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Titanium Reagents for the Synthesis of 2-Substituted Benzo[*b*]thiophenes on the Solid Phase

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Abstract: Titanium(IV) benzylidenes (Schrock carbenes) bearing a masked sulfur nucleophile in the ortho position were generated from thioacetals with use of low-valent titanocene complex $Cp_2Ti[P(OEt)_3]_2$ and alkylidenated Merrifield resin-bound esters to give enol ethers. Treatment of the resin-bound enol ethers with a 5:5:90 mixture of TFA, TFAA, and dichloromethane led to cleavage from resin, removal of the *tert*-butyldimethylsilyl (TBDMS) protecting group, and concomitant cyclization to complete the traceless solid-phase synthesis (SPS) of benzothiophenes. Switching the nature of the linker from acid-stable to acid-sensitive ensured good purity.

The synthesis of 2-substituted benzo[*b*]thiophenes is important as such compounds have a range of useful pharmaceutical properties. Zileuton **1**, for example, is a potent and selective inhibitor of 5-lipoxygenase,[1] while many 2-substituted benzothiophenes are selective estrogen receptor modulators and one such compound, raloxifene **2** (Figure 1), is used to treat osteoporosis.[2] Some inhibit serine proteases, such as thrombin[3,4] and factor Xa,[5] and so have potential as anticoagulants, or inhibit the cysteine protease cathepsin K providing a potential alternative route for the treatment of osteoporosis.[6] Others may be anticancer agents reversing multidrug resistance,[7] or binding tubulin.[8,9] There are also examples of 2-substituted benzothiophenes acting as dopamine D3 receptor antagonists,[10] inhibiting cell adhesion[11] and showing promise as antiallergy agents.[12]

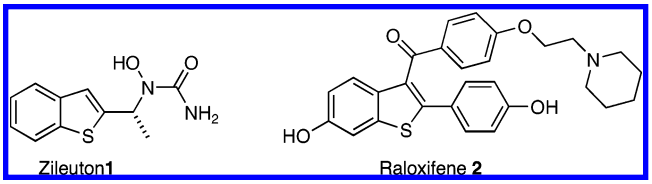

FIGURE 1. Examples of 2-substituted benzo[*b*]thiophene drugs

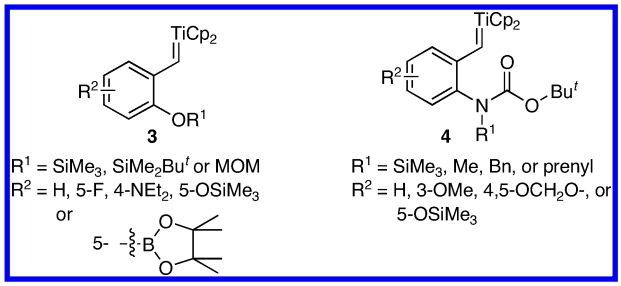

FIGURE 2.

We have recently shown that titanium benzylidene reagents[13−16] **3** and **4** (Figure 2) bearing a protected oxygen or nitrogen nucleophile in the ortho position are easy to generate from thioacetals using low-valent titanium species, $Cp_2Ti[P(OEt)_3]_2$ **5**, and benzylidenate esters to give enol ethers.[17] A range of functionality is tolerated, including boronate, acetal, fluoro, and some amino and carbamate groups, and the reagents have been used for the solid-phase synthesis of benzofurans[13,15,16] and indoles[14,15] in high purity. The reagents work better on the solid phase because of the ease of purification following alkylidenation reaction and also ensure the high purity of products by switching the nature of the linker from acid-stable to acid-sensitive.

