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Regioselective Synthesis of 4- and 7-Alkoxyindoles from 2,3-Dihalophenols: Application to the Preparation of Indole Inhibitors of Phospholipase A_2

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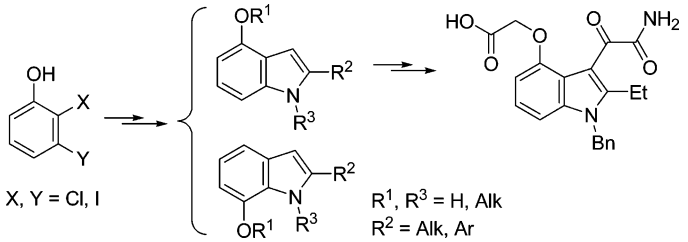

An efficient and regioselective synthesis of 4- and 7-alkoxyindoles has been developed from commercially available starting materials such as 3-halophenols and 3-chloroanisole. Directed ortho-metalation followed by two palladium-catalyzed processes, a Sonogashira coupling and a tandem amination/cyclization reaction, allows the synthesis of regiochemically pure 4- and 7-substituted indoles. This strategy has been successfully applied to the preparation of 2-[3-(2-amino-2-oxoacetyl)-1-benzyl-2-ethyl-1*H*-indol-4-yloxy]-acetic acid (LY315920), a known inhibitor of phospholipase A_2.

Introduction

The indole nucleus is a prominent structural unit frequently found in numerous natural products and pharmaceutically active compounds.[1] Thus, the search for new methodologies to obtain this scaffold with different substitution patterns is a current major objective in organic synthesis.[2] Among indole derivatives, those with oxygen-bearing substituents at the benzo moiety are important compounds and many of these are known to be synthetic medicines and physiologically active substances (serotonin, melatonin, psilocin, etc.).[3] Moreover, the hydroxyindoles can be transformed into different carbon-functionalized indoles by Pd-catalyzed reactions of the corresponding triflates.[4] Since electrophilic functionalization of the indole core occurs at the pyrrole nucleus, direct regioselective substitution at the benzenoid portion is rather problematic (especially the 4-position of the indole ring system, which is much less electron-rich than other positions).[5] So the most common methods for preparing indoles having substituents at the C4-position are based on the construction of the pyrrole ring from suitably functionalized benzene derivatives. In this field, 4-hydroxyindole[6] derivatives have been mainly prepared by Pd-catalyzed cross-coupling of 3-alkoxy-2-haloanilines with alkynes and further cyclization.[7]

Also, 7-alkoxyindoles are interesting intermediates for further transformations. One of the most suitable approaches to such compounds is the Bartoli synthesis of 7-substituted indoles by reaction of an ortho-substituted nitroaromatic compound with

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(1) (a) Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1983; Vol. 25, Part IV. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73−103.

(2) (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920.

(3) (a) Sakagami, H.; Ogasawara, K. *Heterocycles* **1999**, *51*, 1131−1135. (b) Shirota, O.; Hakamata, W.; Goda, Y. *J. Nat. Prod.* **2003**, *66*, 885−887.

(4) See for instance: (a) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170−1176. (b) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Biorg. Med. Chem. Lett.* **2004**, *14*, 4891−4895.

(5) Functionalization at the 1-, 2-, and 3-positions of the indole ring can be effected easily by conventional methods: Sundberg, R. J. *Indoles*; Academic Press, London, 1996.

(6) Although 4-hydroxyindole is commercially available, it is quite expensive to be used as starting material in multigram preparations.

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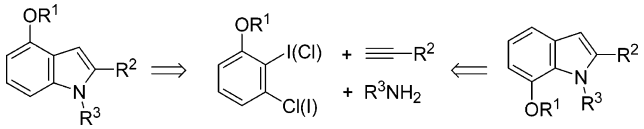
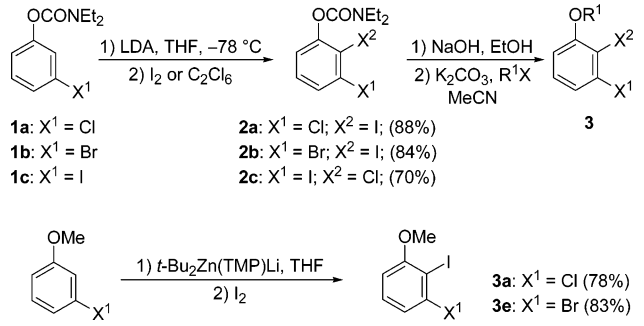
SCHEME 1. Retrosynthetic Analysis of Regioselectively Oxy-Substituted Indoles



SCHEME 2. Synthesis of 2,3-Dihalophenyl Ethers 3



excess vinylmagnesium halide.[8] However, the application of this strategy to 7-alkoxy derivatives gave only modest yields of the 2,3-unsubstituted indole moiety.[9]

We have recently reported a new and efficient preparation of 2,3-dihalophenols from commercially available 3-halophenols using the *O*-carbamate-directed metalation methodology.[10] In this context, we envisaged that these functionalized phenols could be appropriate starting materials for the regioselective synthesis of 4- or 7-alkoxyindole derivatives by selective Sonogashira monoalkynylation, followed by a one-pot Pd-catalyzed amination and subsequent cyclization (Scheme 1).

