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A Novel Palladium-Mediated Coupling Approach to 2,3-Disubstituted Benzo[*b*]thiophenes and Its Application to the Synthesis of Tubulin Binding Agents

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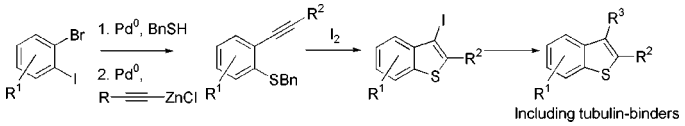
ABSTRACT



Flexible, convergent access to 2,3-disubstituted benzo[*b*]thiophenes has been developed. The most concise approach involves sequential coupling of *o*-bromoiodobenzenes with benzylmercaptan and zinc acetylides to give benzyl *o*-ethynylphenyl sulfides which react with iodine to give 3-iodobenzo[*b*]thiophenes in a *5-endo-dig* iodocyclization. These iodides can be further elaborated using palladium-mediated coupling and/or metalation techniques. This method has been applied to the synthesis of some novel tubulin binding agents.

Benzo[*b*]thiophenes serve as very useful heterocyclic cores to a host of drugs and drug candidates as well as providing useful properties in the development of new and interesting materials.[1] Benzo[*b*]thiophene derivatives currently in pharmaceutical use or development include estrogen receptor antagonists,[2] antimitotic agents,[3] modulators of multidrug resistance,[4] angiogenesis inhibitors,[5] cognition enhancers,[6] and antifungal[7] and antiinflammatory[8] agents to name but a few. A specific example is the tubulin binding agent **1**, an analogue of the natural product combretastatin A-4 (**2**) (Figure 1).[3a,b] The emergence of such valuable chemothera-

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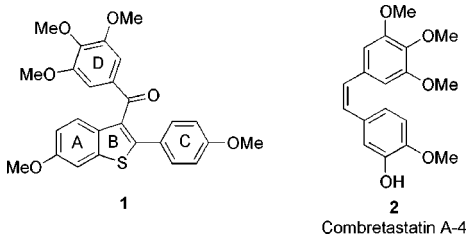
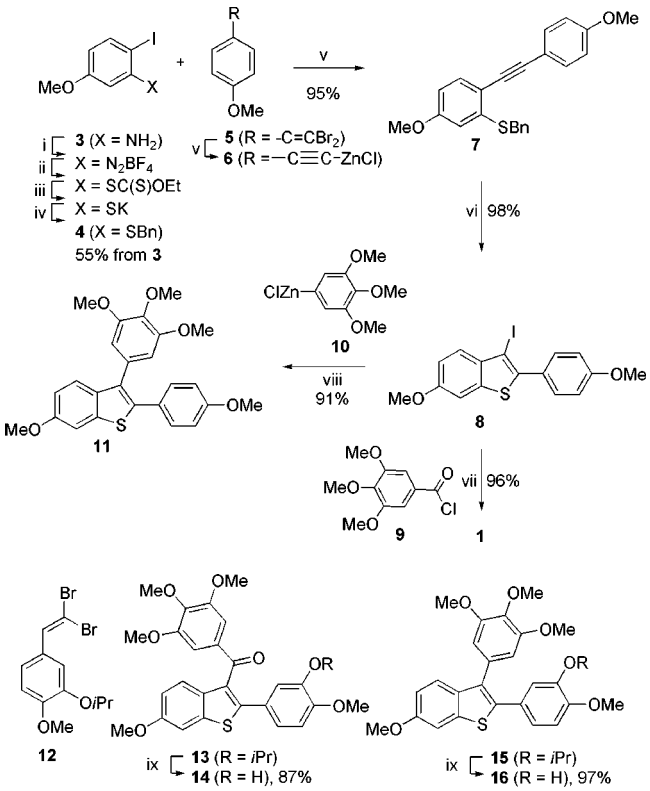


Figure 1.

peutic agents has stimulated new investigations into the concise synthesis of 2,3-disubstituted benzo[*b*]thiophenes.[1,9] Here we report a highly convergent protocol for rapid construction of 2,3-disubstituted benzo[*b*]thiophenes. The approach involves a combination of palladium-mediated coupling and iodocyclization reactions. The scope of this new method has been explored in the context of a brief structure−activity relationship study of analogues of **1**. Compounds with enhanced affinity for tubulin have been discovered.