We here describe adaptation of this approach to the synthesis of 2-substituted benzo[*b*]thiophenes.[18] We intended to generate novel thio-functionalized titanium

(1) Hsiao, C.-N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629−2632.
(2) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081−1111.
(3) Sall, D. J.; Bastian, J. A.; Briggs, S. L.; Buben, J. A.; Chirgadze, N. Y.; Clawson, D. K.; Denney, M. L.; Giera, D. D.; Gifford-Moore, D. S.; Harper, R. W.; Hauser, K. L.; Klimkowski, V. J.; Kohn, T. J.; Lin, H.-S.; McCowan, J. R.; Palkowitz, A. D.; Smith, G. F.; Takeuchi, K.; Thrasher, K. J.; Tinsley, J. M.; Utterback, B. G.; Yan, S.-C. B.; Zhang, M. *J. Med. Chem.* **1997**, *40*, 3489−3493.
(4) Johnson, M. G.; Bronson, D. D.; Gillespie, J. E.; Gifford-Moore, D. S.; Kalter, K.; Lynch, M. P.; McCowan, J. R.; Redick, C. C.; Sall, D. J.; Smith, G. F.; Foglesong, R. J. *Tetrahedron* **1999**, *55*, 11641−11652.
(5) (a) Chou, Y.-L.; Davey, D. D.; Eagen, K. A.; Griedel, B. D.; Karanjawala, R.; Phillips, G. B.; Sacchi, K. L.; Shaw, K. J.; Wu, S. C.; Lentz, D.; Liang, A. M.; Trinh, L.; Morrissey, M. M.; Kochanny, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 507−511. (b) Maignan, S.; Guilloteau, J.-P.; Choi-Sledeski, Y. M.; Becker, M. R.; Ewing, W. R.; Pauls, H. W.; Spada, A. P.; Mikol, V. *J. Med. Chem.* **2003**, *46*, 685−690. (c) Shrader, W. D.; Young, W. B.; Sprengeler, P. A.; Sangalang, J. C.; Elrod, K.; Carr, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1801−1804.
(6) Fenwick, A. E.; Garnier, B.; Gribble, A. D.; Ife, R. J.; Rawlings, A. D.; Witherington, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 195−198.
(7) Norman, B. H.; Dantzig, A. H.; Kroin, J. S.; Law, K. L.; Tabas, L. B.; Shepard, R. L.; Palkowitz, A. D.; Hauser, K. L.; Winter, M. A.; Sluka, J. P.; Starling, J. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3381−3386.
(8) (a) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341−2343. Pinney, K. P.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081−1086. (b) Pinney, K. P.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081−1086.
(9) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651−654.
(10) Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594−4597.
(11) Boschelli, D. H.; Connor, D. T.; Lesch, M. E.; Schrier, D. J. *Bioorg. Med. Chem.* **1996**, *4*, 557−562.
(12) Connor, D. T.; Cetenko, W. A.; Mullican, M. D.; Sorenson, R. J.; Unangst, P. C.; Weikert, R. J.; Adolphson, R. L.; Kennedy, J. A.; Thueson, D. O.; Wright, C. D.; Conroy, M. C. *J. Med. Chem.* **1992**, *35*, 958−965.
(13) Guthrie, E. J.; Macritchie, J.; Hartley, R. C. *Tetrahedron Lett.* **2000**, *41*, 4987−4990.
(14) Macleod, C.; Hartley, R. C.; Hamprecht, D. W. *Org. Lett.* **2002**, *4*, 75−78.
(15) Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387−401.
(16) McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389−4392.
(17) Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763−2793.
(18) Roberts, C. F.; Hartley, R. C. *Abstr. Pap. Am. Chem. Soc.* **2003**, *226*, 388-ORGN.

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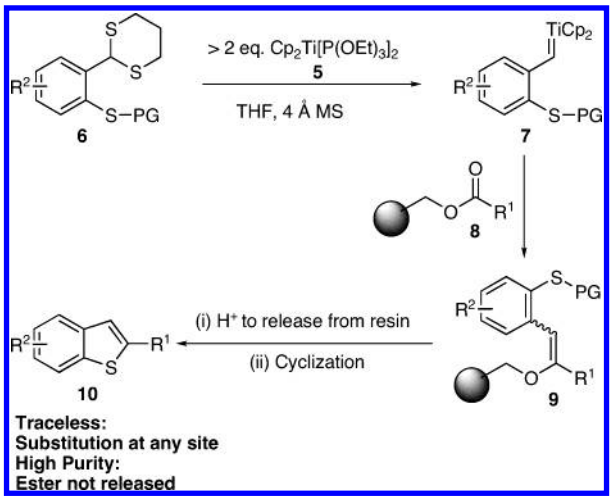
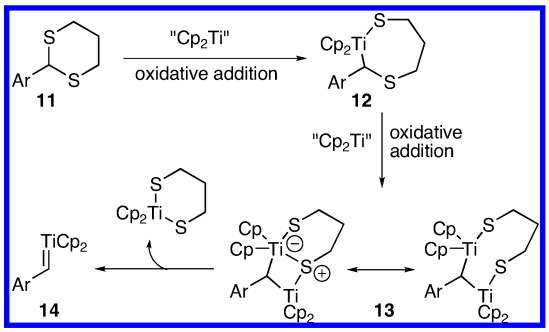
SCHEME 1



