ORGANIC LETTERS

2003
Vol. 5, No. 23
4377−4380

Iodine-Induced Reaction Cascades for the Rapid Construction of Variously Substituted Benzothiophenes†

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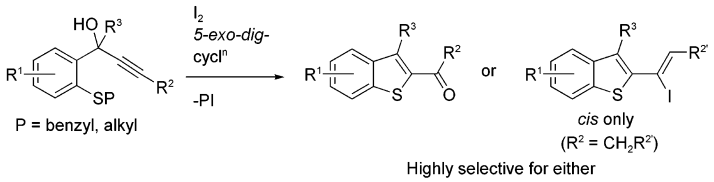
Received August 31, 2003

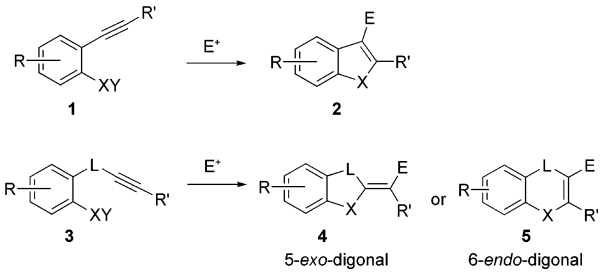
ABSTRACT



Readily accessible propynols with a 2-thioxyphenyl substituent selectively undergo 5-*exo*-iodocyclization followed by tandem rearrangement and elimination or substitution processes to give selective access to either 2-acyl- or 2-(1-iodoalkeny)-benzo[*b*]thiophene systems.

In our ongoing efforts to maximize the molecular diversity available from a limited set of substrates using a minimal set of optimized protocols, we have focused on the synergistic relationship of processes such as metalation, halogenation, iodocyclization, and palladium-mediated coupling (direct, carbonylative, and heteroannulative).[1] In this regard we and others have been involved in the synthesis of various benzofused heterocycles **2** through 5-*endo*-digonal cyclization reactions of arylalkynes bearing *ortho* related heteroatomic nucleophiles (X) **1** (Scheme 1).[1−3] These cyclizations

Scheme 1



are generally mediated by an electrophile (E), such as iodine (iodocyclization) or a catalytic palladium(II) intermediate (heteroannulative coupling). We have utilized these reactions

† Some aspects of this work were conducted at the Department of Chemistry, Australian National University, Canberra, ACT, 0200, Australia.

(1) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670. (b) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341. (c) Chaplin, J. H.; Flynn, B. L. *J. Chem. Soc., Chem. Commun.* **2001**, 1594. (d) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (e) Banwell, M. G.; Flynn, B. L.; Wills, A. C.; Hamel, E. *Aust. J. Chem.* **1999**, *52*, 767 (f) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun*. **1997**, 207.

(2) For reviews see a−e: (a) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42. (b) Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. 2, p 2193. (c) Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. 2, p 2227. (d) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613. (e) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (f) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (g) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. (h) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (i) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (j) Yue, D.; Larock, R. C. *Abstracts of Papers, 223rd ACS National Meeting*; Orlando, Florida, USA, April 7−11; American Chemical Society: Washington, DC, 2002. (k) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607. (l) Arcadi, A.; Cacchi, S.; Di Guiseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (m) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.

10.1021/ol035663a CCC: $25.00
Published on Web 10/23/2003

in the efficient synthesis of potent new analogues, **7**−**10**, of the tubulin polymerization inhibitor combretastatin A4, **6** (Figure 1).[1,4,5]

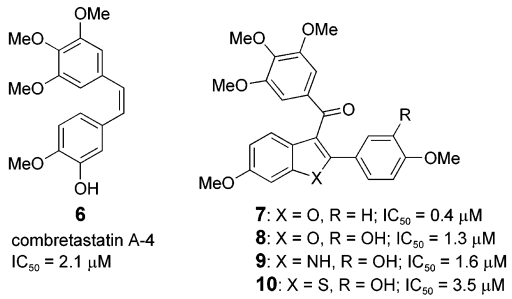


Figure 1. IC_{50} = concentration required to inhibit the extent of tubulin polymerization by 50%.

