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2,3-Disubstituted Benzofuran and Indole by Copper-Mediated C–C Bond Extension Reaction of 3-Zinciobenzoheterole

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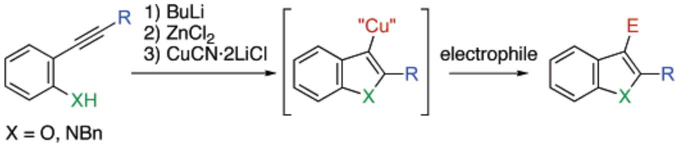
ABSTRACT



A metalative 5-endo-dig cyclization reaction of 2-ynylphenoles or anilines effected by BuLi and ZnCl$_2$ produces 3-zinciobenzoheteroles in excellent yield. These intermediates have been transmetalated to the corresponding cuprates and allowed to react with electrophiles to produce a variety of 2,3-disubstituted benzofurans and indoles.

2,3-Disubstituted benzofurans and indoles form the core of numerous natural products and have considerable pharmacological potential.[1] We previously reported a new method[2] for preparation of this class of compounds by zinc-mediated cyclization of 2-ynylphenol or aniline (**1**), followed by palladium-catalyzed C−C bond extension.[3] In this previous method, we relied largely on Et$_2$Zn to obtain the crucial zinc intermediate,[4] bis(benzofuran-3-yl)zinc or (benzofuran-3-yl)-ethylzinc, that shares the same organometallic core structure with **2** except the chlorine ligand on the metal atom. While such intermediates smoothly underwent Pd-catalyzed reactions with aryl and alkenyl halides, they resisted reaction with other carbon electrophiles that would offer more diverse synthetic possibilities. In addition, the reaction using Et$_2$Zn gave 5−10% recovery of the protio product **4** (E = H), which is due to the fast, sluggish cyclization, causing in situ competitive protonation of the zinc intermediate by **1**. In this Letter, we report a more synthetically useful procedure that allows quantitative generation of the 3-zinciobenzoheterole **2** and subsequent copper-mediated coupling with a variety of carbon electrophiles to give 2,3-disubstituted benzofurans and indoles.

A hint of the solution was already provided in our previous synthesis of indoles,[2] where ZnCl$_2$ instead of Et$_2$Zn tends to give better results. Optimization of the reaction conditions

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[†] PRESTO, Japan Science and Technology Corporation (JST).

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(3) Benzofuran: (a) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−2368. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432−1434. (c) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. (d) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803−11812. Indole: (e) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671−2681 and references therein.

(4) Metallobenzofuran. (a) Hg: Larock, C. R.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218−4227. (b) Li: Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 1655−1657. 3-Metalloindole. (a) Li: Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757−761. (b) Zn: Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158−3175. (c) Hg: Ramachandran, L. K.; Witkop, B. *Biochemistry* **1964**, *3*, 1603−1611. (d) B: Zheng, Q.; Yang, Y.; Martin, A. R. *Tetrahedron Lett.* **1993**, *34*, 2235−2238. (e) Mg: DeGraw, J. I.; Kennedy J. G.; Skinner, W. A. *J. Heterocycl. Chem.* **1966**, *3*, 67−69. (f) Sn: Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1994**, *35*, 2405−2408. (g) Sn: Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899−1906.

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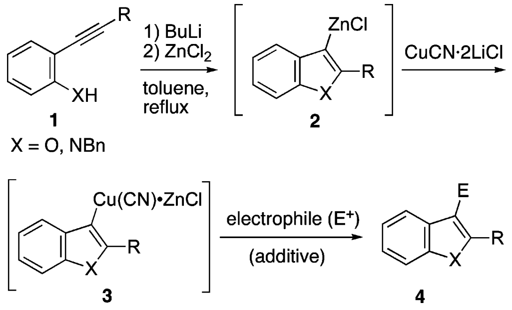
Scheme 1. Cyclization of 2-Ynylphenol (or aniline) **1** to 3-Zinciobenzoheterole **2** and Trapping with Electrophiles



allowed us to achieve the cyclization and the subsequent transformations with much higher efficiency. Thus, we first deprotonated acetylenic phenol **1a** (X = O, R = Ph) with BuLi (1.0 equiv), and then added $ZnCl_2$ (1.0 equiv) to obtain the corresponding zinc phenoxide as a clear homogeneous solution. Removal of the solvent in vacuo followed by addition of toluene and heating at reflux for 1 h resulted in the formation of the zinc intermediate **2a** that was isolated quantitatively as its protonated form **4a** (E = H) (Table 1, entry 1). No starting material (**1a**) was recovered. An additional merit is that the new procedure does not require tetramethylethylenediamine (TMEDA) that was mandatory in the Et_2Zn-mediated method.