So, in this paper we report the easy preparation of indole derivatives, oxygen-functionalized at the C-4 or C-7 position, by the above referred strategy. The efficiency of this methodology is demonstrated by the straightforward synthesis of an indole inhibitor of phospholipase A_2.

Results and Discussion

According to the retrosynthetic analysis shown in Scheme 1, our first goal was the efficient preparation of 2,3-dihalophenyl ethers **3**. As we have previously reported,[10] *ortho*-lithiation of 3-halocarbamates **1**[11] and trapping of the intermediate anions with iodine or hexachloroethane gives rise to *O*-2,3-dihalophenyl carbamates **2** in high yields (Scheme 2). Subsequent alkaline hydrolysis affords the corresponding 2,3-dihalophenols, which without further purification were treated with alkyl or trialkylsilyl halides under standard basic conditions, allowing the preparation of 2,3-dihalophenyl ethers **3** in moderate to high yields (Scheme 2 and Table 1).[12] For the synthesis of 3-chloro-2-iodoanisole **3a** and 3-bromo-2-iodoanisole **3e**, an alternative and direct route might involve direct *ortho*-metalation of commercially available 3-haloanisoles and subsequent iodination. To test this possibility, 3-chloroanisole was treated with several organolithium reagents or lithium amides (*s*-BuLi/TMEDA, *t*-BuLi, or LDA) under different conditions, but only products derived from the formation of intermediate benzyne derivatives could be detected. Gratifyingly, we found that the use of lithium di-*t*-butyltetramethylpiperidinozincate[13] was effective for the *ortho*-metalation of 3-chloroanisole, and so the subsequent treatment of the intermediate arylzincate with iodine gave **3a** in 78% yield (Scheme 2). In the same way, direct *ortho*-zincation of 3-bromoanisole gave rise to **3e** in 83% yield (Scheme 2). However, this methodology was unsuccessful when applied to 3-iodoanisole, probably due to a competitive iodine−zinc exchange.[13b]

TABLE 1. Preparation of 2,3-Dihalophenyl Ethers 3

entry	product	R^1	X_1	X_2	yield[a] (%)
1	**3a**	Me	Cl	I	90
2	**3b**	Bn	Cl	I	85
3	**3c**	CH_2CO_2t-Bu	Cl	I	71
4	**3d**[b]	*i*-Pr_3Si	Cl	I	81
5	**3e**	Me	Br	I	80
6	**3f**	Me	I	Cl	89
7	**3g**	Bn	I	Cl	74
8	**3h**[b]	*i*-Pr_3Si	I	Cl	80

[a] Isolated yield based on starting *O*-2,3-dihalophenyl carbamates **2**. [b] Prepared with imidazole as base and CH_2Cl_2 as solvent.

Our next objective was the preparation of *o*-alkynylhaloarenes **4**−**6** through Sonogashira cross-coupling reactions from 2,3-dihalophenyl ethers **3**. Initial experiments performed with the standard catalytic system ($[PdCl_2(PPh_3)_2]$, CuI, and a base) were unsuccessful. We think that the steric hindrance of our substrates could delay the coupling, and so the presence of CuI in the reaction medium may result in the formation of some Cu(I) acetylides that could readily undergo an oxidative homocoupling reaction.[14] Modified Pd-catalyzed Sonogashira-type reactions under copper-, and amine-free conditions have recently appeared in the literature.[15] Gratifyingly, we found that the use of $PdCl_2(PPh_3)_2$ (6 mol %) combined with TBAF·$3H_2O$ (3 equiv) under solvent-free conditions[15e] provided fast cross-coupling reactions with several terminal alkynes (Scheme 3).

(7) (a) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511. (b) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921−923. (c) Jia, Y.; Zhu, J. *Synlett* **2005**, 2469−2472. 4-Alkoxy-3-formylindoles have been prepared by a one-pot thallation−iodination−alkoxylation reaction sequence from 3-formylindole; see Somei, M.; Yamada, F.; Kunimoto, M.; Kaneko, C. *Heterocycles* **1984**, *22*, 797−801.

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(9) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611−617.