To further extend upon this efficient access to benzofused heterocyclic analogues of combretastatin A4, **6**, we have investigated the capacity of homologated systems, **3**, to selectively undergo related 6-*endo*- or 5-*exo*-digonal cyclizations reactions (Scheme 1). In the course of this ongoing study, we have uncovered a remarkably efficient and effective means of preparing variously substituted benzo[*b*]-thiophenes through selective iodine-induced reaction cascades where L in **3** is a readily accessible secondary or tertiary alcohol. We report these findings herein.

The iodocyclization precursor, propynol **14**, was prepared from the isopropyl-protected isovanillin **11** via a sequence involving bromination (**12**), nucleophilic aromatic substitution with sodium benzylthiolate (**13**), and reaction with lithium 4-methoxyphenylacetylide (Scheme 2). Iodocyclization of **14** was expected to proceed in a 5-*exo*-fashion with concomitant loss of the benzyl group to provide **15** (Scheme 2).[6] However, this product was not isolated; instead the 2-aroylbenzo[*b*]thiophene **18** was obtained in good yield (90%). Formation of this product was rationalized as resulting from a reaction cascade that commences with initial iodocyclization of the benzyl sulfide **14** to give **15**, which undergoes immediate 1,3-hydroxyl migration, proceeding through allylic cation **16**, to give **17**, followed by elimination HI to give **18**, in a self-catalyzing process.

The preparation of 3-substituted analogues of **18** simply requires the use of tertiary rather than secondary propynols, and several approaches to these were explored (Schemes 3 and 4). The 1,3-diarylpropynol **20** was prepared from **13** by reaction with the lithium acetylide obtained from treatment

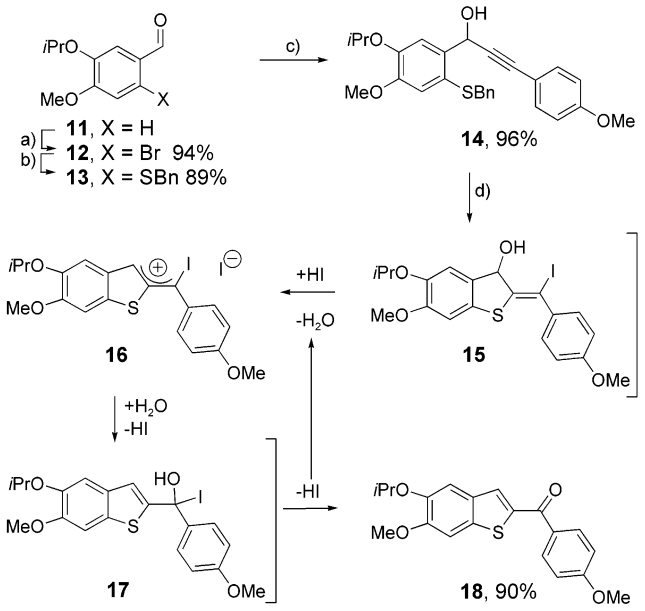
(3) For a review on related cyclization not involving benzofused heterocycles, see: Knight, D. W. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 2002; Vol. 14, Chapter 2, p 19.

(4) For a review on combretastain A-4, see: Griggs, J.; Metcalfe, J. C.; Hesketh, R. *Lancet Oncol.* **2001**, *2*, 82.

(5) For structurally related TPI compounds, see: Pinney, K. G.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, H. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081.

(6) Ren, X-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org Chem.* **1995**, *60*, 6468.

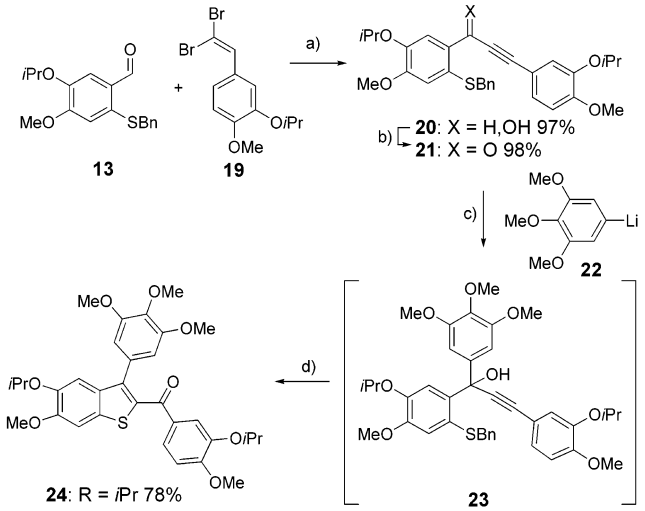
Scheme 2[a]



[a] Reagents and conditions: (a) *N*-bromosuccinimide, DMF, 80 °C; (b) NaH, BnSH, THF, 40 °C; (c) 2 × *n*BuLi, *β*,*β*-dibromo-4-methoxystyrene, THF, −78 to 18 °C; (d) I_2, CH_2Cl_2, 18 °C.

