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Facile Solid-Phase Construction of Indole Derivatives Based on a Traceless, Activating Sulfonyl Linker

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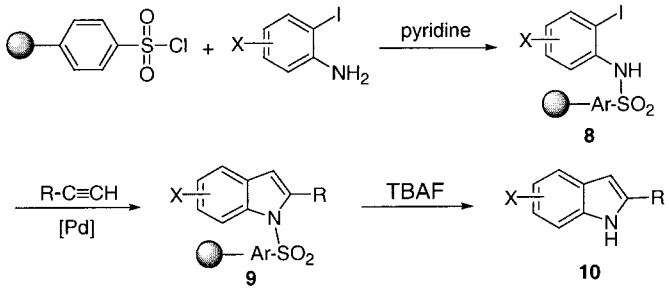
ABSTRACT



Palladium-mediated coupling/intramolecular indole cyclization of terminal alkynes with resin 8, followed by cleavage of the sulfonamide linkage, were executed under mild conditions to provide diverse indoles 10 in excellent yield and purity. This chemistry benefits from a dual-activation process that derives from use of a traceless *N*-sulfonyl linker. Also, direct mercuration of 9 (X = H, R = 4-Me-C_6H_4), followed by palladium-mediated coupling with methyl acrylate, efficiently provided 3-functionalized product 12.

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Thus, there has been a great deal of interest in the development of strategies for generating heterocyclic libraries on solid supports.[2] Given that the indole nucleus is present in a wide variety of biologically active compounds, we[3] and others[4] have devised efficient solid-phase syntheses of indole derivatives for the generation of indole-based combinatorial libraries. However, all of these solid-phase methods are based on amide, ester, or ether linkers, which remain in the final products after cleavage. Since extraneous substituents such as $CONH_2$, CO_2H, or OH could well be undesirable in certain libraries, there is a need to develop solid-phase synthetic routes to indoles that rely on traceless linkers. Already, there have been several traceless-linker strategies described for the solid-phase synthesis of small organic molecules, such as those involving silicon,[5] oxidation-labile,[6] and safety-catch[7] linkers, as well

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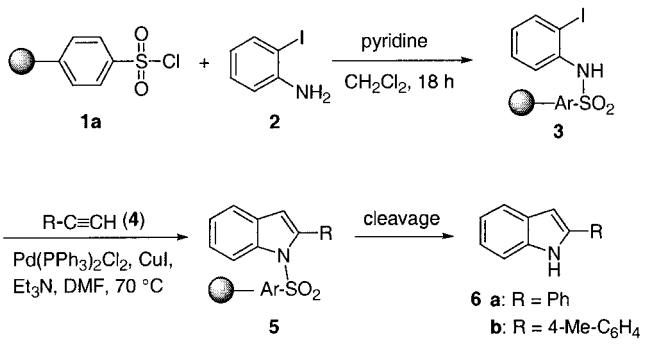
as cyclization/cleavage.[8] A traceless solid-phase synthesis of indoles based on a THP resin was also recently disclosed.[9] Herein, we report our synthetic studies on the construction of indoles on the solid phase with a traceless sulfonyl linker, which further capitalizes on a "dual-activation process". That is, the traceless sulfonyl linker serves as an activating group to facilitate indole cyclization and, after indole formation, is activated and poised for cleavage under mild conditions.

A particularly useful approach to 2-substituted indoles involves palladium-mediated heteroannulation of 2-iodoanilines with terminal alkynes.[3c,4a,b,10] Thus, an aryl iodide is coupled with a terminal alkyne to form the sp^2-sp coupling product, which then undergoes intramolecular cyclization to form an indole ring. In this process, unlike the palladium-mediated heteroannulation of a 2-haloaniline with an internal alkyne,[3b,11] activation of the amine is required to effect the cyclization. The efficiency of the cyclization depends on the nitrogen substituent and on forcing conditions, such as a strong base and high temperature, which are normally applied with substituents such as acyl or alkoxycarbonyl.[10a,12] By contrast, when the amine is activated by a strong electron-withdrawing group such as sulfonyl, *the sp^2-sp coupling and the indole cyclization can occur in one pot under relatively mild conditions*.[3c,13] Therefore, we considered employing a sulfonyl resin attached to nitrogen as a traceless and activating linker for the solid-phase synthesis of indoles. Sulfonyl linkers have been developed[14] and used for various chemical transformations on the solid phase.[14a,15] Cleavage of a sulfonyl linker from nitrogen in solid-phase synthesis can require inconvenient conditions, such as anhydrous HF; however, this linkage in our chemistry can be easily removed from the indole nitrogen under mild conditions.