The synthesis of **1** and analogues **11**, **14**, and **16** commenced with readily available 2-iodo-5-methoxyaniline (**3**) (Scheme 1).[10] A sequence involving diazotation, xanthate substitution, methanolysis, and benzylation converted **3** into the benzyl sulfide **4** in an overall 55% yield.[11,12] This multistep conversion of **3** to **4** is amenable to large scale preparations and requires chromatography only after the last step. Iodide **4** was coupled to ethynyl zinc species **6** (obtained directly from β,β-dibromostyrene **5** by addition of 2 equiv of *n*-BuLi and zinc chloride), giving **7** in an excellent yield (95%).[13,14] Reaction of **7** with iodine led to a rapid *5-endo-dig* iodocyclization to give 3-iodobenzo[*b*]thiophene **8** in an almost quantitative yield (98%).[15,16] Lithiation of **8** and reaction with commercially available 3,4,5-trimethoxybenzoyl chloride **9** afforded **1** in high yield (96%). Negishi coupling of **8** with arylzinc chloride **10** gave the non-carbonyl

Scheme 1[a]



[a] Reagents and conditions: i. HBF_4, $NaNO_2$, H_2O; ii. KSC(C)OEt, DMF; iii. MeOH, KOH; iv. KOH(aq), BnCl, *n*-Bu_4NHSO_4 cat., CH_2Cl_2; v. 2 × *n*-BuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$ 2 mol %, **4**; vi. I_2, CH_2Cl_2; vii. 2 × *t*-BuLi, THF, **9**; viii. **10** (from 3,4,5-trimethoxyiodobenzene, 2 × *t*-BuLi, THF and $ZnCl_2$), $Pd(PPh_3)_2Cl_2$ 2 mol %, ix. $AlCl_3$ 3 equiv, CH_2Cl_2.

containing analogue **11** (91%). This synthetic approach to **1** and **11** was repeated using the different β,β-dibromostyrene **12**[13a] to afford **13** and **15**. The isopropyl ethers in **13** and **15**[12] were selectively cleaved using aluminum trichloride to provide **14** and **16**, respectively.[12,17]

The bromo equivalent of iodide **4**, benzyl 5-bromo-3-methoxyphenyl sulfide (**19**), proved even more accessible (Scheme 2). Regioselective bromination of commercially available 3-iodoanisole (**17**) with NBS to give **18** is followed by chemoselective substitution of the iodide in **18** with benzylmercaptan under palladium catalysis to give **19** (96% from **17**).[18,19] Although less reactive than the corresponding aryl iodide **4**, the bromide **19** could still be efficiently coupled with zinc acetylides (derived from β,β-dibromostyrenes) using a modification of the procedure described above for the coupling of **4** and **5** to give **7**. After conversion of **20** to the corresponding zinc acetylide (not shown), bromide **19**, $Pd(PPh_3)_2Cl_2$, and triphenylphosphine were added. The

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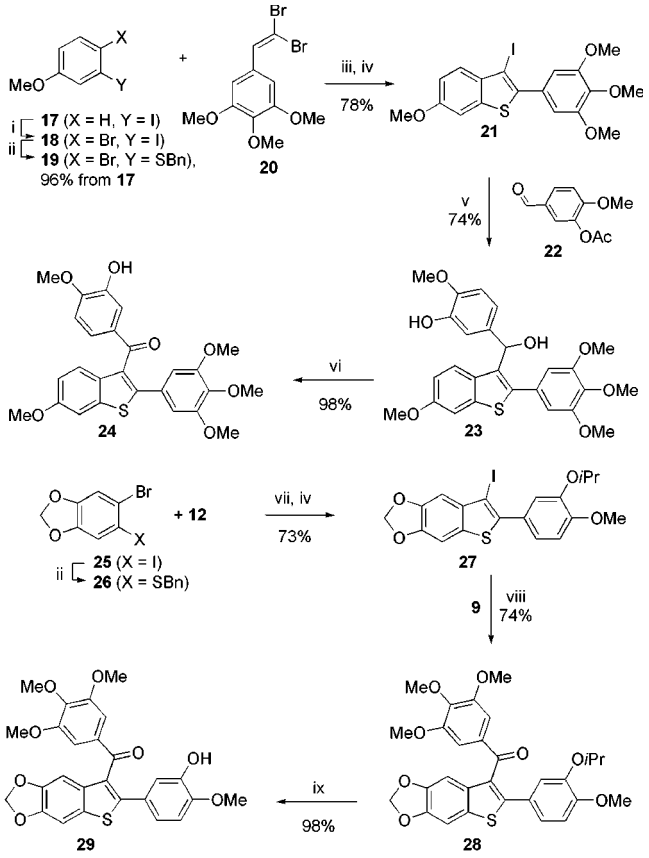
Scheme 2[a]



