Pergamon

Tetrahedron Letters 42 (2001) 4751–4754

TETRAHEDRON LETTERS

Efficient synthesis of 3-substituted 2-arylindoles via Suzuki coupling reactions on the solid phase

Han-Cheng Zhang,* Hong Ye, Kimberly B. White and Bruce E. Maryanoff

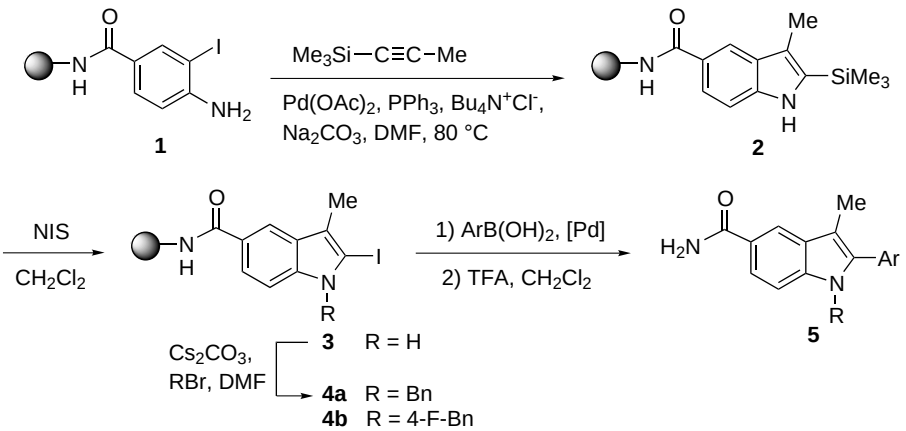
Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA 19477-0776, USA

Received 7 May 2001; accepted 15 May 2001

Abstract—2-Aryl-3-alkylindoles were prepared on solid phase via palladium-mediated heteroannulation of 1-alkyl-2-(trimethylsilyl)acetylene with amide resin-bound *o*-iodoaniline **1**, followed by transformation of trimethylsilyl to iodide and then Suzuki coupling reactions. Traceless synthesis of symmetrical and unsymmetrical 2,3-diarylindoles was achieved via palladium-mediated one-pot coupling/intramolecular indole cyclization of aryl-substituted terminal alkynes with sulfonyl resin-bound *o*-iodoaniline **6**, followed by regioselective bromination and Suzuki coupling reactions.

The 2-arylindole unit is present in diverse biologically active molecules, and various 2-aryl-3-alkylindoles and 2,3-diarylindoles exhibit interesting biological activities,[1] such as antiestrogen,[1b,d] 5-HT_{2A} antagonism,[1f] anti-inflammatory,[1a,c,g] and cytotoxicity.[1e] Introduction of an aryl group into the 2- or 3-position of an indole ring is usually achieved either by de novo indole ring construction,[2] such as Fischer indole synthesis,[1a] or cross-coupling reactions of 2- or 3-indolylmetal species with an aryl halide.[3] Palladium-mediated coupling reactions of 2- or 3-haloindoles with an arylmetal species has also been used for the synthesis of arylindoles,[4] but this application has been somewhat limited by the inaccessibility of the haloindoles.[5] Recently, Gribble disclosed a solution-phase synthesis of symmetrical 2,3-diarylindoles via a stepwise preparation of 2,3-dihaloindoles, followed by one-pot bis-Suzuki coupling reactions.[6] In this regard, we wish to report our studies on the solid-phase synthesis of 2-aryl-3-alkylindoles, symmetrical and unsymmetrical 2,3-diarylindoles via sequential palladium-mediated indole construction, regioselective indole halogenation, and Suzuki coupling reaction.[7]

Given the importance of the indole nucleus in medicinal chemistry, we[8] and others[9] have developed efficient solid-phase methods for the construction of the indole nucleus. However, little work has been done to further functionalize the indole nucleus on the solid support to obtain more diverse indole derivatives. In the palla-



Scheme 1.