benzylidenes **7** from 1,3-dithianes **6** and use them to convert Merrifield resin-bound esters **8** into enol ethers **9** (Scheme 1). Treatment with mild acid would then cleave the enol ethers but would leave any residual esters unaffected so ensuring the purity of the released compounds. Finally, cyclization would give benzothiophenes **10**. This solid-phase synthesis of 2-substituted benzo[*b*]thiophenes would be traceless[19] in that, theoretically, substituents would be allowed at any site, and would be classified as using an *S*sp^2–*C*sp^2 (benzothiophene) linker.[20]

There are many methods for the synthesis of 2-substituted benzo[*b*]thiophenes.[21] Recent approaches include construction of the thiophene moiety by 5-*endo*-*dig* electrophilic[9,22] or radical[23] cyclizations, by intramolecular aldol condensation[24] or other cyclocondensation,[25] and by cyclization of 2-arylthio-ketones,[26] or benzoannelation by electrocyclization–oxidation[27] and by cyclocondensation.[28] However, there is only one method where the heterocyclic ring is formed by nucleophilic attack by the sulfur on a ketone or an oxonium ion derived from an acetal or enol ether and that involves using an *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidothio group as a masked thiol.[29] Methods that employ alkylidenation of carboxylic acid derivatives are also rare: methyl (3-hydroxybenzo[*b*]thiophen-2-yl)carboxylates have been prepared by intramolecular Claisen reaction,[12,30] and intramolecular Wittig reactions with thioesters have been used to make a range of 2-substituted benzo[*b*]thiophenes.[1,31] Dihydrothiophenes have been prepared by titanium alkylidenes reacting intramolecularly with thioesters,[32] but the method has not been applied to benzothiophenes. Although a few solid-phase syntheses of compounds[33] bearing a benzothiophene ring are known,[4,6,34] none have involved the construction of the benzothiophene moiety.[35]

SCHEME 2

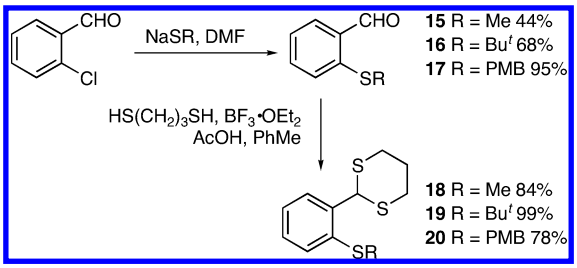


Our proposed approach to 2-substituted benzothiophenes raised a number of questions. Could the 1,3-dithiane moiety be reduced to form the titanium benzylidene without affecting other sulfide functionality? How could problems of chemoselectivity between different sulfur-containing functionality be avoided during the synthesis of the thioacetal substrates? Could we find mild conditions for the final cyclization that would give only volatile side products so that no further purification was necessary? The choice of protecting group would be the key to answering these questions. We postulated that reaction between 2-aryl-1,3-dithianes **11** with titanium(II) complex **5** occurs stepwise giving first intermediate **12** and then bimetallic **13**, which is the reagent added into the flask containing the resin-bound esters (Scheme 2). Rate-determining generation[36] of the Schrock carbene[37] **14** is then followed by rapid alkylidenation[38] of the ester. We decided to make alkyl-protected thiols since they would be easy to prepare, and this functionality would be less reactive toward complex **5** than the dithiane group because the benzylic carbanion in organotitanium intermediate **12** is stabilized both by conjugation with the aromatic ring and by the α-sulfur atom.