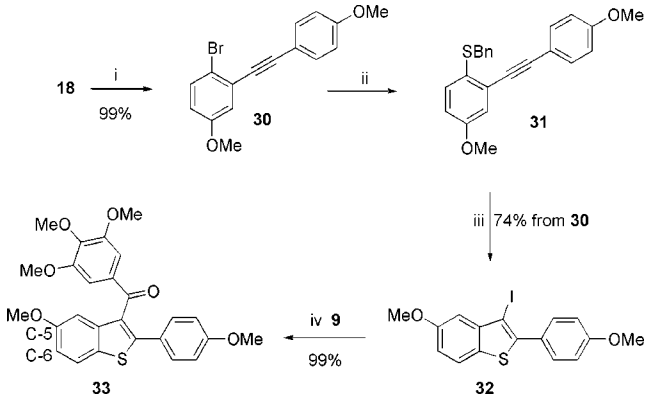
[a] Reagents and conditions: i. NBS, DMF, 80 °C, 4 h; ii. $Pd(dba)_2$ 3 mol %, dppf 3 mol %, BnSH, DMF, Et_3N, 70 °C, 3 h; iii. **20**, 2 × *n*-BuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$ 2 mol %, PPh_3 4 mol % **17,** DMF, 100 °C, 3 h; iv. I_2, CH_2Cl_2; v. *n*-BuLi, THF, **22**, then KOH in MeOH; vi. DDQ, CH_2Cl_2; vii. **12**, 2 × *n*-BuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$ 2 mol %, PPh_3 4 mol %, **26**, DMF, 100 °C, 3 h; viii. *i*-PrMgCl, THF, **9**; ix. $AlCl_3$, 3 equiv, CH_2Cl_2.

resultant solution was diluted with an equal volume of DMF and heated to 100 °C under a slight flow of N_2 to remove THF. Under these conditions coupling proceeded smoothly and the crude product was iodocyclized to afford directly the 3-iodobenzo[*b*]thiophene **21** in a 78% overall yield from **19**. Lithiation of **21** and reaction with the acetylisovanilin **22** and in situ methanolysis of the acetate gave **23** (74%). Alcohol **23** was readily oxidized to ketone **24** using DDQ (98%).

The dioxolane-fused benzo[*b*]thiophene derivative **29** was prepared from commercially available 4-bromo-5-iodo-1,3-benzodioxolane (**25**) (Scheme 2). Chemistry similar to that described in the synthesis of **23** was employed. The 3-iodobenzo[*b*]thiophene **27** was prepared from a sequence of iodide substitution to afford **26** and coupling to the zinc acetylide derived from **12** and iodocyclization**.** Metalation of **27** and reaction with **9** gave **28**, which gave **29** upon deprotection.

The relative placement of substituents in the benzene ring of benzo[*b*]thiophenes can be varied by changing the order of introduction of the alkyne and the benzyl sulfide in certain

Scheme 3[a]



[a] Reagents and conditions: i. 4-methoxyethynylbenzene, $Pd(PPh_3)_2Cl_2$ 1.5 mol %, CuI 3 mol %, DMF, Et_3N; ii. *n*-BuLi, THF, BnSSBn; iii. I_2, CH_2Cl_2; v. *n*-BuLi, THF, **9**.

o-bromoiodobenzenes. This has been demonstrated in the synthesis of **33** from **18** (Scheme 3). Coupling **18** with 4-methoxyphenylacetylene under Sonogashira conditions gave **30**. This product was lithiated and reacted with dibenzyl disulfide to give **31** and iodocyclized to give **32**.[20] Lithiation of **32** and reaction with 3,4,5-trimethoxybenzoyl chloride (**9**) provided **33** in excellent yield (99%). Note that this process has resulted in the methoxy group being located at the C-5 postion rather than at C-6, as was the case in the preparation of **24** from the same *o*-bromoiodobenzene **18** (Scheme 2).

Biological Studies. Tubulin binding agents are of interest in view of their potential to act as both antimitotics and as selective inhibitors of tumor vasculature growth.[21,22] Combretastatin A-4 (**2**) is an example of such a tubulin binding agent which is currently undergoing clinical trials as an anticancer agent. The poor solubility of **2** in suitable solvents, as well as its tendency to isomerize to its inactive *E*-isomer, has prompted a number of studies directed at the preparation of more soluble, configurationally stable analogues.[23] Pinney and co-workers have developed the benzo[*b*]thiophene analogue **1** as a ring fused, configurationally stable analogue of **2** (Figure 1).[3a,b]

We have used our novel approach to benzo[*b*]thiophenes to prepare some analogues of **1**, including some which more closely resemble the *cis*-stilbene pharmacophore of combretastatin A-4 (**2**), compounds **11**, **13**−**16**, **23**, **24**, **29**, and **33**.[24] These compounds were first evaluated for inhibition of

(20) Attempts to introduce the benzylthiol by palladium-mediated substitution of the aryl bromide in **30** with benzyl mercaptan have so far failed.

