Synthesis of 4-functionalized-1*H*-indoles from 2,3-dihalophenols†

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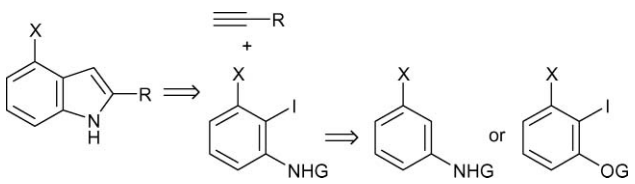
Received 17th March 2010, Accepted 21st June 2010
First published as an Advance Article on the web 8th July 2010
DOI: 10.1039/c004360e

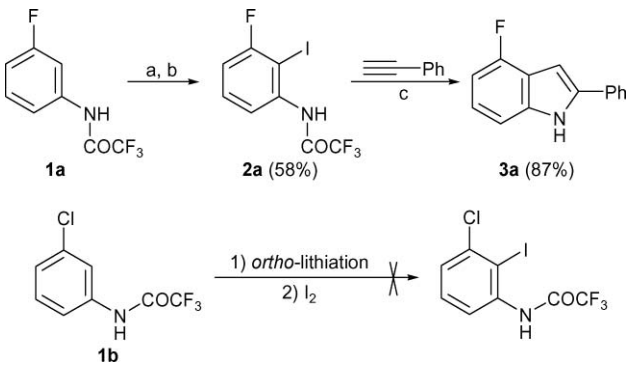
A new synthesis of 4-halo-1*H*-indoles has been developed from easily available 2,3-dihalophenol derivatives. The key steps are Smiles rearrangement and a one-pot or stepwise Sonogashira coupling/NaOH-mediated cyclization. Subsequent functionalization allows access to a wide variety of 2,4- or 2,3,4-regioselectively functionalized indoles.

The indole scaffold is a prominent structural motif found in numerous natural products and biologically active compounds.[1] The combination of classical and modern methods, mainly transition-metal-based reactions, has provided access to a wide variety of polysubstituted indoles.[2] Despite the fact that many methodologies are continuously being developed, the regioselective formation of 4-functionalized indoles is especially challenging. Some reported approaches to prepare 4-substituted indoles involve thallation,[3] mercuriation,[4] or lithiation[5] of adequately 3-functionalized indoles, as well as the palladium-catalyzed regioselective reduction of 4,6-dibromoindoles,[6] and the selective 7-lithiation of 4,7-dibromoindoles.[7] In recent years, a few concrete examples of 4-haloindoles have also been prepared by thermolytic rearrangement of α-aryl azirines,[8] Mo-catalyzed reductive cyclization of nitroaromatics,[9] and Pd-catalyzed coupling of 1,3-dichloro-2-iodobenzene with imines.[10] Nevertheless, the most used strategy to access to this type of indole derivatives involves the heterocyclic construction by ring-closure methodologies starting from properly substituted aromatic precursors.[11] We envisaged that another entry to this interesting class of heterocycles could involve the functionalization of 4-halo-1*H*-indoles, which could be easily accessible from 3-halo-2-iodoaniline derivatives through tandem Sonogashira coupling/heteroannulation reactions (Scheme 1). Although no direct routes are known for these 2,3-dihaloanilines,[12] we reasoned that they could be efficiently prepared from 3-haloaniline derivatives through *o*-metallation reactions, in an analogous way as our reported procedure for the synthesis of 2,3-dihalophenols from 3-halophenol derivatives.[13] Alternatively, 2,3-dihaloanilines could be obtained from 2,3-dihalophenols through the "Smiles rearrangement" methodology.[14]



Scheme 1 Retrosynthetic analysis for the synthesis of 4-halo-2-substituted-1*H*-indoles.

To the best of our knowledge, the only reported example of the *o*-lithiation of a 3-haloaniline derivative and subsequent trapping of the organolithium intermediate with electrophiles was due to Soll and co-workers.[15] These authors described the *o*-lithiation of *N*-trifluoroacetyl-3-fluoroaniline **1a** with *t*BuLi/TMEDA followed by its treatment with bromine or methyldisulfide. So first, we tried to apply these reaction conditions to get 3-fluoro-2-iodotrifluoroacetanilide **2a** from **1a** using iodine as electrophilic reagent. Under these conditions we were able to isolate **2a** in 58% yield (Scheme 2). This compound serves as a useful starting material for the efficient preparation of 4-fluoro-2-phenyl-1*H*-indole **3a** through a domino palladium/copper-catalyzed coupling-cyclization process (Scheme 2).[16]



Scheme 2 *ortho*-Lithiation of 3-haloaniline derivatives **1**. Synthesis of 4-fluoroindole **3a**. *Reagents and conditions*: (a) *t*BuLi/TMEDA (2.2 equiv), THF, −78 °C, 40 min; (b) I_2, −78 °C to rt; (c) $PdCl_2(PPh_3)_2$ (3 mol%), CuI (5 mol%), Et_2NH (1.5 equiv), DMA, 80 °C.