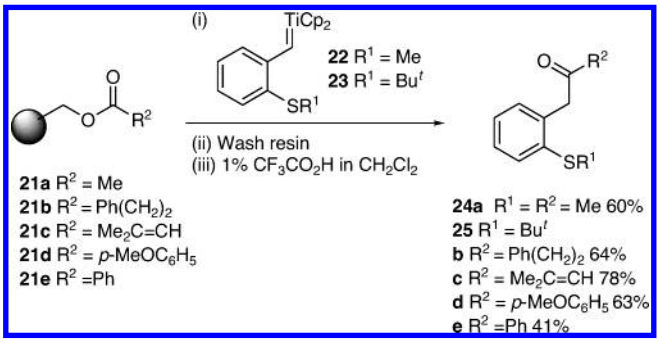
Initially, we prepared methyl-, *tert*-butyl-, and *p*-methoxybenzyl-protected thiols by nucleophilic displacement of chloride from 2-chlorobenzaldehyde,[39] and con-

(19) Blaney, P.; Grigg, R.; Sridaran, V. *Chem. Rev.* **2002**, *102*, 2607–2624.
(20) Comely, A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1012–1032.
(21) (a) Engel, J.; Oepen, G. In *Heteroarenes I, Part 2*, 4th ed.; Kreher, R. P., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1994; Vol. E6b, pp 217–274. (b) Campaigne, E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 4, p 863.
(22) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011–6013.
(23) (a) Aitken, R. A.; Garnett, A. N. *Synlett* **2001**, 228–229. (b) McDonald, F. E.; Burova, S. A.; Huffmann, L. G., Jr. *Synthesis* **2000**, 970–974.
(24) Gallagher, T.; Pardoe, D. A.; Porter, R. A. *Tetrahedron Lett.* **2000**, *41*, 5415–5418.
(25) Shevelev, S. A.; Dalinger, I. L.; Cherkasova, T. I. *Tetrahedron Lett.* **2001**, *42*, 8539–8541.
(26) (a) Kim, S.; Yang, J.; DiNinno, F. *Tetrahedron Lett.* **1999**, *40*, 2909–2912. (b) Katritzky, A. R.; Serdyuk, L.; Xie, L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1059–1064.
(27) Yang, S.-M.; Shie, J.-J.; Fang, J.-M.; Nandy, S. K.; Chang, H.-Y.; Lu, S.-H.; Wang, G. *J. Org. Chem.* **2002**, *67*, 5208–5215.
(28) Suresh, J. R.; Barun, O.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 8153–8160.
(29) Watanabe, M.; Date, M.; Kawanishi, K.; Akiyoshi, R.; Furukawa, S. *J. Heterocycl. Chem.* **1991**, *28*, 173–176.
(30) Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Demontis, S.; Fattuoni, C.; Melis, S. *Tetrahedron* **2002**, *58*, 4529–4533.
(31) Arnoldi, A.; Carughi, M. *Synthesis* **1988**, 155–157.
(32) Rahim, M. A.; Fujiwara, T.; Takeda, T. *Synlett* **1999**, 1029–1032.
(33) Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753.
(34) Yamashita, D. S.; Dong, X.; Oh, H.-J.; Brook, C. S.; Tomaszek, T. A.; Szewczuk, L.; Tew, D. G.; Veber, D. F. *J. Comb. Chem.* **1999**, *1*, 207–215.
(35) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
(36) Hughes, D. L.; Payack, J. F.; Cai, D. W.; Verhoeven, T. R.; Reider, P. J. *Organometallics* **1996**, *15*, 663–667.
(37) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999.
(38) Meurer, E. C.; Santos, L. S.; Pilli, R. A.; Eberlin, M. N. *Org. Lett.* **2003**, *5*, 1391–1394.
(39) Schwartz, J. A. *Synth. Commun.* **1986**, *16*, 565–570.