(10) Sanz, R.; Castroviejo, M. P.; Fernández, Y.; Fañanás, F. J. *J. Org. Chem.* **2005**, *70*, 6548−6551.

(11) We have optimized the conditions for the ortho-lithiation of **1a** by using LDA instead of our initially reported conditions (*s*-BuLi/TMEDA).

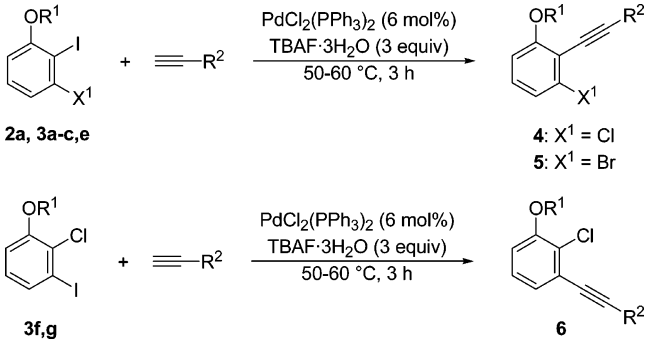
(12) The protection of the hydroxy group of 2,3-dihalophenols turns out to be necessary because coupling of 3-halo-2-iodophenols with terminal alkynes under copper−palladium-catalyzed conditions afforded benzo[*b*]-furan derivatives. See ref 10.

(13) Developed by Kondo and Uchiyama for the chemoselective deprotonative zincation of functionalized aromatic compounds: (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540. (b) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514−8515.

(14) (a) For a review, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657. (b) Buchwald and Gelman have indeed found that CuI has a deleterious effect on Sonogashira couplings: Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996.

(15) For selected papers: (a) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935−2937. (b) Cheng, J.; Sun, Y.; Wang. F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428−5432. (c) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752−5755. (d) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391−393. (e) Liang, Y.; Xie, Y.-X.; Li, J.-H. *J. Org. Chem.* **2006**, *71*, 379−381. (f) Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535−2537.

SCHEME 3. Synthesis of *o*-Alkynylhaloarenes 4−6



As demonstrated in Table 2, coupling of 3-chloro-2-iodophenyl ether derivatives **2a** and **3a**−**c** with three different terminal alkynes afforded the corresponding *o*-alkynylchloroarenes **4** in moderate to high yields (Table 2, entries 1−7). Also, 3-bromo-2-iodoanisole **3e** underwent coupling with phenylacetylene, giving rise to *o*-alkynylbromoarene **5a** (Table 2, entry 8). In the same way, alkyl 2-chloro-3-iodophenyl ethers **3f** and **3g** also worked in the coupling reaction, giving rise to the *o*-alkynylchloroarenes **6** in high yields (Table 2, entries 9−12). Although this methodology has also been applied to activated and deactivated aryl chlorides,[15e] with our substrates the reactions were always selective for the cross-coupling of the aryl iodides.[16] However, when we tried to apply this strategy to silyl ether **3d**, the reaction with phenylacetylene afforded 4-chloro-2-phenylbenzo[*b*]furan as a sole product (Table 2, entry 13).[10] In this case, cross-coupling and removal of the silyl group took place at once, and so a cyclization occurs. Then, we attempted to apply this process to 2-chloro-3-iodophenol, in which closure to the benzofuran is not possible. In this case, the reaction afforded the expected product **6e**, although in lower yield (Table 2, entry 14), showing that protection of the hydroxy group improves the Sonogashira coupling under these copper-, amine-, and solvent-free conditions.

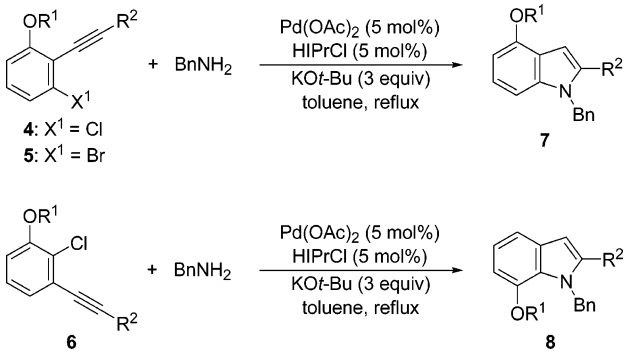
Once we had prepared *o*-alkynylhaloarenes **4**−**6**, we investigated the best conditions to synthesize the targeted alkoxyindoles. In recent years, enormous progress has been achieved in Pd(0)-catalyzed amination reactions as a versatile method for the synthesis of amines from aryl halides.[17] Even aryl chlorides have been demonstrated as suitable substrates for this kind of process, particularly under palladium/imidazolium salt catalytic systems.[18] In this context, 2-substituted indoles have been recently accessed from *o*-alkynylhaloarenes by amination and further cyclization.[19] Also, Ackermann[20] has reported the use of an *N*-heterocyclic carbene palladium complex as catalyst for this kind of indole synthesis, whereas Tang and Hu[21] used Pd-