However, when we tried to apply the *o*-lithiation strategy to 3-chlorotrifluoroacetanilide **1b** we did not observe any lithiation reaction. At low temperature (−78 °C) the starting material is recovered and if the reaction mixture is allowed to reach room temperature the addition of *t*BuLi to the trifluoroacetamide moiety is observed.[17] Moreover, it is known that although *t*BuLi is able to metallate the *meta* isomers of *N*-(Boc)fluoro- and chloroanilines at low temperatures, it has been also shown that it was not possible to prevent the subsequent elimination of lithium halide and the generation of benzyne intermediates.[18]

Having seen that the *o*-lithiation methodology is not useful for accessing 2,3-dihaloaniline derivatives other than those bearing a fluorine atom at the *meta* position, we then turned our attention to the use of 2,3-dihalophenol derivatives as starting materials. Several methods have been developed for the conversion of phenols to anilines such as the Bucherer reaction,[19] the activation of phenols with $(EtO)_2POCl$,[20] or 4-chloro-2-phenylquinazoline.[21] Although the Pd-catalyzed coupling of amines with aryl triflates or tosylates

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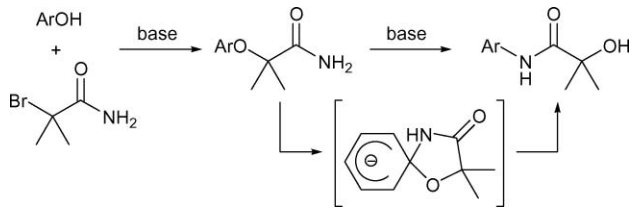
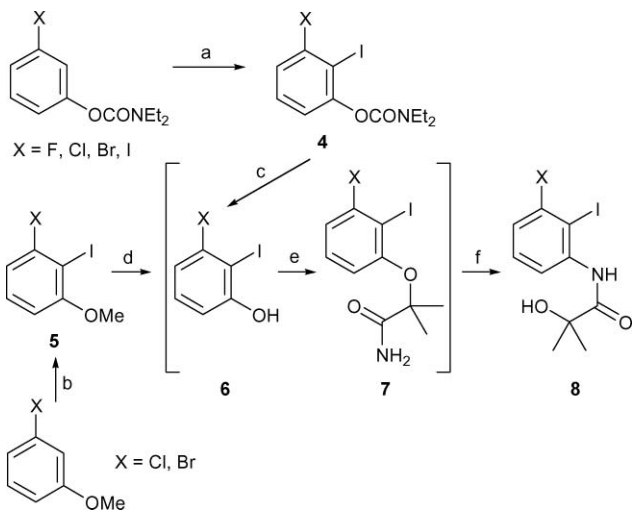
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^1H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c004360e

has been recently developed,[22] the presence of an iodine atom on our substrate precludes the use of this strategy. Besides the Pd- and Cu-catalyzed processes, Smiles rearrangement could be considered the most suitable procedure for preparing *N*-arylamines from phenols.[23] This methodology requires the initial conversion of the corresponding phenol into a 2-aryloxy-2-methylpropanamide.[24] Under basic conditions, this intermediate undergoes rearrangement to give a *N*-aryl-2-hydroxypropionamide, whose formation must involve nucleophilic attack of the amide anion to give a spiro intermediate followed by its breakdown and protonation (Scheme 3). In addition, upon hydrolysis the generated anilide could afford the corresponding aniline.



Scheme 3 Alkylation-Smiles rearrangement sequence.