To test this process, we first used 2-iodoaniline **2** and the commercially available PS-TsCl resin **1a** (polystyrene sulfonyl chloride; Argonaut Technologies). We loaded resin **1a** with **2** in the presence of pyridine/CH_2Cl_2 to give resin-bound precursor **3** (Scheme 1). Treatment of resin **3** with phenylacetylene (**4**, R = Ph, 6 molar equiv), a catalytic amount of $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (20 mol %), and Et_3N in DMF at 70 °C for 6 h resulted in a black reaction mixture. After

Scheme 1



washing, the resulting resin was subjected to cleavage. An initial attempt to cleave the sulfonyl linker with KOH, the most common base used in solution-phase deprotection of the tosyl group from indole nitrogen, proved to be problematic. For example, cleavage of **5** (R = Ph) with 5% KOH in MeOH/1,4-dioxane/water (1:1:0.1) occurred very slowly at 23 °C. Increasing the reaction temperature to 70 °C for 5 h afforded desired indole **6a** with only 41% yield and 67% purity as determined by HPLC (Table 1, entry 1). Prolonging

Table 1. Cleavage of Resin [**5** (R = Ph) → **6a**]

entry	rgt (mol equiv)	solvent	T (°C)	time (h)	yield[a] (%)	purity[b] (%)
1	KOH (10)	*c*	70	5	41	67
2	*t*-BuOK (10)	THF	0	3	68	93
3	*t*-BuOK (10)	THF	0	6	82	82
4	*t*-BuOK (10)	THF	25	3	100	94
5	Me_3SiOK (10)	THF	0	3	8	35
6	Mg	*d*	25	5	11	29
7	K_2CO_3 (10)	*c*	70	7	26	69
8	CsF (5)	THF	70	5	0	-
9	CsF (5)	DMF	100	5	66	92
10	KF (5)	DMF	100	5	0	-
11	TBAF (5)	THF	70	5	100	95

[a] Crude yields (based on loading level of resin **3**). [b] Determined by reversed-phase HPLC. [c] MeOH/1,4-dioxane/water (1:1:0.1). [d] THF/MeOH (1:1).

the reaction time at 70 °C increased the cleavage, but more impurities were also generated. Therefore, efforts were made to identify a relatively mild method to effectively cleave this sulfonyl linker. Other bases, a variety of fluoride reagents, and a reductive cleavage method using magnesium were surveyed. As shown in Table 1, potassium *tert*-butoxide was much better than KOH for the cleavage of **5** (R = Ph), providing desired product **6a** in quantitative yield with 94%

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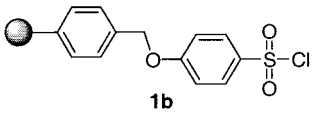
purity (entry 4). However, the application of this base to combinatorial synthesis could be limited since strongly basic conditions may not accommodate a wide variety of functional groups. Fortunately, tetrabutylammonium fluoride[16] (TBAF, 5 molar equiv) in THF at 70 °C for 5 h proved to be excellent, providing cleaved product **6a** in quantitative yield (after removal of the TBAF) with 95% purity (entry 11). TBAF was easily eliminated from the crude product by aqueous washing. This mild cleavage method should allow the synthesis of diverse indole derivatives bearing either base- or acid-sensitive functional groups.