TABLE 2. Preparation of *o*-Alkynylhaloarenes 4−6 from 2,3-Dihalophenyl Ethers 3

entry	starting material	R^1	R^2	product	yield[a] (%)
1	**3a**	Me	Ph	**4a**	92
2	**3a**	Me	*n*-Bu	**4b**	68
3	**3a**	Me	*n*-Pr	**4c**	70
4	**3b**	Bn	Ph	**4d**	49
5	**3b**	Bn	*n*-Bu	**4e**	63
6	**3c**	CH_2CO_2t-Bu	*n*-Bu	**4f**	59
7	**2a**	$CONEt_2$	*n*-Bu	**4g**	80
8	**3e**	Me	Ph	**5a**	67
9	**3f**	Me	Ph	**6a**	82
10	**3f**	Me	*n*-Bu	**6b**	53
11	**3g**	Bn	Ph	**6c**	94
12	**3g**	Bn	*n*-Bu	**6d**	84
13	**3d**	*i*-Pr_3Si	Ph	*b*	*c*
14	*d*	H	*n*-Bu	**6e**	34

[a] Isolated yield based on starting ethers **3**. [b] 4-Chloro-2-phenyl-benzo[*b*-]furan was obtained. [c] Not determined. [d] 2-Chloro-3-iodophenol was used as starting material.

SCHEME 4. Synthesis of 4-Alkoxyindoles 7 and 7-Alkoxyindoles 8



$(OAc)_2$/*t*-Bu_3P as the catalytic system. We tested both methods with *o*-alkynylchlorophenyl ether **4e**, using benzylamine as the amine partner, and we obtained the best results by using Ackermann's conditions. So, we carried out the amination reactions of our previously synthesized 2-alkynyl-3-chlorophenyl ethers **4** with benzylamine under $Pd(OAc)_2$/1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (HIPrCl) system catalysis (5 mol %), in toluene at reflux, and with KO*t*-Bu as base (3 equiv) (Scheme 4). In this way, 4-alkoxy-*N*-benzyl-2-substituted indoles **7** were obtained in usually high yields after 2−3 h of reaction (Table 3, entries 1−5).[22] Also, *o*-alkynylbromophenyl ether **5a** afforded the indole **7a** under the same reaction conditions and in a similar yield as the corresponding *o*-alkynylchloroarene derivative **4a** (Table 3, entry 1).

In a similar manner, the amination of 3-alkynyl-2-chlorophenyl ethers **6** with benzylamine under the same reaction conditions afforded good yields of the 7-alkoxy regioisomeric indoles **8** (Scheme 4 and Table 3, entries 6−9). However, the attempt to synthesize the indole from the free hydroxy derivative **6e** resulted in complete consumption of the starting material, but the 7-hydroxyindole derivative could not be isolated in pure form and significant yield.

(16) We have observed that the reaction of 3-bromo-2-iodoanisole **3e** with phenylacetylene (2 equiv) gave rise to a small amount of 2,3-bis-(phenylethynyl)anisole. Formation of this side product could be inhibited by using only a slight excess of the alkyne (1.2 equiv).

(17) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley−VCH: Weinheim, Germany, 2000; pp 195−262.

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(19) An alternative approach consisting of a hydroamination and a subsequent intramolecular Pd-catalyzed amination reaction has also been reported: Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042−3044.

(20) (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439−442. (b) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311−11316.

(21) Tang, Z.-Y.; Hu, Q.-S. *Adv. Synth. Catal.* **2006**, *348*, 846−850.

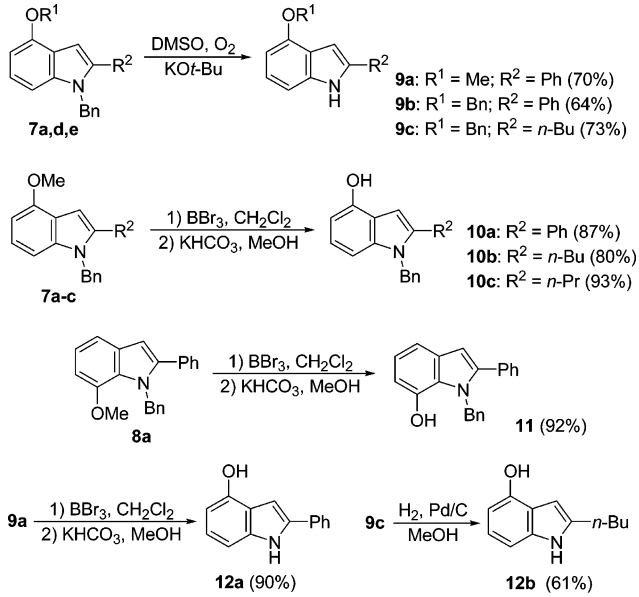
(22) Ackermann has also reported that the Sonogashira coupling reaction and the indole formation from *o*-chloroiodobenzene could be carried out in a one-pot manner using a single catalytic system consisting of $Pd(OAc)_2$, CuI, HIPrCl, and Cs_2CO_3. However, when we tried this one-pot approach using **3b** and phenylacetylene as starting materials, the reaction did not work, probably due to the presence of the Cu(I) salt, which favours the oxidative homocoupling of the alkyne.