Interestingly, some one-pot procedures have been described in the literature for this two-steps sequence.[25] The Smiles protocol proved suitable for our purpose and so the required 3-halo-2-iodophenols **6** were generated by basic hydrolysis of the corresponding *O*-2,3-dihalophenylcarbamates **4**,[13a] or by BBr_3-mediated deprotection of 2,3-dihaloanisoles **5**[13b,26] (Scheme 4). The crude phenols **6** were treated with an excess of 2-bromo-2-methylpropionamide[27] and NaOH in DMF at room temperature providing 2-aryloxy-2-methylpropionamides **7** (Scheme 4). Although these intermediates **7** could be easily isolated, it is not necessary to do it and so, the addition of an excess of NaOH to the DMF solution of **7** and subsequent warming to 60 °C



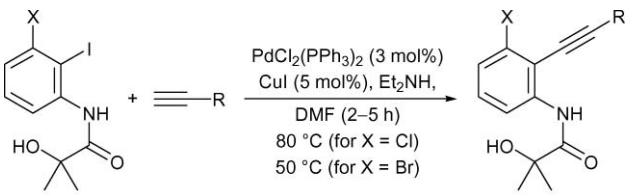
Scheme 4 Synthesis of *N*-(3-halo-2-iodophenyl)-2-hydroxy-2-methylpropanamides **8** from 2,3-dihalophenol derivatives **4** and **5**. *Reagents and conditions*: (a) i) LDA, THF, −78 °C; ii) I_2 (see ref. 13*a* and ESI); (b) i) tBu$_2$Zn(TMP)Li, THF; ii) I_2 (see ref. 13*b*, 26 and ESI); (c) NaOH (10 equiv), EtOH; (d) i) BBr_3, CH_2Cl_2; ii) $NaHCO_3$, MeOH; (e) i) NaOH (3 equiv), DMF, rt; ii) $BrC(Me)_2CONH_2$ (3 equiv), rt; (f) NaOH (9 equiv), 60 °C.

Table 1 Preparation of dihaloanilides **8** from *O*-2,3-dihalophenyl carbamates **4** or 2,3-dihaloanisoles **5**

Entry	Starting material	X	Product	Yield (%)[a]
1	**4a**	F	**8a**	83
2	**4b**	Cl	**8b**	82
3	**4c**	Br	**8c**	81
4	**4d**	I	**8d**	79
5	**5a**	Cl	**8b**	86
6	**5b**	Br	**8c**	85

[a] Isolated yield with reference to starting material **4** or **5**.

Table 2 Synthesis of 2-alkynyl-3-haloanilides **9** and **10**



8b: X = Cl
c: X = Br

9: X = Cl
10: X = Br

Entry	Starting material	X	Alkyne (R)	Product	Yield (%)[a]
1	**8b**	Cl	Ph	**9a**	86
2	**8b**	Cl	nBu	**9b**	90
3	**8b**	Cl	nC$_5$H$_{11}$	**9c**	81
4	**8b**	Cl	cC$_6$H$_9$[b]	**9d**	80
5[c]	**8b**	Cl	SiMe$_3$	**9e**	81
6	**8c**	Br	Ph	**10a**	80
7	**8c**	Br	nBu	**10b**	85
8	**8c**	Br	nC$_5$H$_{11}$	**10c**	79
9	**8c**	Br	cC$_6$H$_9$[b]	**10d**	86
10[c]	**8c**	Br	SiMe$_3$	**10e**	71
11	**8c**	Br	3-Th[d]	**10f**	74

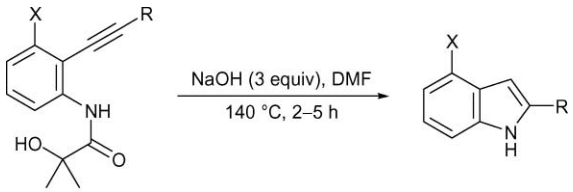
[a] Isolated yield after column chromatography with reference to starting material **8**. [b] 1-Cyclohexenyl. [c] Carried out at 40 °C for 6 h. [d] 3-Thienyl.

afforded *N*-aryl-2-hydroxypropionamides **8** in high overall yields from the starting 3-halo-2-iodophenol derivatives **4** or **5** (Scheme 4 and Table 1). It is remarkable that 3-halo-2-iodoanilides **8** could be efficiently prepared from the corresponding phenol derivatives **4** or **5** in a three-step, two-pot process (phenol deprotection–alkylation–rearrangement). Moreover, compounds **8** are easily isolated at the end of the reaction by simple addition of water to precipitate them. The filtered products proved to be pure enough for the next step without further chromatographic purification.

With a reliable procedure for the preparation of 3-halo-2-iodoanilides **8** and with the synthesis of 4-haloindoles in mind, then we checked the suitability of these dihaloderivatives for a selective Sonogashira coupling with terminal alkynes. By careful control of the reaction temperature in order to avoid dialkynylation processes, 2-alkynyl-3-haloanilides **9** and **10** could be obtained in good yields by Pd–Cu catalysis. Aryl-, alkyl-, heteroaryl-, alkenyl-, and trialkylsilyl-substituted alkynes proved to be useful partners for this coupling reaction that takes place in usually high yields (Table 2).

