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Chemistry of aminophenols. Part 2: A general and efficient synthesis of indoles possessing a nitrogen substituent at the C4, C5, C6, and C7 positions

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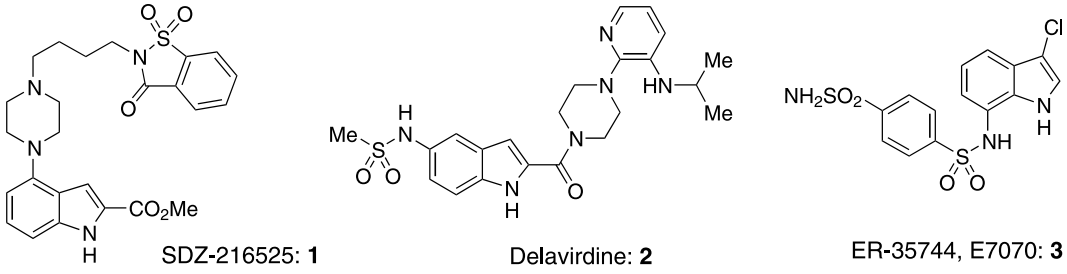
Abstract—A general and efficient synthesis of indoles possessing a nitrogen substituent at the C4, C5, C6, and C7 positions has been developed. Starting from commercially available nitro 2-aminophenols, 5-, 6-, and 7-arenesulfamoylindoles were synthesized via a base-promoted ring closure of 2-alkynylanilides, reduction of the nitro group, and sulfonylation. C4 nitrogen substituted indoles were synthesized from 2-chloro-1,3-dinitrobenzene via cyclization of 2-alkynyl-1,3-diaminobenzene as the key step. © 2002 Elsevier Science Ltd. All rights reserved.

Indoles possessing nitrogen substituents on the ring skeleton are often found to exhibit biological activity. As illustrated in Scheme 1, the C4 nitrogen substituted indole, SDZ-216525 **1**, is a 5-HT_7 selective agonist.[1] Delavirdine **2** is one of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) approved for HIV therapy.[2] Zafirlukast is an LTD_4 antagonist effective against exercise-induced asthma, in antigen-induced bronchospasm, and for protection in cold-air challenge studies.[3] Another C5 nitrogen substituted indole, LY334370, is a selective 5-HT1F receptor agonist.[4] It was reported to be a potent inhibitor of neurogenic dural inflammation and was tested for treatment of migraine although it was suspended from phase III clinical trials due to non-mechanism based liver toxicity. The C7 nitrogen substituted indole, ER-35744, E7070 **3**, was reported to be in phase I clinical trials for anticancer activity and is thought to affect the progression of the cell cycle in the G1 phase with inhibition of expression of cyclin E and phosphorylation of cdk2.[5] In connection with our study on diversity-oriented synthesis of bioactive heterocycles from readily available commercial reagents,[6] we undertook a general and efficient synthesis of indoles possessing a nitrogen substituent at the C4, C5, C6, and C7 positions.

Three commercially available nitro 2-aminophenols, i.e. 2-amino-5-nitrophenol **4a**, 2-amino-4-nitrophenol **4b**, and 2-amino-3-nitrophenol **4c**, were used in our synthesis of C5, C6, and C7 nitrogen substituted indoles **10a–c** (Scheme 2).[7] Selective protection of the amino group in **4a**,**b** was carried out by treatment with an acyl chloride, for example, butyryl chloride, in the presence of pyridine in refluxing THF to give **5a**,**b** in 86% and 97%



Scheme 1. Selected examples of bioactive nitrogen substituted indoles.

Keywords: coupling reactions; indoles; phenols; triflates.