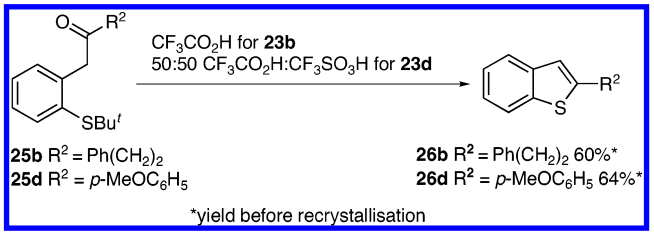
SCHEME 3



SCHEME 4



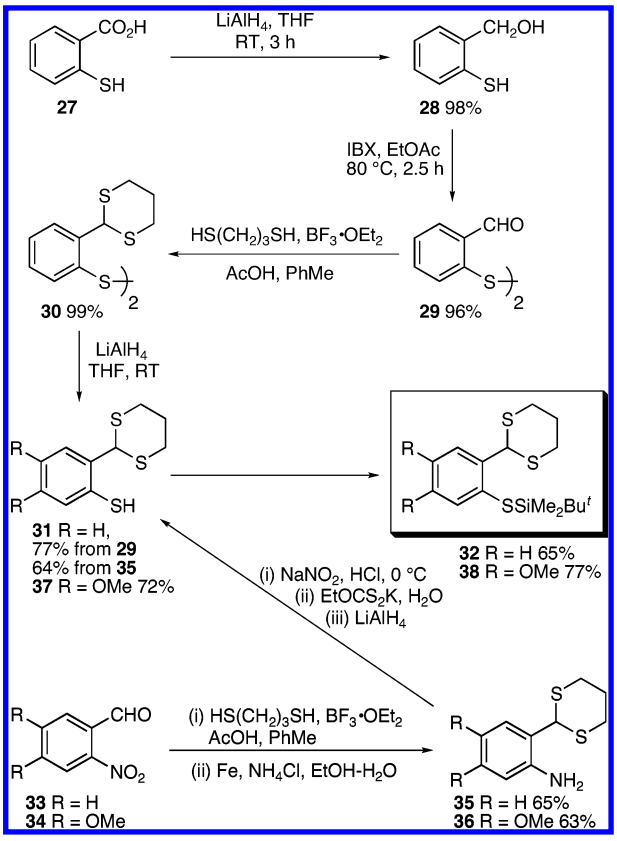
SCHEME 5



version of the resulting 2-alkylthio-benzaldehydes **15**−**17** into thioacetals **18**−**20** (Scheme 3). Resin-bound esters **21a**−**e** contained within small porous polypropylene reactors were prepared from Merrifield resin.[40] Unsurprisingly, *p*-methoxybenzyl aryl sulfide **20** did not give an effective benzylidenating agent. It is likely that the benzylic sulfide reacts with the low-valent titanium complex **5**. However, a titanium reagent, presumably titanium benzylidene **22**, could be generated from thioacetal **18** and reacted with resin-bound ester **21a** to give ketone **24a** following cleavage from resin under mild acid conditions. This showed that chemoselectivity was possible (Scheme 4). More importantly, titanium benzylidene **23**, generated from aryl *tert*-butyl sulfide **19**, could be used to make ketones **25b**−**e** in moderate to good yield based on resin loading, and ketones **25b** and **25d** could be cyclized to give benzothiophenes **26b** and **26d** (Scheme 5). However, the cyclization conditions were harsh and recrystallization of the benzothiophenes was required to obtain pure samples.

We realized that *tert*-butyldimethylsilyl protection[41] of the thiol might be more effective because although S−Si

SCHEME 6



bonds would be cleaved easily under acidic conditions, the functionality should be stable to low-valent titanium complexes as the silicon atom would be resistant to reduction. Initially, we synthesized TBDMS sulfide **32** from readily available 2-mercaptobenzoic acid **27** by modifying the route of Kasmai and Mischke[42] for the preparation of 2-mercaptobenzaldehyde (Scheme 6). Thus, reduction to the alcohol **28** was followed by oxidation with a PCC silica gel homogenate[43] or with MnO_2[42] to give disulfide **29** in 83% or 70% yield, respectively. Using IBX[44] in ethyl acetate[45] gave disulfide **29** cleanly in higher yield, but if heat spots were allowed to develop during the addition of IBX, use of this reagent led to explosion (CAUTION). Thioacetal formation gave disulfide **30** and reduction then gave thiol **31**, which was protected as the TBDMS sulfide **32** by adaptation of a reported method for protecting phenols.[46] However, a more general route began from readily available 2-nitrobenzaldehydes **33** and **34**. Thioacetal formation and reduction by the method we have previously described[15] gave aniline derivatives **35** and **36**. Using the method of Hori et al.,[47] diazonium ion formation and S_NAr displacement of nitrogen with potassium ethyl xanthate was followed by reduction of the resulting *S*-aryl xanthates to give thiols

(40) (a) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476−1482. (b) Merrifield, R. B. *Adv. Enzymol.* **1969**, *32*, 221.