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(23) See ref 13a and references cited therein.

(24) During the course of these studies, Pinney and co-workers also prepared compound **14**: Pinney, K. G.; Chen, Z.; Mocharla, V. P.; Choony, N.; Strong, T. Synthesis of a Benzo[*b*]thiophene-Based Vascular Targeting Prodrug and Related Anti-Tubulin Ligands. *Abstracts of Papers*, 220th National Meeting of the American Chemical Society, Division of Organic Chemistry; Washington, D.C., August 20−24, 2000; American Chemical Society: Washington, D.C., Abstract No. 196.

Table 1. Effects of Benzo[*b*]thiophenes on Tubulin Polymerization, Colchicine Binding, and Growth of Burkitt Lymphoma CA46 Cells

compd	inhibition of tubulin polymerization[a] IC_{50} (μM)	inhibition of colchicine binding (% inhibition)[b] 5 μM inhibitor	50 μM inhibitor	inhibition of cell growth IC_{50} (nM)
1[c]	>40*[d]		28	2000
2	2.1 ± 0.1	94		1
14	3.5 ± 0.3	6	61	500
23	6.1 ± 0.8	5	73	>1000
29	>40*[d]	2	31	>1000

[a] The tubulin concentration was 10 μM. Inhibition of extent of assembly was the parameter measured. [b] The tubulin concentration was 1.0 μM and the [^{3}H]colchicine concentration was 5.0 μM. [c] Data from ref 3a. [d] The asterisk indicates that the rate but not the extent of assembly was inhibited by compound concentrations as high as 40 μM.

tubulin assembly, and those that displayed inhibitory effects were also examined for inhibitory effects on the binding of [^{3}H]colchicine to tubulin and for cytotoxicity in human Burkitt lymphoma CA46 cells (Table 1; methodologies as described in ref 3a). The newly synthesized compounds were compared in contemporaneous experiments to the potent antimitotic combretastatin A-4 (**2**), generously provided by Prof. G. R. Pettit, Arizona State University.

Compounds **11**, **13**, **15**, **16**, **24**, and **33** showed no effect on tubulin assembly at concentrations as high as 40 μM and were not further studied and are not included in Table 1.

Compound **1** had shown[3a] an unusual inhibitory effect on tubulin polymerization in that low concentrations (up to about 3−4 μM) inhibited the rate of assembly. Little further effect on either rate or extent of assembly occurred at concentrations as high as 40 μM. It was postulated that this phenomenon was due to limited aqueous solubility of **1**. Compound **29** showed a similar inhibitory pattern on assembly, but in direct comparisons to **1** at low concentrations, **29**, was clearly less active than **1**, and therefore rate effects were not examined in detail. Two compounds, **14** and **23**, displayed typical progressive inhibition of all parameters of assembly (initiation, assembly rate, assembly extent), and quantitative measurements of the assembly extent were performed relative to **2** (IC_{50}, 2.1 μM). Compound **14** was about half as active (IC_{50}, 3.5 μM) and **23** about one-third as active (IC_{50}, 6.1 μM) as **2**. In addition, compound **14** (but not **23**) was distinctly more active than **1** as both an inhibitor of colchicine binding to tubulin and of growth of CA46 cells. Compound **14**, however, was far less active than combretastatin A-4 (**2**) in these latter assays.

In SAR terms, vicinal hydroxyl and methoxyl groups in the C ring (as in **2**) enhance the activity and perhaps the solubility of this class of compounds (**14** vs **1**). The bridged carbon between the B and D rings is essential (cf. **11** and **1**; **14** and **16**). The relative positioning of the C and D rings on the 3-carboxybenzo[*b*]thiophene skeleton is important (cf. **24** and **14**). Fusion of a 1,3-dioxolane ring to the A ring is undesirable (**29** vs **14**), as is moving the methoxyl group from position C-6 to C-5 (**33** vs **1**).

Conclusion. A flexible method for the construction of benzo[*b*]thiophenes has been developed. The protocol gives direct access to a range of substitution patterns making it an ideal process for structure−activity relationship studies of biologically active molecules. This point has been demonstrated in the structural refinement of a known lead compound **1**, giving more active compounds **14** and **23**.

Acknowledgment. The authors thank the Australian Research Council for financial support including an Australian Research Fellowship to B.L.F.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds involved in the synthetic sequence leading to **14** and **16** from **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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