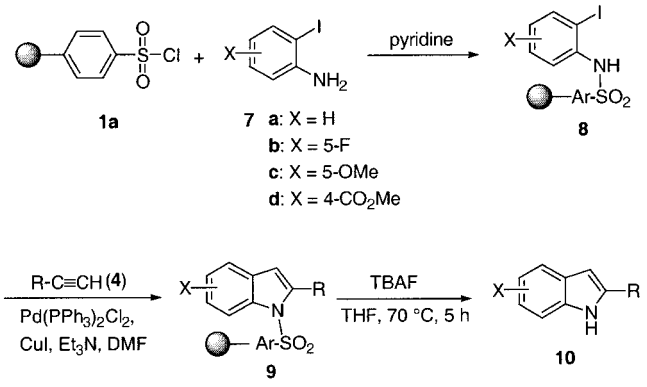


1b

The results in Table 1 clearly demonstrate that the palladium-mediated sp^2-sp coupling of **3** with phenylacetylene (**4**, R = Ph) and sulfonyl linker-activated indole cyclization occur efficiently in one pot under relatively mild conditions. The cleavage of the sulfonamide linkage could also be executed under mild conditions due to its activation via indole formation. When a Merrifield resin-based sulfonyl chloride **1b**[14a] was used instead of **1a**, the chemistry was equally effective. For example, by using the same procedure as described above, 2-iodoaniline was loaded onto resin **1b**, reacted with 4-ethynyltoluene in the presence of the palladium catalyst, and cleaved with TBAF to afford **6b** in quantitative yield with 92% purity.

With these results in hand, we examined the scope of this solid-phase method for the synthesis of diverse indoles by using commercially available PS-TsCl resin **1a** and TBAF as a cleavage reagent. This dual-activation process turned out to be very robust. As shown in Scheme 2 and Table 2,

Scheme 2



excellent yields (>85%) and purities (>90%) were achieved for most cases.[17] The terminal alkyne, **4**, is able to carry diverse functionality such as alkyl, ether, thioether, alcohol, acetal, aryl with electron-donating and electron-withdrawing groups, and heterocycles. The substituent on 2-iodoaniline **7** can be either electron-donating or electron-withdrawing. When **7** bore an electron-withdrawing substituent, such as for **7b** and **7d**, it was loaded onto PS-TsCl resin **1a** in $ClCH_2$-

Table 2. Traceless Solid-Phase Synthesis of Indoles **6** and **10**[a]

entry	X	R	T (°C)	time (h)	yield[b] (%)	purity[c] (%)
1	H	Ph	70	6	100	95
2	H	4-Me-C_6H_4	70	8	97	95
3	H	4-F-C_6H_4	75	6.5	100	98
4	H	4-MeO-C_6H_4	75	6.5	95	97
5	H	Bu	75	5	89	92
6	H	$MeOCH_2$	75	5	97	93
7	H	$HOCH_2CH_2$	75	5	90[d]	-
8	H	$(EtO)_2CH$	75	5	94[e]	-
9	6-F	$PhSCH_2$	70	6	85	98
10	6-F	6-MeO-2-Np	70	6	97	95
11	6-MeO	4-NO_2-C_6H_4	60	6	90	96
12	6-MeO	4-Me-C_6H_4	60	16	98	85
13	6-MeO	6-MeO-2-Np	60	6	85	91
14	6-MeO	$MeOCH_2$	60	6	94	86
15	5-CO_2Me	Bu	70	6	87	94
16	5-CO_2Me	2-pyridyl	70	6	87	100
17	5-CO_2Me	$PhSCH_2$	70	6	85	100

[a] Np = naphthyl. Conditions: (1) Pd-mediated coupling/indole cyclization (**8** → **9**): alkyne (6−8 molar equiv; for volatile alkynes, such as in entries 5 and 6, 10−15 molar equiv was used), CuI (0.2 molar equiv), $Pd(PPh_3)_2Cl_2$ (0.1 molar equiv), Et_3N−DMF (1:6−8); (2) resin cleavage (**9** → **10**): TBAF (5 molar equiv), THF, 70 °C, 5 h. [b] Crude yields (based on the loading level of resin **8**). All products gave satisfactory analytical data. [c] Determined by reversed-phase HPLC. [d] 50% of 2-vinylindole was observed in crude product by ^1H NMR. [e] The compound was unstable under reversed-phase HPLC condition. ^1H NMR showed a single product.

