ORGANIC LETTERS

2001
Vol. 3, No. 24
3827−3830

Solid-Phase Synthesis of 2,3,5-Trisubstituted Indoles

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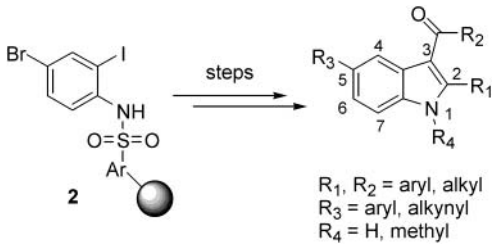
Received August 1, 2001

ABSTRACT



2,3,5-Trisubstituted indoles are synthesized in three steps starting from resin-bound aniline 2. R1 is introduced by a palladium-mediated coupling of the aryl iodide with terminal alkynes followed by intramolecular cyclization to form the indole core. Acylation at C-3 with an acid chloride in the presence of $AlCl_3$ catalyst introduces R2. The indole C-5 position is then diversified either by Sonagashira or Suzuki couplings with the aryl bromide. Finally, indole N-1 can be modified by post-cleavage methylation.

Indole and indole-like structures are found in numerous natural products with interesting biological functions[1] and as a result have attracted considerable attention from organic chemists.[2] With recent advances in solid-phase synthesis,[3] many combinatorial approaches to generate indole libraries have been described.[4] Most of the previous solid-phase methodologies have utilized linkers that leave a polar functional group (e.g., COOH, $CONH_2$) after cleavage.[4] More recent strategies involve a traceless linkage through N-1 using sulfonamide,[5a] carbamate,[5b] and tetrahydropyran linkers,[5c] such that no extraneous polar tethering substituents are obtained upon cleavage. The ability to introduce diverse substituents on the benzo ring would further expand the scope of solid-phase indole chemistry. Herein we report the solid-phase combinatorial synthesis of 2,3,5-trisubstituted indoles using a traceless sulfonamide linker.

4-Bromo-2-iodoaniline was loaded onto the commercially available PS-TsCl resin (polystyrene sulfonyl chloride; Argonaut Technologies) in the presence of pyridine and 1,2-dichloroethane (Scheme 1) to give the resin-bound sulfonamide **2**. Using a slightly modified method from Zhang et al.,[5a] **2** is coupled to various terminal alkynes and cyclized

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(1) (a) Kerber, V. A.; Gregianini, T. S.; Paranhos, J. T.; Schwambach, J.; Farias, F.; Fett, J. P.; Fett-Neto, A. G.; Zuanazzi, J. A. S.; Quirion, J. C.; Elizabetsky, E.; Henriques, A. T. *J. Nat. Prod.* **2001**, *64*, 677−679. (b) Gerasimenko, I.; Sheludko, Y.; Stockigt, J. *J. Nat. Prod.* **2001**, *64*, 114−116.

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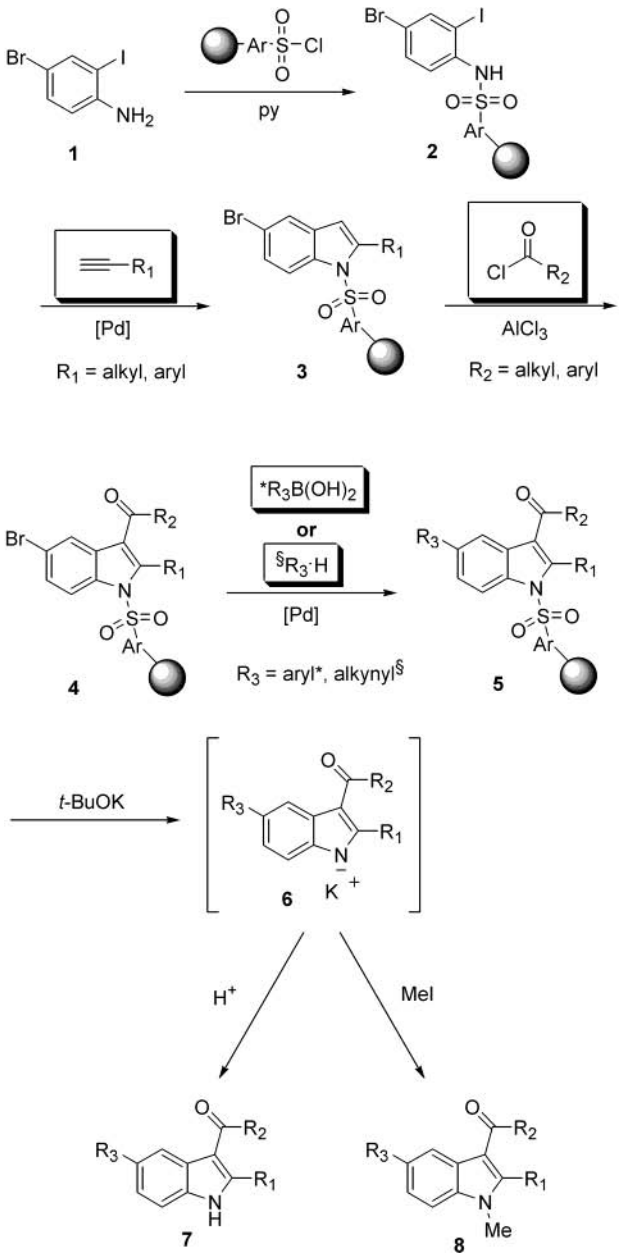
10.1021/ol016525t CCC: $20.00
Published on Web 10/31/2001