By taking advantage of our reported procedure for the synthesis of 2-substituted indoles by NaOH-mediated cyclization of 2-alkynylaniline derivatives,[28] 4-halo-1*H*-indoles **11** and **12** were

Table 3 Synthesis of 4-halo-1*H*-indoles **11** and **12** from 2-alkynyl-3-haloanilides **9** and **10**



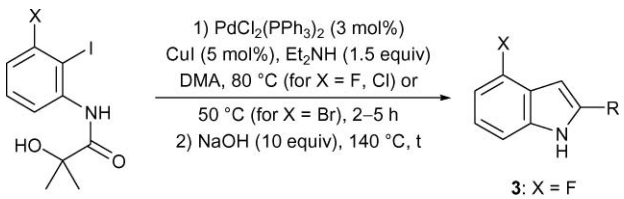
9: X = Cl
10: X = Br

11: X = Cl
12: X = Br

Entry	Starting material	X	R	Time/h	Product	Yield (%)[a]
1	**9a**	Cl	Ph	4	**11a**	79
2	**9b**	Cl	*n*Bu	2.5	**11b**	86
3	**9c**	Cl	nC_5H_{11}	2.5	**11c**	84
4	**9d**	Cl	cC_6H_9[b]	2.5	**11d**	81
5	**9e**	Cl	$SiMe_3$	4	**11e**[c]	73
6	**10a**	Br	Ph	5	**12a**	83
7	**10b**	Br	*n*Bu	3	**12b**	80
8	**10c**	Br	nC_5H_{11}	2.5	**12c**	82
9	**10d**	Br	cC_6H_9[b]	4	**12d**	76
10	**10e**	Br	$SiMe_3$	5	**12e**[d]	75
11	**10f**	Br	3-Th[e]	3	**12f**	71

[a] Isolated yield after column chromatography referred to starting material **9** or **10**. [b] 1-Cyclohexenyl. [c] 4-Chloro-1*H*-indole (R = H). [d] 4-Bromo-1*H*-indole (R = H). [e] 3-Thienyl.

Table 4 One-pot synthesis of 4-halo-1*H*-indoles **3**, **11** and **12** from 2,3-dihaloanilides **8**



8

3: X = F
11: X = Cl
12: X = Br

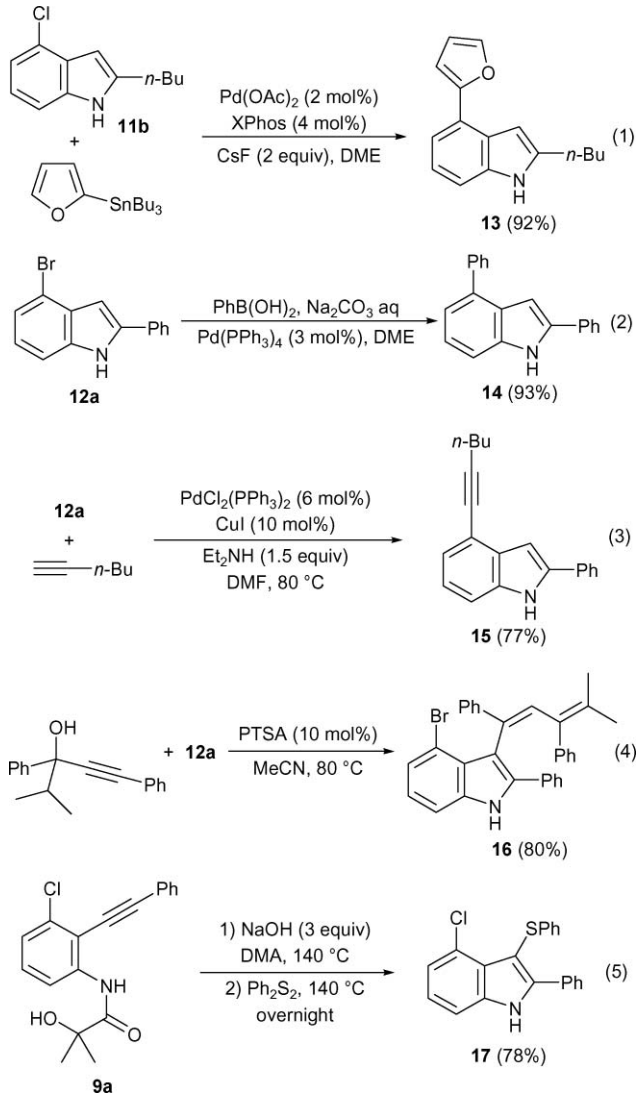
Entry	Starting material	X	R	Time/h	Product	Yield (%)[a]
1	**8a**	F	Ph	4	**3a**	85
2	**8a**	F	*n*Bu	3	**3b**	77
3	**8b**	Cl	Ph	4	**11a**	81
4	**8b**	Cl	*n*Bu	3	**11b**	71
5	**8b**	Cl	cC_6H_9[b]	3	**11d**	82
6[c]	**8b**	Cl	$SiMe_3$	3	**11e**[d]	61
7	**8b**	Cl	3-ClC_6H_4	3	**11f**	75
8	**8b**	Cl	4-F-3-MeC_6H_3	4	**11g**	72
9	**8c**	Br	Ph	4	**12a**	49
10	**8c**	Br	*n*Bu	3	**12b**	55
11	**8c**	Br	3-ClC_6H_4	4	**12g**	48