Table 1. Cyclization of 2-Ynylphenol (or aniline) **1** into Benzofuran (or indole) **4** (E = H)[a]

entry	X	R	time (h)	yield (%)[b] (**4**)
1	O	Ph	1	100 (**4a**)
2	O	*n*-Bu	1	98 (**4b**)
3	O	*t*-Bu	48	98 (**4c**)
4	O	H[c]	2	0 (**4d**)
5	O	(*E*)-styryl	1	100 (**4e**)
6	O	2-thienyl	1	96 (**4f**)
7	O	CH_2OMOM[d]	1	86 (**4g**)
8	NBn	Ph	1	100 (**4h**)
9	NBn	*n*-Bu	2	97 (**4i**)
10	NBn	*t*-Bu	16	98 (**4j**)
11	NBn	H[c]	2	99 (**4k**)
12	NBn	(*E*)-styryl	2	48 (**4l**)

[a] Reaction conditions: BuLi (1.0 equiv), 0 °C to room temperature, 30 min, then $ZnCl_2$ (1.0 equiv), toluene, 120 °C. [b] Isolated yield. [c] 2.0 equiv of BuLi, $ZnCl_2$ was used. [d] MOM = methoxymethyl.

Cyclization of a hexynyl substrate **1b** (X = O, R = *n*-Bu) also took place quantitatively (entry 2), with 95% deuterium incorporation upon DCl/D_2O quenching (86% incorporation by the Et_2Zn cyclization). 2-*tert*-Butylbenzofuran (**4c**) that was obtained earlier in a modest 50% yield can now be synthesized in quantitative yield (entry 3). Various other alkynyl phenols bearing styryl, thienyl, or CH_2OMOM substituents (**1e**−**g**) reacted smoothly to give the corresponding 2-substituted benzofurans in excellent yield (entries 5−7). 2-Ethynylphenol **1d** resisted cyclization, which stands in stark contrast to the smoothness of the cyclization for an aniline couterpart giving **4k** in 99% yield. Poor stability of 3-metallobenzofuran compared with the indole counterpart[3] could explain the intolerance for another metal atom at position 2.

The reaction proceeded equally well with 2-ynylanilines **1h**−**j** under similar conditions (entries 8−11). For substrate **1l** (X = NBn, R = (*E*)-styryl), the yield was modest (entry 12) because of the instability of the starting material.

We tentatively attribute the large difference of the reactivity between Et_2Zn-generated bisphenoxyzinc and the BuLi/$ZnCl_2$-generated phenoxyzinc chloride (**2**) to increased Lewis acidity of the zinc atom. We also attribute the lack of necessity to employ TMEDA to the presence of LiCl, whose Cl anion acts as a ligand to the zinc atom and prevents the formation of unproductive aggregates. We defer further discussion until we obtain concrete pieces of structural and mechanistic evidence.

The zinc intermediate **2** was found to be a much more useful intermediate than those reported earlier.[2] In the presence of CuCN•2LiCl,[5] **2** gave a variety of compounds, most of which are unavailable by our previous method (Table 2). 3-Allyl benzoheteroles **5** and **7** were obtained in quantitative yield (entries 1 and 3). The butyl-substituted intermediate **2b** was slightly less reactive than the phenyl-substituted **2a**, but still gave the desired 3-allyl-2-butylbenzofuran **6** in good yield (entry 2). The reaction with cinnamyl bromide was completely S_N2 selective (entry 4), in contrast to the S_N2' selectivity of less hindered zinc reagents.[5,6] Coupling with benzoyl chloride gave 3-aroyl benzoheteroles **9** and **10** in good yield (entries 5 and 6). The method thus provides an easy access to 2-substituted 3-aroyl benzofurans and indoles that are useful for the pharmacological studies.[7]

