Cu makes terminal carbon of **4** more electrophilic. Then Palladium gets converted in its original state affording intermediate **6**. With the assistance of [DBU]Ac as a base, the nitrogen atom or oxygen acts as a nucleophile and attacks the copper coordinated alkyne **7** to give the indole-containing copper intermediate **8**. Protonolysis of **8** provides the corresponding indole (or benzo[b]furan) product **9** (Scheme-3).

CONCLUSION

We have demonstrated a concise and practical method for the synthesis of indoles and benzo[b]furans. Both heterocycles could be obtained in good to moderate yield by the reactions of 2-iodoaniline or 2-iodophenol with terminal alkynes under mild conditions, namely in the presence of CuI, $Pd(OAc)_2$, and a basic ionic liquid [DBU]Ac in toluene as the co-solvent. It is worth noting that simple aliphatic substituted terminal alkynes could be tolerated to smoothly produce indole and benzo[b]furan derivatives. Therefore, this method is complementary to those of the previously reported Cu-catalyzed coupling/cyclizations.

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