TABLE 3. Preparation of Alkoxyindoles 7 and 8 from *o*-Alkynylhaloarenes 4−6

entry	alkyne	R^1	R^2	product	yield[a] (%)
1	**4a**	Me	Ph	**7a**	84[b]
2	**4b**	Me	*n*-Bu	**7b**	79
3	**4c**	Me	Pr	**7c**	57
4	**4d**	Bn	Ph	**7d**	89
5	**4e**	Bn	*n*-Bu	**7e**	75
6	**6a**	Me	Ph	**8a**	63
7	**6b**	Me	*n*-Bu	**8b**	74
8	**6c**	Bn	Ph	**8c**	70
9	**6d**	Bn	*n*-Bu	**8d**	64

[a] Isolated yield based on starting alkynes **4**−**6**. [b] Yield obtained starting from 2-alkynyl-3-bromoanisole **5a** was 82%.

SCHEME 5. Synthetic Transformations of Indoles 7−9



Selective *N*-debenzylation of several *N*-benzylindoles **7** with KO*t*-Bu/DMSO and oxygen at room temperature cleanly afforded *N*-H indoles **9a**−**c** in moderate yields (Scheme 5).[23] It is significant that this procedure does not affect the *O*-benzyl group of indoles **7d** and **7e**. However, this methodology gave rise to poor yields of the corresponding *N*-H indoles for 7-benzyloxyindole derivatives **8c** and **8d**. Very good results were obtained for the *O*-demethylation[24] of several *N*-benzyl-4-methoxyindoles **7a-c** and *N*-benzyl-7-methoxyindole **8a**. The cleavage of the *O*-methyl groups with BBr_3 afforded 4-hydroxyindoles **10a**−**c** and 7-hydroxyindole **11**, respectively, in excellent yields (Scheme 5). Moreover, the same procedure could also be applied to the *O*-demethylation of 4-methoxy-2-phenylindole **9a**, giving rise to 4-hydroxy-2-phenylindole **12a** in high yield (Scheme 5). Finally, whereas the *N*-debenzylation of **10a** under standard hydrogenolysis conditions (Pd/C) did not afford **12a**, we have succeeded in the *O*-debenzylation of **9c**, and so 2-butyl-4-hydroxyindole **12b** could also be prepared (Scheme 5).

In the last years, group IIA of secreted phospholipases A_2 (sPLA$_2$s) has received the most attention among the sPLA$_2$s because it was the first nonpancreatic sPLA$_2$ to be discovered, and it is found in high levels in patients suffering from inflammatory diseases.[25] Consequently, chemical intervention of this class of enzyme has become an important topic for medicinal chemistry research at several pharmaceutical companies. Among the reported inhibitors of sPLA$_2$,[26] indole 3-glioxamides with additional oxygenated functionalities at the benzenoid ring appear to be the most potent inhibitors of sPLA$_2$.[27] Figure 1 shows the structure of LY315920 that was chosen for clinical evaluation as an inhibitor of human nonpancreatic sPLA$_2$ at Lilly Research Laboratories.[27a] More recently, Gelb and co-workers[28] have reported that this and other indole analogues are also the first potent inhibitors of mammalian group X (mGX) of sPLA$_2$s.

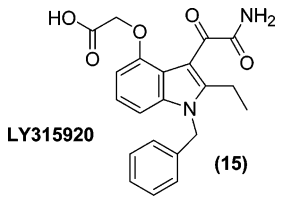
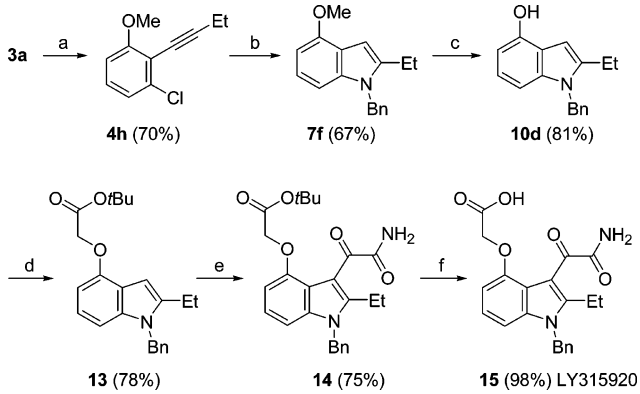


FIGURE 1. Structure of sPLA2 inhibitor LY315920.