[a] Isolated yield after column chromatography with reference to starting material **8**. [b] 1-Cyclohexenyl. [c] Sonogashira coupling was carried out at 40 °C for 6 h. [d] 4-Chloro-1*H*-indole (R = H).

obtained in high yields by treatment of *o*-alkynylanilides **9** and **10** with excess of NaOH at high temperature (Table 3). Interestingly, in the case of starting from 3-halo-2-(trialkylsilylethynyl) anilides **9e** or **10e**, 4-chloro-1*H*-indole **11e** or 4-bromo-1*H*-indole **12e** were respectively obtained by further cleavage of the silyl group under the reaction conditions (Table 3, entries 5 and 10).

Moreover, 4-haloindoles **3**, **11** or **12** could also be prepared by a one-pot procedure starting from 2,3-dihaloanilides **8** without isolation of any intermediate (Table 4). Whereas this one-pot protocol nicely works for the synthesis of 4-fluoroindoles **3** and 4-chloroindoles **11** (Table 4, entries 1–8), 3-bromo-2-iodoanilide **8c** leads to lower yields of 4-bromoindoles **12** (Table 4, entries 9–11). The formation of several side-products from **8c** is probably be due to competitive Pd-catalyzed reactions involving the C–Br bond. For the synthesis of these indole derivatives **12** the two-step sequence was found more appropriate.

Finally, we decided to check the usefulness of these 4-haloindoles **11** and **12** as precursors of 4-functionalized-1*H*-indoles (Scheme 5). For instance, chloro derivative **11b** was subjected to Pd-catalyzed Stille coupling with



Scheme 5 Synthetic applications of 4-haloindoles.

2-(tributylstannyl)furan,[29] affording 4-(2-furanyl)indole **13** in high yield (eqn (1)). On the other hand, 2,4-diphenylindole **14** and 4-alkynylindole derivative **15** are readily accessible from 4-bromo-1*H*-indole **12a** by Suzuki and Sonogashira cross-coupling reactions, respectively, under standard Pd-catalysis (eqn (2) and (3)).[30] Besides Pd-catalyzed processes, by applying our recently developed allenylation of 2-arylindoles with tertiary propargylic alcohols,[31] 3-dienylindole **16** was obtained in high yield (eqn (4)). It was also possible to synthesize a 3-arylthio-4-halo-2-substituted-1*H*-indole like **17** by introduction of the arylthio group at C-3 under the basic conditions required for the cyclization step (eqn (5)).[32]

In summary, we have developed an efficient route to 4-halo-1*H*-indoles from 3-halo-2-iodophenol derivatives using the Smiles rearrangement and a NaOH-mediated cyclization as the key steps. 3-Halo-2-iodoanilides were obtained in high yields from *O*-3-halo-2-iodophenyl *N*,*N*-diethylcarbamates or 3-halo-2-iodoanisoles without any chromatographic purification. Their subsequent coupling with terminal alkynes and cyclization under treatment with NaOH allow the access to challenging 4-haloindoles with a variety of substituents at C-2. In addition, the usefulness of these 4-haloindoles produced by this chemistry as intermediates for further transformations has been briefly outlined, including reactions that afford 2,4- and 2,3,4-functionalized indoles.

Acknowledgements

We gratefully thank Junta de Castilla y León (BU021A09 and GR-172) and Ministerio de Educación y Ciencia (MEC) and FEDER (CTQ2007-61436/BQU) for financial support. V. G. thanks MEC for a predoctoral FPU fellowship.

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