* Corresponding author.

PII: S0040-4039(01)00857-7

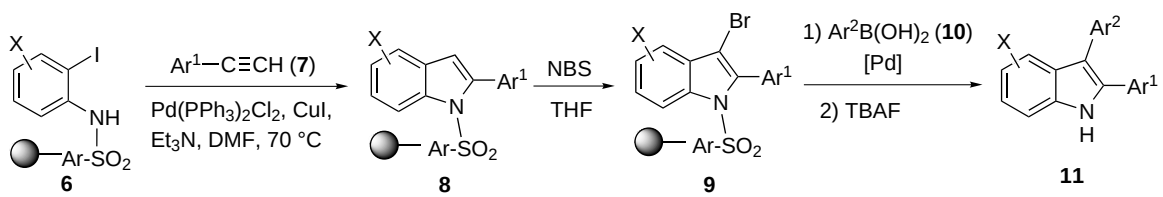
dium-mediated heteroannulation of unsymmetrical internal alkynes with a resin-bound *o*-iodoaniline,[8b,10] excellent regioselectivity was achieved by using a trimethylsilylalkyne, where the bulky trimethylsilyl group served as a regiochemistry directing group to provide 2-(trimethylsilyl)-3-alkylindole predominantly. This silyl group could then be easily removed during resin cleavage with trifluoroacetic acid (TFA)[8b] or serve as a useful precursor to other 2-substituted indole derivatives via silyl group transformation. We identified an efficient method to convert this 2-(trimethylsilyl)-3-alkylindole to diverse 2-aryl-3-alkylindoles on the solid phase via iodination and a Suzuki coupling reaction. Thus, palladium-mediated heteroannulation of 1-methyl-2-(trimethylsilyl)acetylene with resin-bound *o*-iodoaniline **1**[8b] at 80°C for 5 h afforded 2-(trimethylsilyl)-3-methylindole **2** (Scheme 1). Treatment of resin **2** with *N*-iodosuccinimide (NIS) in methylene chloride at 23°C for 2 h cleanly provided resin-bound 2-iodoindole **3**. In solution phase, a 2-haloindole has been obtained via directed 2-lithiation of an *N*-protected indole, followed by quenching lithiated species with a halogen.[6,11] Indole **3** was alkylated with benzyl bromide or 4-fluorobenzyl bromide in DMF to give **4a** or **4b**, respectively. Suzuki coupling of resin-bound 2-iodoindoles **3** or **4** with various arylboronic acids occurred smoothly to provide, after resin cleavage with TFA, 2-aryl-3-methylindoles **5** with good to excellent yields and high purity (Table 1). For the Suzuki coupling reaction, procedure B was generally more effective than procedure A.