(41) (a) Takeda, K.; Sumi, K.; Hagisawa, S. *J. Organomet. Chem.* **2000**, *611*, 449−454. (b) Still, I. W. J.; Natividad-Preyra, R.; Toste, F. D. *Can. J. Chem.-Rev. Can. Chim.* **1999**, *77*, 113−121. (c) Tanabe, Y.; Okumura, H.; Nagaosa, M.; Murakami, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1467−1472. (d) Kraus, G. A.; Andersh, B. *Tetrahedron Lett.* **1991**, *32*, 2189−2192. (e) Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *47*, 3336−3339.

(42) Kasmai, H. S.; Mischke, S. G. *Synthesis* **1989**, 763−765.

(43) Luzzio, F. A.; Fitch, R. W.; Moore, W. J.; Mudd, K. J. *J. Chem. Educ.* **1999**, *76*, 974−975.

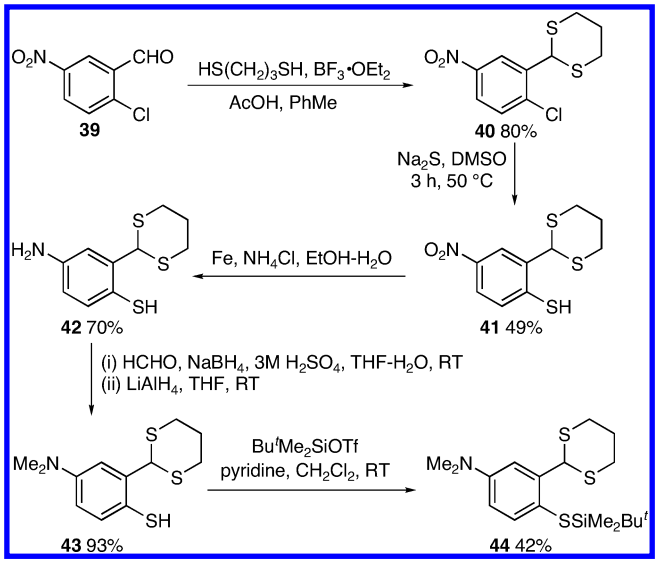
(44) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(45) More J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.

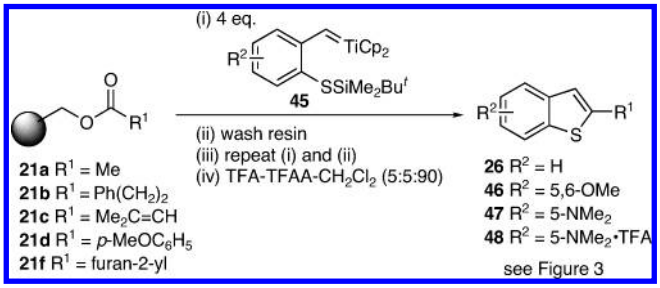
(46) Lei, H.; Atkinson, J. *J. Org. Chem.* **2000**, *65*, 2560−2567.

(47) Hori, M.; Kataoka, T.; Shimizu, H.; Ban, M.; Matsushita, H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 187−194.

SCHEME 7



SCHEME 8



31 and **37** in good yield. Silyl protection was accomplished as before to give TBDMS sulfides **32** and **38**.

An amino substituent could be introduced by using 2-chloro-5-nitrobenzaldehyde **39** as the starting material (Scheme 7). Conversion into thioacetal **40**, followed by nucleophilic displacement of the chloride with sodium sulfide[48] gave thiol **41**. An intractable mixture of compounds was formed when displacement of the chloride by the sulfide dianion was attempted on the unprotected aldehyde **39**. Reduction of the nitro group gave aniline derivative **42**. Finally, *N*-methylation[49] to give thiol **43** was followed by TBDMS protection to give the substrate **44** for titanium benzylidene formation.