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(17) **Typical procedure:** To a solution of 5-fluoro-2-iodoaniline (**7b**; 400 mg, 1.69 mmol) and pyridine (222 mg, 2.8 mmol) in 1,2-dichloroethane (5 mL) was added PS-TsCl resin (Argonaut Technologies, Inc.; 352 mg, 0.56 mmol) in one portion. The suspension was stirred at 50 °C for 18 h, filtered, washed sequentially with CH_2Cl_2, MeOH, and Et_2O, and dried in vacuo to give resin **8** (X = 5-F; 470 mg). A suspension of resin **8** (X = 5-F; 89 mg, 0.11 mmol) in DMF (4 mL) was treated with 6-methoxy-2-naphthylacetylene (120 mg, 0.66 mmol), CuI (4.2 mg, 0.022 mmol), Et_3N (0.5 mL), and $Pd(PPh_3)_2Cl_2$ (7.7 mg, 0.011 mmol). After being stirred at 70 °C for 6 h, the black mixture was filtered, washed sequentially with DMF, water, MeOH, CH_2Cl_2, MeOH, and Et_2O, and dried in vacuo. The resulting resin was suspended in THF (6 mL) and treated with Bu_4NF (1.0 M in THF, 0.55 mL, 0.55 mmol). The mixture was stirred at 70 °C for 5 h and then filtered and washed with THF. The combined filtrates were evaporated, and the residue was dissolved in EtOAc (60 mL). The solution was washed with water (3 × 30 mL) and brine (20 mL) and dried (Na_2SO_4). Concentration in vacuo furnished 31 mg (97% yield) of the indole **10** (X = 6-F, R = 6-MeO-2-Np; Table 2, entry 10) with 95% purity determined by reversed-phase HPLC. MS *m/z* 292 (MH^+); FAB-HRMS calcd for $C_{19}H_{14}FNO + H^+$ 292.1138, found 292.1127. The structure was confirmed by ^1H NMR.

CH_2Cl and the reaction temperature was increased to 50 °C. It is noteworthy with 3-butyn-1-ol as the alkyne component that about 50% (based on ^1H NMR) of 2-vinylindole was obtained in the final product **10** (Table 2, entry 7). This dehydration might be attributed to the electron-withdrawing nature of the sulfonyl linker attached to the indole nitrogen. Thus, a sulfonyl resin-bound 2-vinylindole, a potentially useful resin-bound intermediate for the solid-phase synthesis of biological active compounds, such as tetrahydrocarbazoles via Diels−Alder reaction, can be accessed by treating resin **9** (R = $HOCH_2CH_2$) with an appropriate acid.

The usefulness of a sulfonyl linker is illustrated further in the functionalization of the 3-position of resin-bound indoles **9**. We sought a resin-bound organometallic from **9**, which should be a useful precursor for the introduction of diverse substituents into the 3-position. Our preliminary results with direct mercuration[18] of **9** (X = H, R = 4-Me-C_6H_4) were very promising. Treatment of **9** (X = H, R = 4-Me-C_6H_4) with mercury(II) acetate and a catalytic amount of $HClO_4$ afforded synthetically versatile resin-bound organomercurial **11** (Scheme 3). The 3-indolylmercury species could be converted to other organometallics or coupled with a suitable substrate by either a catalytic or a stoichiometric process. For example, coupling of **11** with methyl acrylate in the presence of stoichiometric $Pd(OAc)_2$ gave, after resin cleavage with TBAF, 2,3-disubstituted indole **12** in 60% isolated yield. A resin-bound organomercurial might also be useful for the study of relatively unexplored solid-phase radical reactions.[19] The sulfonyl linker could also be used as an activating group to direct the solid-phase deprotonation at the 2-position of indole followed by reaction with a variety of electrophiles. The investigation of this sulfonyl linker-directed metalation of indole, and its applications in chemical library synthesis, are in progress and will be reported in due course.

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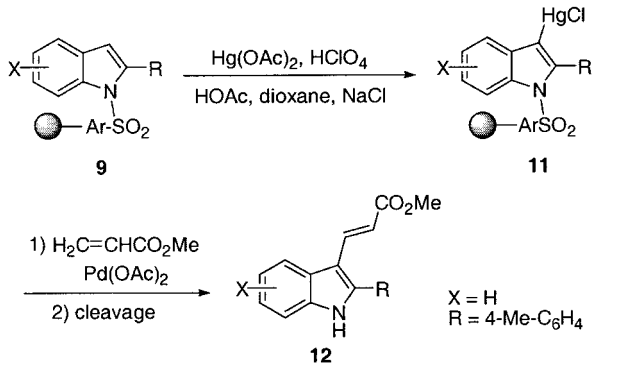
Scheme 3



In conclusion, we have described a facile traceless solid-phase construction of diverse indoles based on a sulfonyl linker via a dual-activation process. We have also shown that a sulfonyl linker is effective during mercuration at the 3-position of indole on a solid support. Given the ready availability of a variety of terminal alkynes, the high loading and low price of the PS-TsCl resin, the mild reaction conditions, and high yields, our traceless-linker method should be valuable for the generation of indole-based combinatorial libraries.

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Supporting Information Available: Characterization data (^1H NMR and MS) for the compounds in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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