Our process could also be applied to the synthesis of other 2-aryl-3-(substituted-alkyl)indole derivatives by using an appropriate 1-(substituted-alkyl)-2-(trimethylsilyl)acetylene.[8b] However, an attempt to prepare 2,3-diarylindoles was less successful since the regioselectivity of heteroannulation of an 1-aryl-2-(trimethylsilyl)-acetylene with **1** decreased significantly. For example, the heteroannulation of 1-phenyl-2-(trimethylsilyl)acetylene with resin **1** under the same conditions as described in Scheme 1 afforded only 56% of desired 2-trimethylsilyl-3-phenylindole, along with 27% of the regioisomer, 3-trimethylsilyl-2-phenylindole derivative.[8b] We recently reported a facile solid-phase construction of 2-substituted indole derivatives via palladium-mediated coupling/intramolecular indole cyclization of terminal alkynes based on a traceless, activating sulfonyl linker.[8d] When an aryl-substituted terminal alkyne was used, the process could be applied to the regiospecific synthesis of a 2-arylindole. We have now extended this method for the synthesis of symmetrical and unsymmetrical 2,3-diarylindoles. Thus, palladium-mediated coupling/intramolecular indole cyclization of aryl-substituted terminal alkynes **7** with resin **6**[8d] afforded resin-bound 2-arylindoles **8** (Scheme 2). The regioselective halogenation at the 3-position of **8** was achieved with *N*-bromosuccinimide (NBS, 3–4 equiv.) in 1,4-dioxane or THF at 60°C to afford 2-aryl-3-bromoindoles **9**. Less clean results were observed when DMF was used as solvent or NIS as halogenating agent. Suzuki coupling reactions of resins **9** with various aryl(heteroaryl)boronic acids **10** was followed by resin cleavage with tetrabutylammonium fluoride (TBAF, 5 mol equiv.)[8d] in THF to provide unsymmetrical 2,3-diarylindoles **11** with good to excellent yields and high purity (Table 2).[12] Starting with appropriate aryl-substituted terminal alkynes and arylboronic acids, our process could provide symmetrical 2,3-diaryl indoles, as prepared by one-pot bis-Suzuki coupling reactions in solution phase.[6] However, the latter approach has not been successful so far for unsymmetrical 2,3-diarylindoles via tandem bis-Suzuki coupling of 2,3-dihaloindoles.[6] Our method can also be used for the

Table 1. Solid-phase synthesis of 2-arylindoles **5**[a]

Entry	R	Ar	Procedure	Time (h)	Yield (%)[b]	Purity (%)[c]
1	H	Ph	A	20	68[d]	
2	H	4-Me-C_6H_4	A	26	65[d]	
3	H	4-MeO-C_6H_4	B	6	93	89
4	H	1-Naphthyl	B	6	96	98
5	H	Ph	A	20	85	90
6	4-F-Bn	4-Me-C_6H_4	A	18	75[d]	
7	4-F-Bn	4-MeO-C_6H_4	B	6	74[d]	

[a] Conditions for the Pd-mediated Suzuki coupling of resins **3** or **4**: $ArB(OH)_2$ (5 equiv.), K_2CO_3 (5 equiv.), $Pd_2(dba)_3$ (0.1 equiv., procedure A) or $Pd(PPh_3)_4$ (0.1 equiv., procedure B), DMF (procedure A) or 9:1 DMF–H_2O (procedure B), 80°C.
[b] Crude yields unless noted otherwise (for four or five steps; based on the loading level of resin **1**). All products gave satisfactory analytical data.
[c] Determined by reverse-phase HPLC.
[d] Isolated yields.

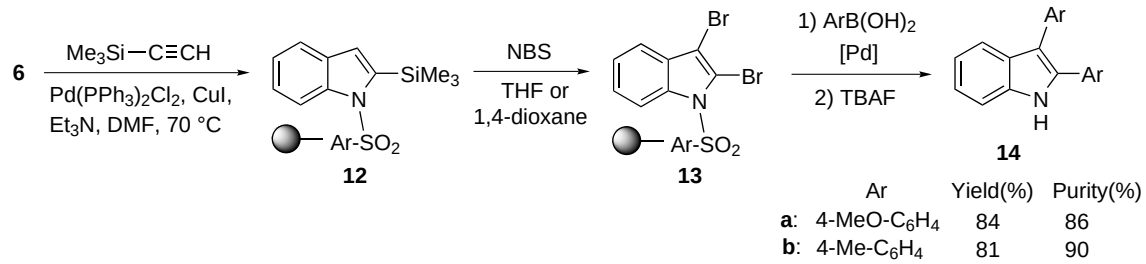


Scheme 2.