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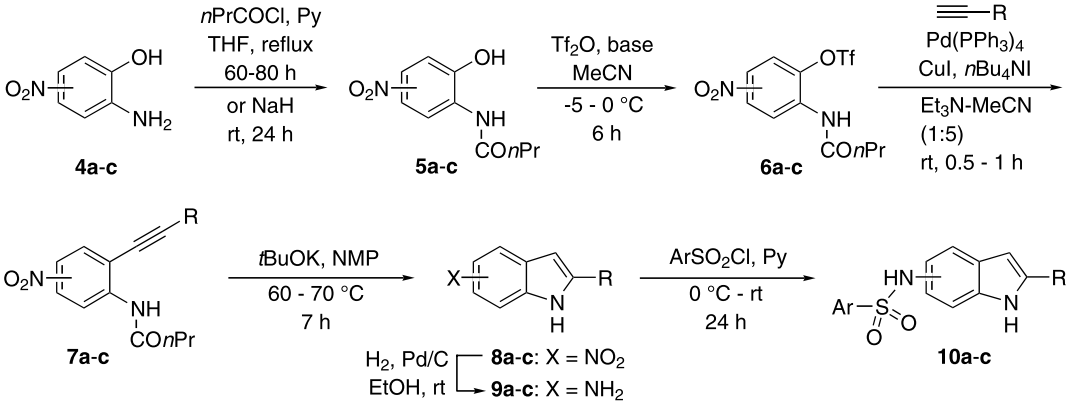
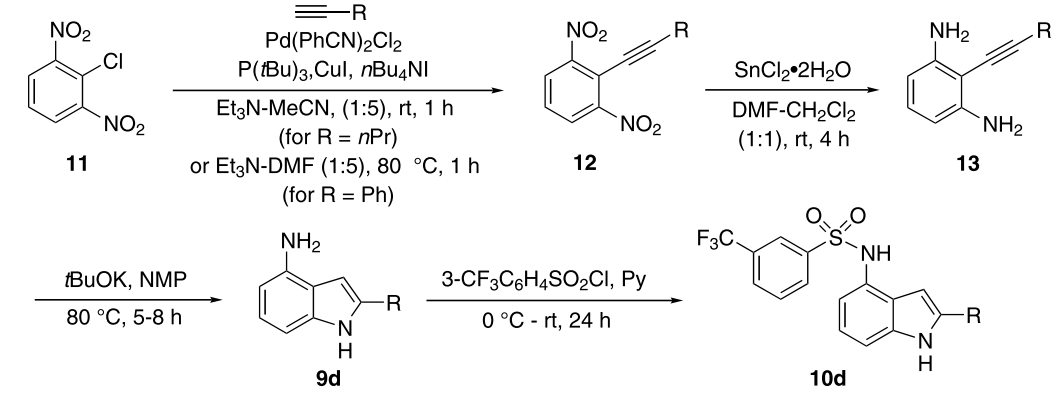
yield, respectively. Under the heating conditions, the undesired *O*-acylation products gradually rearranged to the *N*-acylation product and only the anilides **5a**,**b** were obtained.[8] Acylation of **4c** did not work well using pyridine as the base, therefore, **5c** was obtained from **4c** using NaH and butyryl chloride (rt, 24 h) in 60% yield. The triflates **6a–c**, prepared from **5a**,**b** (NaH, Tf_2O, 80% and 87%) and **5c** (Et_3N, Tf_2O, 94%), underwent a facile cross-coupling reaction with 1-alkynes catalyzed by 10 mol% $Pd(PPh_3)_4$ and 30 mol% CuI in the presence of an additive, nBu_4NI (150 mol%),[6] in Et_3N/MeCN (1:5).[9] To evaluate the reactivity of alkyl and aryl 1-alkynes with the triflates, 1-pentyne and phenylacetylene were used in the cross-coupling reactions, which were complete within 0.5–1 h to provide **7a–c** in excellent yields (Table 1, entries 1–4, 7, and 8).

We carried out the ring closure reaction within the 2-alkynylanilides **7a–c** using 1.2 equiv. of ^{t}BuOK in NMP at 60–70°C.[6,10] It was found that the nitro group survived the basic conditions without significant decomposition. The nitro indoles **8a–c** were isolated in 72–86% yields (Table 1). Reduction of the nitro group in **8a–c** (R = Ph) over Pd/C in EtOH with hydrogen furnished the amino indoles **9a–c** (R = Ph, 85–96% yields), which were converted into the arenesulfamoylindoles **10a–c** (Scheme 2 and Table 1, entries 2, 4–6, and 8). For the C5 substituted indoles, the product **10a** was obtained in 84% yield. To demonstrate the generality of the sulfonamide formation, for the C6 amino indole **9b** (R = Ph), three arenesulfonyl chlorides were used to form **10b-1**, **10b-2**, and **10b-3**, respectively, in 70–80% yields (Table 1, entries 4–6). The C7 arenesulfamoylindole **10c** was synthesized similarly in 73% yield (Table 1, entry 8).