SCHEME 6. Synthesis of Indole Inhibitor of Phospholipase A_2 15 (LY315920)[a]



[a] Reagents and conditions: (a) EtC≡CH (excess), $PdCl_2(PPh_3)_2$ (6 mol %), TBAF·3H$_2$O (3 equiv), 50−60 °C; (b) $BnNH_2$ (1.2 equiv), $Pd(OAc)_2$ (5 mol %), HIPrCl (5 mol %), *t*-BuOK (3 equiv), toluene, reflux; (c) (1) BBr_3 (6 equiv), CH_2Cl_2, −78 to 20 °C, 16 h; (2) $KHCO_3$ (6 equiv), MeOH, 0 to 20 °C, 1 h; (d) NaH (1.2 equiv), $BrCH_2CO_2t$-Bu (1.1 equiv), DMF; (e) (1) $(COCl)_2$, CH_2Cl_2; (2) HMDS (1.2 equiv); (f) TFA, CH_2Cl_2.

In this context, our attention was turned to employing the methodology described above for the synthesis of indole inhibitor of phospholipase A_2 **15** (LY315920) (Scheme 6). Thus, starting from 3-chloro-2-iodoanisole **3a**, prepared as described in Scheme 2 from commercially available 3-chloroanisole, the cross-coupling reaction with 1-butyne under copper-free condi-

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tions gave rise to 2-(1-butynyl)-3-chloroanisole **4h**. Amination of this *o*-alkynylchloroarene derivative with benzylamine in the presence of base and the *N*-heterocyclic carbene palladium complex yielded *N*-benzylindole **7f**. *O*-Demethylation was again accomplished by treatment with BBr_3, and the 4-hydroxyindole **10d** was obtained in high yield. Its treatment with NaH and further alkylation with *t*-butyl bromoacetate in DMF afforded *t*-butyl oxyethanoate derivative **13**. The corresponding 3-glyoxylamide derivative **14** was easily prepared by treatment with oxalyl chloride followed by hexamethyldisilazane.[29] Finally, deprotection of the *t*-butyl ester with TFA yielded almost quantitatively the targeted *N*-benzyl-2-ethylindole derivative **15** in good overall yield and in only seven steps from commercially available 3-chloroanisole (Scheme 6). This synthesis favorably competes with the reported sequences, which make use of expensive starting materials or require several steps.[27,28] It is important to remark that this synthetic strategy could be applied to the synthesis of a small library of related compounds from easily available starting materials.

Conclusions

In summary, we have presented an efficient route to indoles regioselectively functionalized at 4- or 7-positions with oxygen-bearing substituents. The starting materials, 2,3-dihalophenyl ethers **3**, are easily prepared by directed *ortho*-metalation reactions from commercially available 3-halophenols or 3-haloanisoles. The copper-free Sonogashira cross-coupling reaction has the advantage of producing only trace amounts of homocoupling products of terminal alkynes and affords the corresponding *o*-alkynylhalobenzene derivatives. Finally, Pd-catalyzed amination and subsequent cyclization allow the synthesis of the oxygen-functionalized indoles in good overall yields. A short synthesis of an indole inhibitor of phospholipase A_2 with this strategy as the key step shows that this methodology may be expected to find application in medicinal chemistry programs and for the synthesis of many indole derivatives.

Experimental Section

Optimized reaction conditions for our previously reported[10] synthesis of *O*-2,3-dihalophenyl carbamates **2** are given in the Supporting Information.