Table 2. Traceless solid-phase synthesis of 2,3-diarylindoles **11**[a]

Entry	X	Ar^1	Ar^2	Yield (%)[b]	Purity (%)[c]
1	H	4-Me-C_6H_4	4-MeO-C_6H_4	85	93
2	H	4-Me-C_6H_4	4-CO_2Me-C_6H_4	94	87
3	H	4-Me-C_6H_4	4-Pyridyl	92	84
4	H	4-F-C_6H_4	4-MeO-C_6H_4	86	85
5	H	4-F-C_6H_4	4-Cl-C_6H_4	86	92
6	H	4-F-C_6H_4	Ph	87	91
7	H	4-NO_2-C_6H_4	4-MeO-C_6H_4	87	96
8	H	4-NO_2-C_6H_4	1-Naphthyl	91	99
9	H	4-NO_2-C_6H_4	3-Thieyl	93	96
10	H	4-NO_2-C_6H_4	4-MeS-C_6H_4	99	96
11	5-CO_2Me	Ph	2-Naphthyl	85	82
12	5-CO_2Me	Ph	3,4-OCH_2O-C_6H_3	86	98

[a] Conditions for Suzuki coupling of resins **9**: $Ar^2B(OH)_2$ (4 equiv.), K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), DMF, 90°C, 5–10 h.
[b] Crude yields for four steps; based on the loading level of resin **6**. All products gave satisfactory analytical data.
[c] Determined by reverse-phase HPLC.



Scheme 3.

synthesis of other 3-substituted 2-arylindoles via Heck- or Stille-type coupling of **9**.

When aryl-substituted terminal alkyne **7** was replaced with (trimethylsilyl)acetylene, the palladium-mediated coupling/intramolecular indole cyclization of resin **6** provided resin-bound 2-trimethylsilylindole **12** (Scheme 3). One-pot treatment of **12** with excess NBS in THF or 1,4-dioxane afforded 2,3-dibromoindole **13** (use of NIS was less successful). It is noteworthy that conversion of the trimethylsilyl group in resin **12** to a halide was more difficult than that in resin **2** probably partially due to the electronic effect. One-pot bis-Suzuki coupling of **13** with 4-methoxybenzeneboronic acid followed by resin cleavage afforded 84% yield (86% purity by HPLC) of symmetrical 2,3-diarylindole **14a**.[13] Similarly, bis-Suzuki coupling of resin **13** with 4-methylbenzeneboronic acid gave 81% yield (with 90% purity) of **14b**.

In conclusion, we have developed facile solid-phase approaches to 2-aryl-3-alkylindoles and 2,3-diarylindoles via palladium-mediated indole formation, followed by regioselective halogenation of indole ring and Suzuki coupling reactions. The sulfonyl linker approach proved to be particularly efficient for the traceless synthesis of symmetrical or unsymmetrical 2,3-diarylindoles, as well as other 2-arylindole derivatives. These methods should prove valuable for the generation of biologically interesting arylindole-based chemical libraries.

Acknowledgements

We thank Drs. Dennis Hlasta and Alessandro Moretto for helpful discussions and support.

References

1. (a) Szmuszkovicz, J.; Glenn, E. M.; Heinzelman, R. V.; Hester, Jr., J. B.; Youngdale, G. A. *J. Med. Chem.* **1966**, *9*, 527; (b) von Angerer, E.; Knebel, N.; Kager, M.; Ganss, B. *J. Med. Chem.* **1990**, *33*, 2635; (c) Ismail, M. M. F.; Shmeiss, N. A. M. M.; El-Diwani, H. I.; Arbid, M. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36B*, 288; (d) Biberger, C.; von Angerer, E. *J. Steroid Biochem. Mol. Biol.* **1998**, *64*, 277; (e) Medarde, M.; Ramos, A. C.; Caballero, E.; De Clairac, R. P.-L.; Lopez, J. L.; Gravalos, D. G.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2303; (f) Stevenson, G. I.; Smith, A. L.; Lewis, S.; Michie, S. G.; Neduvelil, J. G.; Patel, S.; Marwood, R.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697; (g) Nakkady, S. S.; Fathy, M. M.; Hishmat, O. H.; Mahmond, S. S.; Ebeid, M. Y. *Boll. Chim. Farm.* **2000**, *139*, 59; (h) Colletti, S. L.; Li, C.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **2000**, *41*, 7825.
2. For a recent review on indole ring synthesis, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
3. (a) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155; (b) Hudkins, R. L.; Diebold, J. L.;

Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218; (c) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158; (d) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831; (e) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025.