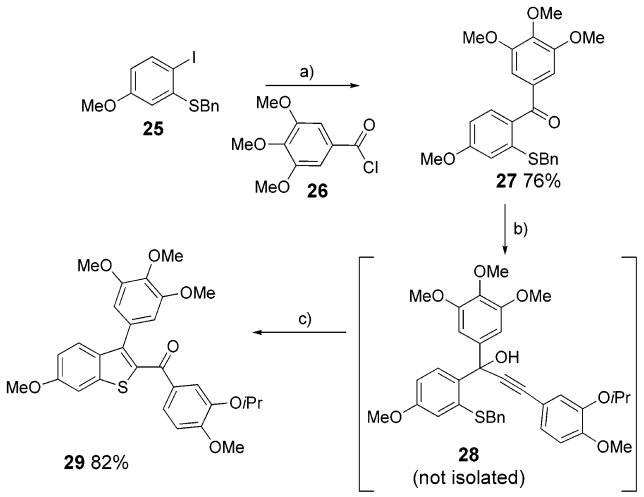
of **19**[1e] with 2 equiv of *n*-butyllithium (Scheme 3). Alcohol **20** was oxidized to the ketone **21** using manganese oxide and reacted with 3,4,5-trimethoxyphenyllithium **22** to give the 1,1,3-triarylpropynol **23**. This material was iodocyclized to give the 2-aroyl-3-arylbenzo[*b*]thiophene **24** in good yield. In this and subsequent reactions (see below) involving 1,1,3-triarylpropynols of the type **23**, the intermediate alcohol was

Scheme 3[a]



[a] Reagents and conditions: (a) **19**, 2 × *n*BuLi, THF, −78 to 18 °C, then **13**, −78 to 18 °C; (b) MnO_2, CH_2Cl_2, 18 °C; (c) **22** (3,4,5-trimethoxyiodobenzene, *n*BuLi), THF, then **21**, −78 to 18 °C; (d) crude **23**, I_2, CH_2Cl_2, 18 °C.

Scheme 4[a]



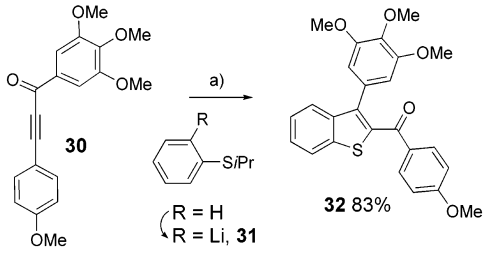
[a] Reagents and conditions: (a) **25**, *n*BuLi, THF, then **26**, −78 to 18 °C; (b) **19**, 2 × *n*BuLi, THF, then **27**, −78 to 18 °C; **(**c) crude **28**, I_2, CH_2Cl_2, 18 °C.

not isolated but converted directly to the benzothiophene by addition of iodine to a dichloromethane extract of the protonated reaction mixture.

Another approach to a 1,1,3-triarylpropynol cyclization precursor involved lithiation of *o*-iodophenylsulfide **25**[1d] and reaction with the acid chloride **26**, giving the ketone **27**, which was reacted with the lithium acetylide generated from **19**, and the crude propynol **28** iodocyclized to give **29** (Scheme 4).

As an alternative to halogen for metal exchange, isopropyl sulfides can be utilized as *ortho*-directing groups in directed metalation.[7] This possibility was exploited in a single-step preparation of **32** from the diarylpropynone **30** (Scheme 5).