Scheme 3 illustrates the synthesis of C4 nitrogen substituted indoles starting from 2-chloro-1,3-dinitrobenzene **11**.[7] The key step is the cross-coupling of **11** with 1-alkynes, which must be conducted using a suitable catalytic system. Although the nitro groups in **11** may activate the C–Cl bond, the steric repulsion makes the cross-coupling difficult. Compound **11** failed to form cross-coupled products with 1-alkynes when PPh_3 was used. Recently, Buchwald and Fu reported a modified catalyst system for the Sonogashira reaction of aryl bromides at room temperature, where a bulky phosphine, P^tBu_3, was used together with $Pd(PhCN)_2Cl_2$.[11] We tried the cross-coupling reaction of **11** with 1-pentyne using 10 mol% $Pd(PhCN)_2Cl_2$, 20 mol% P^tBu_3, 20 mol% CuI, and 150 mol% $^nBu_4NI$[6] in Et_3N/MeCN (1:5). The reaction was complete at room temperature after 1 h giving **12** (R = ^{n}Pr) in 93% yield. However, phenylacetylene failed to couple with **11** at room temperature. Compound **12** (R = Ph) was obtained in 60% yield by carrying out the reaction at 80°C in Et_3N/DMF (1:5). Reduction of the nitro groups in **12** was attempted under different sets of conditions. For example, **12** (R = ^{n}Pr) was reduced to **13** (R = ^{n}Pr) in 51% yield by Fe+HCl (0.5%) in 50% EtOH (reflux, 4 h).

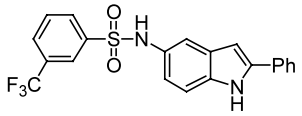
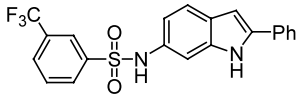
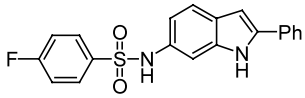
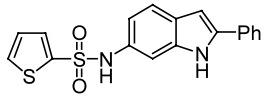
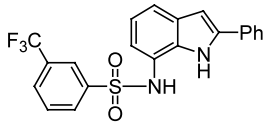
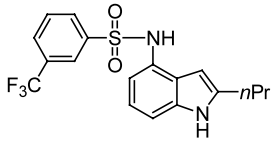
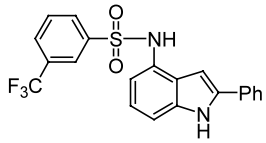


Scheme 2. Synthesis of 5-, 6-, and 7-arenesulfamoylindoles from nitro 2-aminophenols.



Scheme 3. Synthesis of 4-arenesulfamoylindoles from 2-chloro-1,3-dinitrobenzene.

Table 1. Structures and chemical yields of cross-coupling products and nitrogen substituted indoles

entry	ring substituent[a]	R	**7**, yield (%)	**8**, yield (%)	**9**, yield (%)	**10**, yield (%)
1	C5	*n*Pr	**7a**, 95	**8a**, 84		
2	C5	Ph	**7a**, 95	**8a**, 85	**9a**, 85	 **10a**, 84
3	C6	*n*Pr	**7b**, 90	**8b**, 86		
4	C6	Ph	**7b**, 96	**8b**, 84	**9b**, 96	 **10b-1**, 80
5	C6	Ph				 **10b-2**, 70
6	C6	Ph				 **10b-3**, 80
7	C7	*n*Pr	**7c**, 91	**8c**, 72		
8	C7	Ph	**7c**, 90	**8c**, 76	**9c**, 86	 **10c**, 73
9	C4	*n*Pr			**9d**, 75	 **10d-1**, 83
10	C4	Ph			**9d**, 90	 **10d-2**, 75

[a]Indole skeleton numbering was used here.

When $SnCl_2 \cdot H_2O$ (10 equiv.) was used as the reductant in hot EtOH (65°C, 0.5 h),[12] the substrate was consumed but the desired product was not detected. By changing the solvent to DMF/CH_2Cl_2 (1:1), **12** was reduced to **13** by $SnCl_2 \cdot H_2O$ (60 equiv., rt, 4 h) in 66% (R = *n*Pr) and 80% (R = Ph) yields, respectively. Ring closure of **13** was examined under two different conditions. Treatment of **13** with CuI[13] in DMF (100°C, 2 h) afforded the product **9d** in 42% (R = *n*Pr) and 10% yields (R = Ph). Alternatively, high yields were obtained via the *t*BuOK-mediated ring closure in NMP at 80°C for 5 h (**9d**: R = Ph, 90%) and 8 h (**9d**: R = *n*Pr, 75%).[10] Finally, treatment of the C4 amino indoles **9d** with 3-(trifluoromethyl)benzenesulfonyl chloride in pyridine

furnished the C4 arenesulfamoylindoles **10d-1** and **10d-2** in 75–83% yields (Scheme 3 and Table 1, entries 9 and 10).

In summary, we have developed a general synthesis of indoles possessing a nitrogen substituent at the C4, C5, C6, and C7 positions from the commercially available nitro 2-aminophenols **4a**–**c** and 2-chloro-1,3-dinitrobenzene **11**. Introduction of diversity at the C2 position can be achieved by using commercially available 1-alkynes. Our synthesis is of interest for the generation of indole libraries. Work toward this goal is currently in progress in our laboratory.

Acknowledgements

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