Scheme 1



intramolecularly to give resin-bound indole **3**. The C-3 position is acylated by treatment with acid chlorides in the presence of catalytic $AlCl_3$ to afford **4**. At this stage the C-5 position can be modified in two ways. A Sonagashira coupling reaction with the 5-bromo substituent affords the alkynylated indole **5**, whereas a Suzuki coupling introduces the corresponding aryl group. Cleavage of **5** from the resin is achieved by saponification of the sulfonamide linker by treatment with *t*-BuOK at room temperature. A post-cleavage methylation at the N-1 position is accomplished by trapping intermediate **6** with excess MeI. This methylation step effectively bifurcates our indole pharmacophore by removing the hydrogen-bond donor from N-1.

To introduce substituents at the C-2 position, we used the conditions previously reported by Zhang et al. (10% $Pd(PPh_3)_2Cl_2$, 20% CuI, DMF, Et_3N, 70 °C, 6 h). However, we found that the reaction occurred with both the 2-iodo and the 4-bromo group.[5a] Because the bromo substituent is required for subsequent functionalization of the indole benzo ring, conditions are needed that selectively couple terminal alkynes to the aryl iodide followed by intramolecular ring closure to complete the indole scaffold. This was achieved by lowering the reaction temperature to room temperature and extending the reaction time to 24 h. Although reactive functional groups such as −OH and −NH could not be carried through the subsequent reactions, other functional groups gave quantitative conversions (Figure 1).

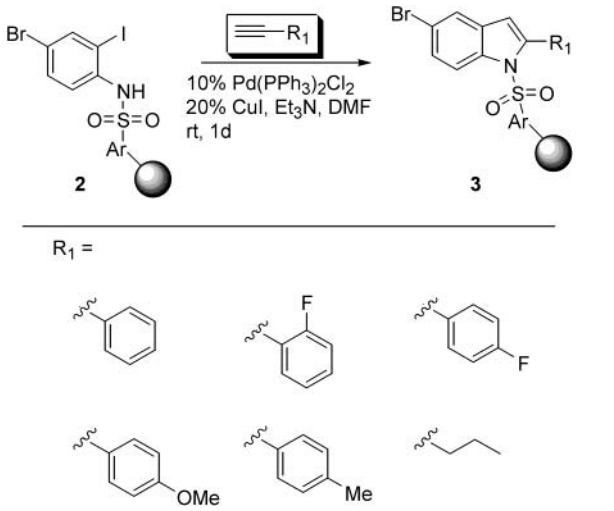


Figure 1. C-2 Substituents (R1) introduced from terminal alkyne precursors.[6]

The indole C-3 position was modified by an acylation reaction. Acylation of indoles at C-3 with unprotected N-1 has been demonstrated using Et_2AlCl;[7] however, the reaction did not proceed with the N-1 electron-withdrawing sulfonamide group. Instead, the use of $AlCl_3$ with a variety of acid chlorides resulted in clean conversion of **3** to **4**.[8] Aromatic acid chlorides generally afforded quantitative conversion (Figure 2), except for those with ortho functional groups (presumably because of steric hindrance with the R1 substituents). The methyl ketone product did not result in side reactions during the basic cleavage step.