Scheme 5[a]

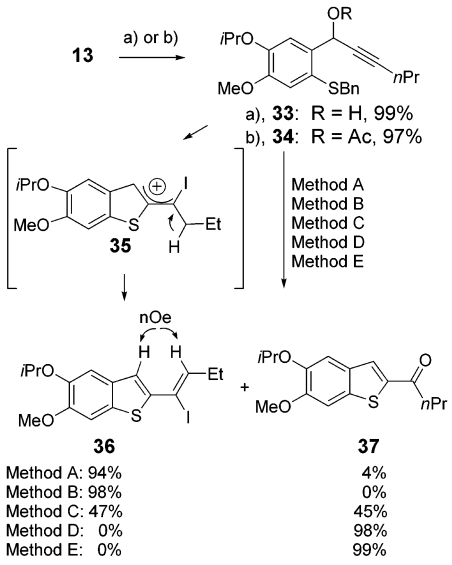


[a] Reagents and conditions: (a) isopropyl benzenesulfide, *n*BuLi, TMEDA, THF, then **30**, −78 to 18 °C, NH_4Cl_{aq} and extraction with CH_2Cl_2 and addition of I_2, 18 °C.

This involved initial coupling of **30** (prepared in a manner similar to that for diarylpropynone **20**) with *ortho*-lithiated isopropyl phenylsulfide **31** and iodocyclization of the crude 1,1,3-triarylpropynol (not shown) to give benzothiophene **32** (Scheme 5). Thus, this process provides for a single-step access to 2-acyl(or aroyl)benzothiophenes from isopropyl phenyl sulfides and propynones or propynals.

We next sought to extend this protocol to alkyl-substituted cyclization precursors (Scheme 6). It soon became apparent

Scheme 6[a]



[a] Reagents and conditions: (a) 1-pentyne, *n*BuLi, THF, then **13**, −78 to 18 °C; (b) same as (a) except Ac_2O is added to reaction prior to workup. Method A: **33**, I_2, CH_2Cl_2, 18 °C. Method B: **34**, I_2, CH_2Cl_2, 18 °C. Method C: **33**, I_2, 1:1 H_2O/CH_3CN, 18 °C. Method D: **33**, I_2, EtOH, 18°C. Method E: **34**, I_2, dry EtOH, 18 °C.

that iodocyclization of alkyl-substituted systems bearing α-hydrogens on the alkyne **33** produce 2-[(*Z*)-1-iodoalkenyl]-benzo[*b*]thiophenes **36** selectively (Method A, Scheme 6). Minor quantities of the ketone **37** were formed but could be avoided altogether if the corresponding acetate **34** was used in the iodocyclization, so as to remove any possibility of a hydroxyl migration (Method B). This alkenyl group presumably forms from elimination of a proton from the intermediate allylic cation **35** or by a concerted elimination of H_2O or AcOH (not shown). The *Z*-stereochemistry was assigned on the basis of the strong nuclear Overhauser enhancement (NOE) observed between the two hydrogens shown. Notably, similar 2-alkenylbenzo[*b*]thiophenes have proven valuable as diene systems in Diels−Alder cycloaddition chemistry.[8]

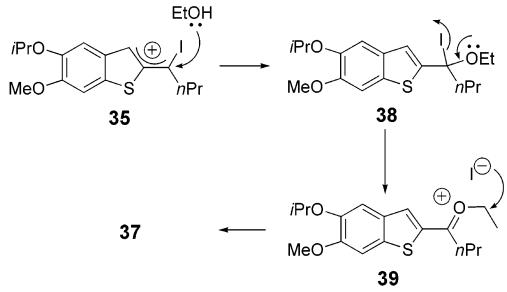
Although this access to 2-[(*Z*)-1-iodoalkenyl]-benzo[*b*]-thiophenes, such as **36**, represents an exciting adjunct to our access to the 2-aroyl systems, we were keen to maximize the scope of the ketone-forming process so that it also included α-hydrogen-containing systems. Several experiments were performed in acetonitrile/water mixtures in the expectation that we might trap **35** with water prior to elimination of the α-proton and obtain **37** selectively. Although this was partially successful, substantial amounts

(7) Sato, R.; Ohyama, T.; Kawagoe, T.; Baba, M.; Nokajo, S.; Kimura, T.; Ogawa, S. *Heterocycles* **2001**, *55*, 145. (b) Cabidda, S.; Fattaoni, C.; Floris, C.; Gelli, G.; Melis, S.; Sotgia, F. *Tetrahedron* **1990**, *46*, 861.