Copper-mediated 1,2-addition to benzaldehyde took place to give the alcohol **11** in good yield (entry 7). When BF_3•OEt_2 was used as an additive, the first addition product further reacted with the second equivalent of the benzofuranyl cuprate **3a** to yield an intriguing, highly substituted methane derivative **12** (entry 8). Michael addition to 2-cyclohexen-1-one in the necessary presence of chlorotrimethylsilane as an additive[8] afforded the corresponding ketones **13**−**15** in good yield (entries 9−11). Diethyl malonate also reacted smoothly in the presence of chlorotrimethylsilane and afforded the benzofuran esters **16** and **17** in excellent yield (entries 12 and 13). The reaction with 3-iodo-2-cyclohexen-1-one gave the conjugated ketone **18** in excellent yield (entry 14).

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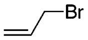
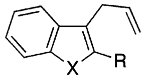
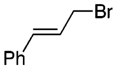
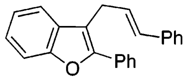
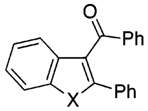
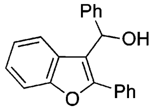
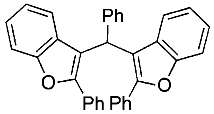
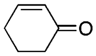
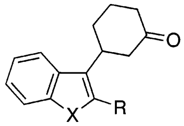
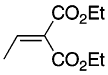
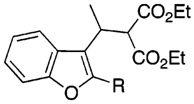
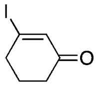
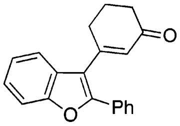
(6) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066.

(7) (a) Twyman, L. J.; Allsop, D. *Tetrahedron Lett.* **1999**, *40*, 9383−9384. (b) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248−7257.

(8) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−3370.

Table 2. Coupling of 3-Zinciobenzoheterole **2** with Various Electrophiles in the Presence of Cu(I)[a]

entry	1	electrophile	conditions	product			yield (%)[b]
1	**1a**		0 °C, 12 h		X = O R = Ph	**5**	97
2	**1b**				X = O R = Bu	**6**	81
3	**1h**				X = NBn R = Ph	**7**	97
4	**1a**		0 °C, 12 h	 (S_N2': S_N2 = 0:100)[c]		**8**	98
5	**1a**	PhCOCl	50 °C, 12 h		X = O	**9**	91
6	**1h**				X = NBn	**10**	72
7	**1a**	PhCHO	50 °C, 12 h			**11**	68
8	**1a**	PhCHO	BF$_3$·OEt$_2$ 50 °C, 12 h			**12**	76
9	**1a**		Me$_3$SiCl 0 °C, 12 h		X = O R = Ph	**13**	77
10	**1b**				X = O R = Bu	**14**	74
11	**1h**				X = NBn R = Ph	**15**	65
12	**1a**		Me$_3$SiCl 0 °C, 12 h		R = Ph	**16**	95
13	**1b**				R = Bu	**17**	83
14	**1a**		0 °C, 12 h			**18**	90

[a] Reaction conditions: a mixture of **2** (1.0 mmol) in toluene (1.0 mL) was cooled to −78 °C and CuCN·2LiCl in THF (1.0 M, 1.0 mL), additive (2.4 mmol), and electrophile (1.2 mmol) were successively added. The mixture was then warmed to the indicated temperature and stirred. When Me$_3$SiCl was used in situ as an additive, the reaction mixture was quenched with tetrabutylammonium fluoride (THF solution, 1.0 mol/L). [b] Isolated yield based on **1**. [c] Determined by ^{1}H NMR.

In most of the cases, the only byproduct was 3-protonated benzoheterole **4** (E = H), which was recovered in 5−20% yield. The new zincio intermediates also react with aryl and alkenyl halides under palladium catalysis (data not shown) and may be used as a general alternative to the previous procedure.

In conclusion, we have developed a procedure for the generation of 3-zincio-2-substituted benzoheteroles **2**, which is superior to the previous method for the lack of necessity of the TMEDA additive, for the much higher yield of the cyclization, and for the versatility of the zinc intermediates for further synthetic elaborations.

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Supporting Information Available: Details of the experimental procedure and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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