We then turned our attention to elaboration of the C-5 position. The bromo substituent was expected to allow modification through various types of palladium-mediated coupling reactions. Using the more vigorous Sonagashira coupling conditions (20% $Pd(PPh_3)_2Cl_2$, 40% CuI, 70 °C), terminal alkynes could be coupled to the C-5 position. Most

(6) All products were synthesized with the depicted R_1 substituents and $R_2 = R_3$ = phenyl (introduced using benzoyl chloride and phenylboronic acid as shown in Scheme 1). RP-LCMS shows >95% purity based on UV absorption at 255 nm.

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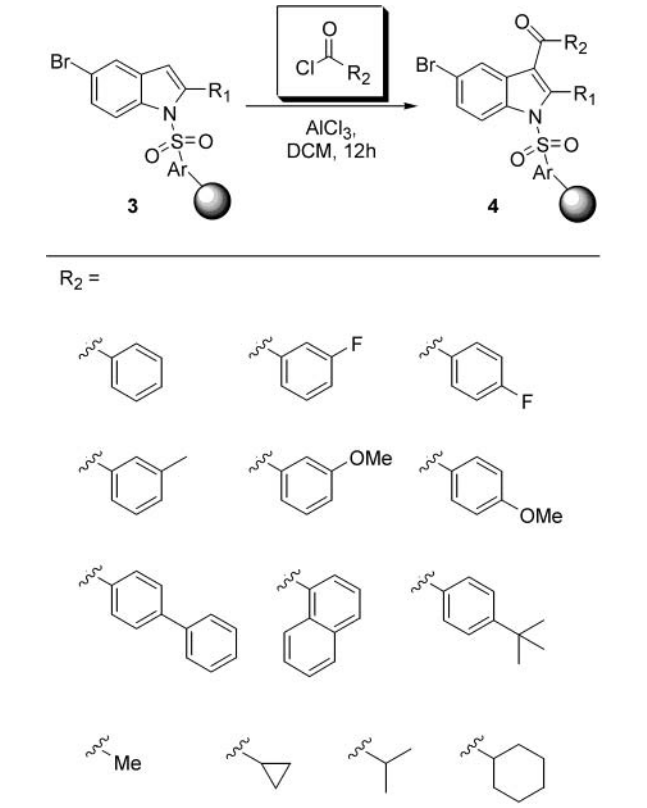

Figure 2. C-3 substituents (R2) introduced from acid chloride precursors.[9]

aryl and alkyl terminal alkynes are compatible, as was the case with the previous Sonagashira coupling step (Figure 3).

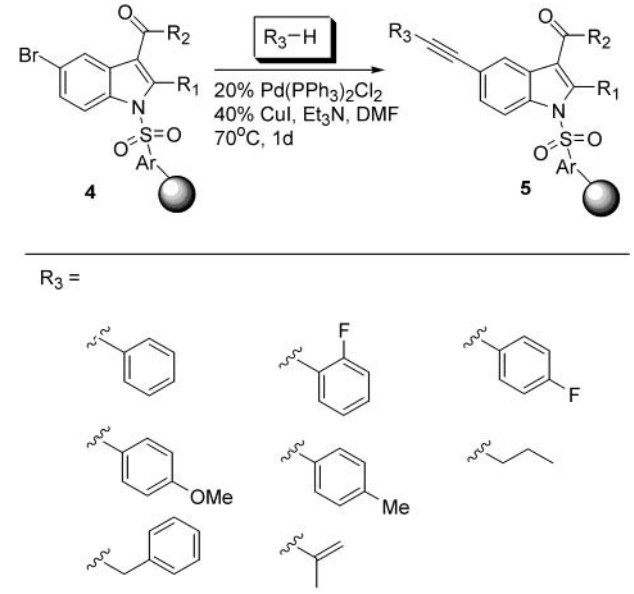

Figure 3. C-5 substituents (R3) introduced from terminal alkyne precursors.[10]

We also explored the use of Suzuki couplings to introduce substitutents at the C-5 position. Initial attempts to use the classical biphasic coupling conditions (15% $Pd(PPh_3)_4$, toluene, aqueous saturated $NaHCO_3$)[11] were successful. However, these conditions did not give reproducible results if the reaction was performed with the resin-bound precursor loaded in the Irori Microkans©. The problem possibly resulted from the uneven diffusion of the two solvent phases into the Microkans©. After extensive optimization, it was found that the use of THF as a cosolvent in the biphasic Suzuki coupling instead of toluene greatly enhanced the miscibility of the two phases. We also found that $Pd(dppf)Cl_2$ in dioxane with K_3PO_4 as the base gave reproducible results.[12] In general, electron-poor and mildly electron-rich boronic acids gave quantitative conversion, while coupling reactions with extremely electron-rich boronic acids proceeded sluggishly[13] (Figure 4). Aryl boronic acids with acidic functional groups