4. (a) Merlic, C. A.; McInnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 7661; (b) Chu, L.; Fisher, M. H.; Goulet, M. T.; Wyvratt, M. J. *Tetrahedron Lett.* **1997**, *38*, 3871; (c) Smith, A. L.; Stevenson, G. I.; Lewis, S.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2693.
5. (a) Joseph, B.; Malapel, B.; Merour, J.-Y. *Synth. Commun.* **1996**, *26*, 3289; (b) Malapel-Andrieu, B.; Merour, J.-Y. *Tetrahedron* **1998**, *54*, 11079.
6. Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717.
7. For Suzuki coupling reactions on the solid phase, see: (a) Franzen, R. *Can. J. Chem.* **2000**, *78*, 957; (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549; (c) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169; (d) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331.
8. (a) Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804; (b) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439; (c) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449; (d) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89.
9. (a) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189; (b) Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963; (c) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307; (d) Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 6473; (e) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317; (f) Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799.
10. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
11. Bergman, J.; Venelman, L. *J. Org. Chem.* **1992**, *57*, 2495.
12. Typical procedure for 2,3-diarylindole **11** (Ar^1=4-NO_2-C_6H_4, Ar^2=3-thienyl, X=H, Table 2, entry 9): To a suspension of resin **8**[8d] (616 mg, 0.67 mmol; Ar^1=4-NO_2-C_6H_4, X=H) in 20 mL of 1,4-dioxane was added NBS (475 mg, 2.67 mol). The mixture was stirred at 70°C for 24 h, and then filtered, washed with DMF, MeOH, CH_2Cl_2, and Et_2O, dried in vacuo to give resin **9** (634 mg). A suspension of resin **9** (150 mg, 0.16 mmol) in DMF (5 mL) was treated with thiophene-3-boronic acid (80.6 mg, 0.63 mmol), K_2CO_3 (65.3 mg, 0.47 mmol), and $Pd(PPh_3)_4$ (18.2 mg, 0.016 mmol). After stirring at 90°C for 8.5 h, the mixture was filtered, washed sequentially with DMF, MeOH, CH_2Cl_2, and Et_2O, and dried in vacuo (145 mg). The resin (140 mg, 0.15 mmol) was suspended in THF (6 mL) and treated with Bu_4NF (1.0 M in THF, 0.76 mL, 0.76 mmol). The mixture was stirred at 70°C for 5 h and then filtered, washed with THF. The combined filtrates were evaporated and the residue was dissolved in EtOAc (100 mL). The solution was washed with water (5×30 mL), brine (30 mL), and dried (Na_2SO_4). Concentration in vacuo furnished 45 mg (93% yield) of the indole **11** (Ar^1=4-NO_2-C_6H_4, Ar^2=3-thienyl, X=H) with 96% purity determined by reverse-phase HPLC. CI-MS *m/z* 321 (MH^+). The structure was confirmed by ^1H NMR.
13. Compound **14a** (indoxole) is an antiinflammatory agent with comparable activity to indomethacin in certain anti-inflammatory and antiarthritic assays: (a) Glenn, E. M.; Bowman, B. J.; Kooyers, W.; Koslowske, T.; Myers, M. L. *J. Pharmacol. Exp. Ther.* **1967**, *155*, 157; (b) Brune, K.; Graf, P.; Glatt, M. *Agents Actions* **1976**, *6*, 159; (c) Klug, R. D.; Krohn, D. L.; Breitfeller, J. M.; Dieterich, D. *Ophthalmic Res.* **1981**, *13*, 122.