Typical Procedure for the Synthesis of 2,3-Dihalophenyl Ethers 3: Synthesis of 3-Chloro-2-iodoanisole (3a; Table 1, Entry 1). To a solution of 3-chloro-2-iodophenyl *N*,*N*-diethylcarbamate **2a** (3.54 g, 10 mmol) in EtOH (100 mL) was added a large excess of NaOH (4 g, 0.1 mol), and the mixture was heated to reflux for 8 h (completion of the hydrolysis was monitored by GC-MS). After the mixture was cooled to room temperature, most of the EtOH was removed under reduced pressure, and the residue was diluted with Et_2O and water. The organic phase was rejected, and then the aqueous solution was carefully neutralized with a 1 M HCl solution. The aqueous solution was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Without further purification the residue was dissolved in CH_3CN (30 mL), and then iodomethane (1.70 g, 12 mmol) and K_2CO_3 (1.52 g, 11 mmol) were added. The mixture was refluxed overnight and then cooled to room temperature. Most of the CH_3CN was evaporated under reduced pressure, and the residue was diluted with H_2O. The aqueous solution was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 20/1) on silica gel to afford **3a** (2.42 g, 90%) as a white solid: mp 51−53 °C (lit.[30] mp 53.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 8.0, 1.4 Hz, 1H), 6.67 (dd, J = 8.0, 1.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.8 (C), 139.7 (C), 129.8 (CH), 121.8 (CH), 108.5 (CH), 91.2 (C), 56.8 (CH_3); EI-LRMS *m*/*z* 270 (M^+ + 2, 32), 268 (M^+, 100), 253 (21), 126 (24); HRMS calcd for C_7H_6ClIO, 267.9152; found, 267.9166. Anal. Calcd for C_7H_6ClIO: C, 31.32; H, 2.25. Found: C, 31.20; H, 2.20.

Alternative Procedure for the Synthesis of 2,3-Dihalophenyl Ethers 3a and 3e: Synthesis of 3-Bromo-2-iodoanisole (3e).[13] To a solution of lithium 2,2,6,6-tetramethylpiperidide (20 mmol, generated from *n*-BuLi and 2,2,6,6-tetramethylpiperidine) in dry THF (30 mL), a solution of *t*-Bu_2Zn (22 mmol, generated from *t*-BuLi and $ZnCl_2$) in dry THF (30 mL) was added at −78 °C, and the reaction mixture was stirred at 0 °C for 30 min. Then 3-bromoanisole (1.87 g, 10 mmol) was added at −78 °C, and the reaction mixture was allowed to reach −30 °C and was stirred at this temperature overnight. To this was added iodine (17.78 g, 70 mmol) in THF (30 mL), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated $Na_2S_2O_3$, and the aqueous solution was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 20/1) on silica gel to afford **3e** (2.60 g, 83%) as a white solid: mp 63−65 °C (lit.[13b] mp 61.5−62 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.0, 1.4 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 1.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.0 (C), 131.1 (C), 130.2 (CH), 125.1 (CH), 108.9 (CH), 94.3 (C), 56.9 (CH_3); EI-LRMS *m*/*z* 314 (M^+ + 2, 100), 312 (M^+, 100), 299 (21), 297 (20), 172 (42), 170 (40); HRMS calcd for C_7H_6BrIO, 311.8647; found, 311.8635.

Typical Procedure for the Synthesis of 2-Alkynyl-3-chlorophenyl Ethers 4, 2-Alkynyl-3-bromophenyl Ether 5a, and 3-Alkynyl-2-chlorophenyl Ethers 6: Synthesis of 3-Chloro-2-phenylethynylanisole (4a; Table 2, Entry 1).[15e] A mixture of 3-chloro-2-iodoanisole **3a** (1.34 g, 5 mmol), phenylacetylene (1.02 g, 10 mmol), $PdCl_2(PPh_3)_2$ (0.211 g, 0.30 mmol), and TBAF·$3H_2O$ (4.73 g, 15 mmol) was stirred under N_2 at 60 °C for the desired time until complete consumption of starting material as monitored by GC-MS (2−3 h). After the mixture was washed with water, extracted with Et_2O (3 × 15 mL), and evaporated, the residue was purified by flash column chromatography (hexane/EtOAc, 20/1) to afford **4a** (1.12 g, 92%) as a brown oil: R_f 0.18 (hexane/EtOAc, 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.57 (m, 2H), 7.39−7.32 (m, 3H), 7.21 (t, J = 8.3 Hz, 1H), 7.06 (dd, J = 8.3, 1.1 Hz, 1H), 6.81 (dd, J = 8.3, 1.1 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.1 (C), 137.2 (C), 131.8 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 123.3 (C), 121.5 (CH), 112.8 (C), 108.8 (CH), 98.9 (C), 82.7 (C), 56.2 (CH_3); EI-LRMS *m*/*z* 244 (M^+ + 2, 37), 242 (M^+, 100), 199 (19), 178 (24), 165 (33); HRMS calcd for $C_{15}H_{11}ClO$, 242.0498; found, 242.0504.