(8) Marrocchi, A.; Minuti, L.; Taticchi, A.; Scheeren, H. W. *Tetrahedron* **2001**, *57*, 4959.

of iodoalkene (1:1 **36**:**37**) were still formed even with large amounts of water (1:1 acetonitrile/water) (Method C). We next attempted the reaction in ethanol to further increase the concentration of the trapping agent. The anticipated enolether and/or the diethylketal (not shown) could then be hydrolyzed to the ketone **37**. To our pleasant surprise, reaction of **33** with iodine in ethanol gave the ketone **37** directly with excellent selectivity over the elimination product **36** (not observed). This product was also achieved even when the acetate **34** was iodocyclized in dry ethanol and a basic workup employed so as to avoid any in situ hydrolysis. It was concluded then that the ketone **37** most likely results from iodide cleavage of the ethyl ether of the oxonium intermediate **39** (Scheme 7).[9]

Scheme 7. Proposed Mechanism for the Conversion of **33** and **34** to **37**

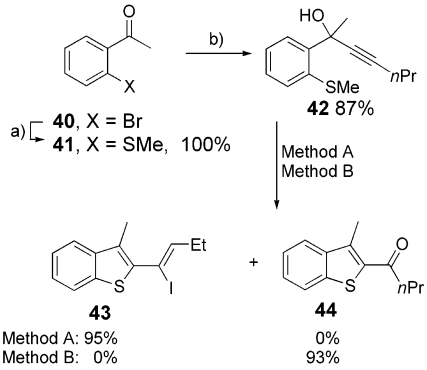


These cyclization processes were also extended to alkyl-substituted tertiary alcohols (Scheme 8). The bromo group in 2-bromoacetophenone **40** was subject to nucleophilic aromatic substitution with sodium methiolate to give the sulfide **41**. This product was converted to the tertiary alcohol **42** using a 1-pentynylcerium species in order to avoid the enolization of the acetophenone **41**, which was observed when the equivalent lithiumacetylide was used. In this case, iodocyclization of the tertiary alcohol **42** gave exclusive formation of the 2-iodoalkenyl system **43**. Also, as with the secondary alcohol **33**, tertiary alcohol **42** also provided exclusive formation of the ketone **44** in ethanol.

We also explored the iodocyclization of the sulfide containing diarylpropynone **21**, which afforded the 5-*exo*-cyclization product, α-iodothioaurone **45**, selectively over the 6-*endo*-cyclization product, 3-iodothioflavone **46**. Although ^{1}H NMR of the crude reaction mixture initially revealed the formation of only one isomer of **45** (presumably

(9) Smith, C. A.; Grutzner, J. B. *J. Org. Chem.* **1976**, *41*, 367.

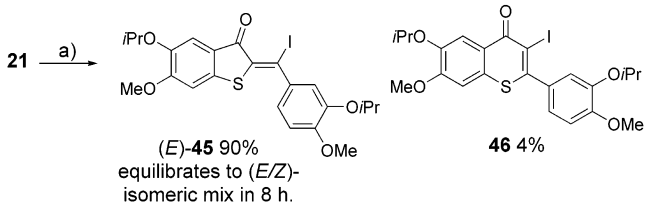
Scheme 8[a]



[a] (a) MeSNa, THF; (b) 1-pentyne, *n*BuLi, $CeCl_3$ THF, then **41**, −78 to 18 °C. Method A: I_2, CH_2Cl_2, 18 °C. Method B: I_2, EtOH, 18°C.

the *anti*-addition product shown) the presence of the donor−acceptor relationship between the carbonyl and aromatic ring in **45** induces a slow isomerization (equilibration achieved after approximately 8 h) leading to a 1:1 thermodynamic mixture of *E*/*Z*-isomers.

Scheme 9



The concise, convergent nature of these reaction protocols, their chemoselectivity, and their capacity to be integrated with related protocols in a complimentary fashion underscore the potential of these new methodologies in the diversity-orientated synthesis of benzothiophene cores. A more extensive investigation into the effects of the various groups L, X, and Y and the reaction conditions on the cyclization of systems **3** (Scheme 1) is currently underway.

Supporting Information Available: Experimental details and spectroscopic data on all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035663A