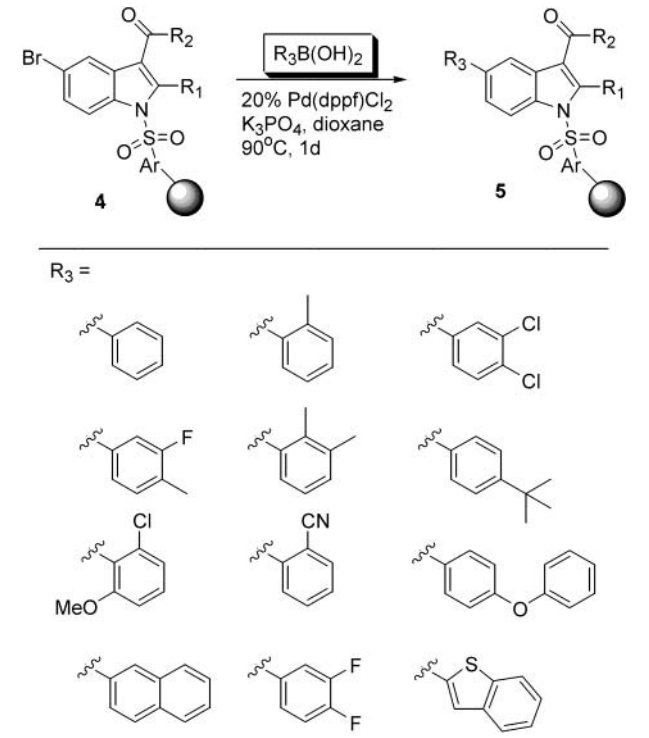

Figure 4. C-5 substituents (R3) introduced from boronic acid precursors.[14]

such as −OH or −NH also did not react. Nevertheless, the reaction conditions were mild enough not to oligomerize boronic acids with chloro substituents. At present, the C-4, C-6, and C-7 positions cannot be easily modified using

(9) All products were synthesized with the depicted R_2 substituents and $R_1 = R_3 =$ phenyl (introduced using phenylacetylene and phenylboronic acid as shown in Scheme 1). RP-LCMS shows >95% purity based on UV absorption at 255 nm.

(10) All products were synthesized with the depicted R_3 substituents and $R_1 = R_2 =$ phenyl (introduced using phenylacetylene and benzoyl chloride as shown in Scheme 1). RP-LCMS shows >95% purity based on UV absorption at 255 nm.

similar approaches as shown in Scheme 1 because of the lack of commercial sources for the corresponding 3-, 5-, or 6-bromo-2-iodoaniline.

Cleavage of the resin-bound 2,3,5-trisubstituted indoles is accomplished using 10 equiv of *t*-BuOK in THF for 5 h at room temperature. A post-cleavage methylation at indole N-1 could be carried out by adding 20 equiv of MeI to the cleavage reaction and shaking for an additional 2 h after the base cleavage. This makes it possible to produce both indoles with either a free hydrogen-bond donor or a hydrophobic group at N-1. However, alkyl halides other than methyl iodide have failed to trap the indole N-1 anion with similar efficiency. The yields ranged from 10% to 20% overall, based on the resin-loading level of **1** (Scheme 1).

In conclusion, we have described a general approach to introduce diverse substituents at the indole C-2, C-3, and C-5 positions. The reaction scheme includes a palladium-mediated coupling/cyclization, an acylation, and either a Sonagashira or Suzuki coupling reaction. A post-cleavage methylation at the indole N-1 is also feasible. Further work involving library synthesis and biological testing is in progress.

Acknowledgment. T.W. thanks Dr. Adam Tomasi and Dr. Nick Winssinger for helpful discussion and support.

Supporting Information Available: LCMS and ^{1}H NMR of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Reaction with 3,4-dimethoxyphenylboronic acid after 1 day still showed ∼30% unreacted starting material plus ∼70% desired product. Elevated temperature and/or prolonged reaction time did not seem to increase the product to starting material ratio.

(14) All products were synthesized with the depicted R_3 substituents and $R_1 = R_2 =$ phenyl (introduced using phenylacetylene and benzoyl chloride as shown in Scheme 1). RP-LCMS shows >95% purity based on UV absorption at 255 nm.