Typical Procedure for the Synthesis of 4-Alkoxyindoles 7 and 7-Alkoxyindoles 8: Synthesis of 1-Benzyl-4-methoxy-2-phenyl-1*H*-indole (7a; Table 3, Entry 1).[20a] To a solution of $Pd(OAc)_2$ (22.4 mg, 0.10 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (HIPrCl) (42.5 mg, 0.1 mmol), and KO*t*-Bu (0.67 g, 6 mmol) in toluene (6 mL) were added 3-chloro-2-phenylethynylanisole **4a** (0.49 g, 2 mmol) and benzylamine (0.26 g, 2.4 mmol) at room temperature. The resulting mixture was stirred at reflux for 2.5 h, after which GC/MS analysis indicated complete conversion of the starting material. CH_2Cl_2 (25 mL) and aqueous HCl (25 mL of a 2 M solution) were added to the cooled reaction

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mixture. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 15/1) to afford **7a** (0.53 g, 84%) as a white solid: mp 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.34 (m, 5H), 7.33−7.20 (m, 3H), 7.09 (t, J = 8.0 Hz, 1H), 7.06−6.99 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.79 (s, 1H), 6.58 (d, J = 7.6 Hz, 1H), 5.37 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.3 (C), 140.5 (C), 139.5 (C), 138.3 (C), 132.8 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 126.0 (CH), 122.8 (CH), 118.9 (C), 104.1 (CH), 100.1 (CH), 99.6 (CH), 55.5 (CH_3), 48.0 (CH_2); IR (KBr) 3062, 1590, 1501, 1484, 1361, 1257, 754, 699 cm^{-1}; EI-LRMS m/z 313 (M^+, 100), 91 (56); HRMS calcd for $C_{22}H_{19}NO$, 313.1467; found, 313.1459. Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.03; H, 6.16; N, 4.42.

Typical Procedure for the *N*-Debenzylation of 4-Alkoxy-1-benzyl-1*H*-indoles 7: Synthesis of 4-Methoxy-2-phenyl-1*H*-indole (9a).[23] 1-Benzyl-4-methoxy-2-phenyl-1*H*-indole **7a** (0.31 g, 1 mmol) was dissolved in DMSO (0.71 mL, 10 mmol). While the solution was stirred at room temperature, KO*t*-Bu (7 mL of a 1 M solution in THF, 7 mmol) was added. Oxygen was then bubbled into the resulting solution for 1 h. Upon completion (determined by GC-MS analysis), the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 8/1) to afford **9a** (0.16 g, 70%) as a white solid: mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.68−7.62 (m, 2H), 7.48−7.40 (m, 2H), 7.33 (tt, J = 7.3, 1.4 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.00 (dd, J = 2.4, 1.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.4 (C), 138.2 (C), 136.6 (C), 132.4 (C), 129.1 (CH), 127.5 (CH), 125.0 (CH), 123.2 (CH), 120.0 (C), 104.5 (CH), 100.1 (CH), 97.2 (CH), 55.5 (CH_3); EI-LRMS m/z 223 (M^+, 100), 218 (99), 180 (52), 152 (30); IR (KBr) 3354, 1603, 1591, 1459, 1237, 1101, 758 cm^{-1}; HRMS calcd for $C_{15}H_{13}NO$, 223.0997; found, 223.1007. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.46; H, 5.95; N, 6.20.

Typical Procedure for the *O*-Demethylation of 4- and 7-Methoxy-1*H*-indoles 7a−c, 7f, 8a, and 9a: Synthesis of 1-Benzyl-2-phenyl-1*H*-indol-4-ol (10a). BBr_3 (6 mL of a 1 M solution in CH_2Cl_2, 6 mmol) was added dropwise to a solution of the corresponding 1-benzyl-4-methoxy-2-phenyl-1*H*-indole **7a** (0.31 g, 1 mmol) in CH_2Cl_2 (40 mL) at −78 °C. The mixture was warmed to room temperature overnight, and then $KHCO_3$ (0.60 g, 6 mmol) was added. The resulting mixture was cooled to 0 °C, and MeOH (20 mL) was added dropwise. After 30 min at 0 °C, the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with water and the separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexane/EtOAc, 4/1) to afford **10a** (0.26 g, 87%) as a white solid: mp 96−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2H), 7.42−7.36 (m, 3H), 7.34−7.22 (m, 3H), 7.08−7.00 (m, 3H), 6.83 (d, J = 8.3 Hz, 1H), 6.76 (s, 1H), 6.60 (d, J = 7.8 Hz, 1H), 5.65 (s, 1H), 5.37 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 149.0 (C), 140.8 (C), 140.0 (C), 138.2 (C), 132.6 (C), 129.3 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 126.0 (CH), 123.0 (CH), 117.9 (C), 104.8 (CH), 103.8 (CH), 98.6 (CH), 48.1 (CH_2); EI-LRMS m/z 299 (M^+, 100), 208 (25), 91 (50); IR (KBr) 3393, 3062, 1466, 1350, 1256, 1237, 762, 696 cm^{-1}; HRMS calcd for $C_{21}H_{17}NO$, 299.1310; found, 299.1301.

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Supporting Information Available: Experimental procedures and spectroscopic and characterization data for the rest of the compounds described in this paper, and copies of the ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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