Neither the disulfide **30** nor the free thiol **31** gave effective alkylidenating agents when treated with 4 equiv of low-valent titanium complex **5**. However, titanium reagents, presumably titanium benzylidenes **45**, could be generated from thioacetals **32**, **38**, and **44** and these alkylidenated resin-bound esters **21a**−**d** (Scheme 8). It was necessary to retreat the resin to obtain good conversion. Optimized conditions for release from resin with concomitant cyclization to give benzothiophenes **26** and **46**−**48** employed a 50:50 mixture of trifluoroacetic acid

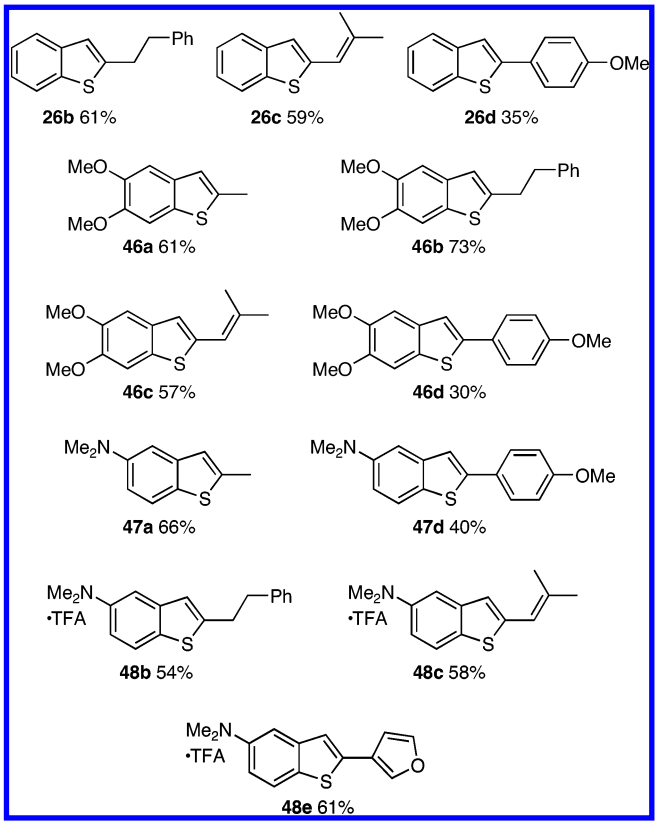


FIGURE 3.

and trifluoroacetic anhydride (as a dehydrating agent) in dichloromethane. The benzothiophenes were isolated in moderate to good yield (based on the original loading of the Merrifield resin, see Figure 3) following solvent removal without any need for purification (see ^{1}H NMR spectra of crude benzothiophenes in the Supporting Information). As in our earlier work with benzofurans,[15] lower yields arose from electron-rich *p*-methoxybenzoate ester **21d**. This would be expected to react more slowly with the nucleophilic titanium benzylidene **45**, allowing alternative routes for the decomposition of the Schrock carbene to compete in the product-determining step.

In conclusion, we have described novel titanium benzylidene reagents that allow a new approach to the synthesis 2-substituted benzothiophenes. We have used these reagents to provide the first examples of the construction of benzothiophenes by solid-phase synthesis.[35] Our method is traceless and ensures the purity of the benzothiophenes by switching the nature of the linker from acid-stable to acid-sensitive.

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Supporting Information Available: Experimental procedures for the preparation of all compounds synthesized; ^{1}H NMR spectra of all compounds synthesized including benzothiophenes **26**, and **46**−**48** as released from resin following solvent removal (with no further purification). This material is available free of charge via the Internet at http://pubs.acs.org.

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(48) Kuo, E.; Hambleton, P.; Kay, D.; Evans, P.; Matharu, S.; Little, E.; McDowall, N.; Jones, C.; Hedgecock, C.; Yea, C.; Chan, A.; Hairsine, P.; Ager, I.; Tully, W.; Williamson, R.; Westwood, R. *J. Med. Chem.* **1996**, *39*, 4608−4621.

(49) Ginmanini, A. *Synthesis* **1980**, 743.