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Novel Route to 2,3-Substituted Benzo[*b*]thiophenes via Intramolecular Radical Cyclization‡

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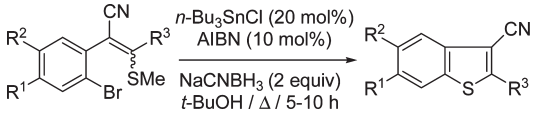

R^1 = H, OCH_3, F; R^2 = H, OMe;
R^3 = SMe, alkyl, aryl, heteroaryl, *N*-amino

A novel route to 2,3-substituted benzo[*b*]thiophenes by intramolecular radical cyclization of polarized ketene dithioacetals derived from *o*-bromoarylacetonitriles or the corresponding 3-(methylthio)-3-alkyl/aryl/heteroaryl analogues has been reported.

Introduction

Benzo[*b*]thiophene represents an important heterocyclic core,[1] as several of its derivatives are shown to display a range of promising pharmaceutical properties such as antipsychotic,[2] antidepressive,[3] antithrombolytic,[4] anti-inflammatory,[5] cognition enhancer,[6] antifungal,[7] antiviral,[8] antiallergic,[9] prostaglandin,[10] dopamine receptor antagonist,[11] and 5-lipoxygenase inhibitor.[12] A number of 2-arylbenzo[*b*]thiophene derivatives have been recognized as therapeutically useful selective estrogen receptor modulators (SERMs) for the treatment of postmenopausal disorders,[13,14] which eventually led to the new commercial drug Raloxifene **1** (Evista, Lilly) for prevention and treatment of osteoporosis in postmenopausal women.[13a,13b] Recently, Raloxifene and its derivatives (such as Arzoxifene **2**)[13c] are also under investigation for breast cancer therapy,[15a,15b] as well as for control and treatment of uterine cancer and Alzhiemer's disease.[16] Recently, a few of the 2-arylbenzo[*b*]thiophenes such as **3a,b** have been

‡ Dedicated to Professor Alan R. Katritzky on his 80th birthday.

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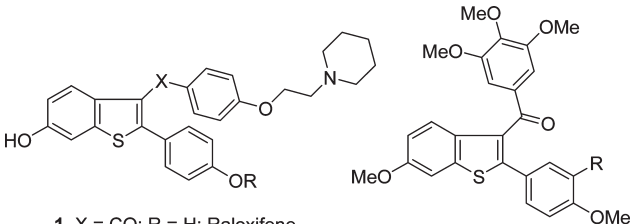
recognized as tubulin polymerization inhibitors[17−19] as rigid analogues of Combretastatin A4.[20]



1, X = CO; R = H; Raloxifene
2, X = O; R = Me; Arzoxifene

3a, R = H
3b, R = OH

Emergence of such promising chemotherapeutic agents has stimulated new investigations into the concise synthesis of 2,3-substituted benzo[*b*]thiophenes.[1,21] The 2-arylbenzo-[*b*]thiophenes are usually synthesized by multistep intramolecular cyclization of thiophenol derivatives developed by Kost and other workers.[13b,22] However, these methods usually required both acidic and/or basic conditions, proved to be nonregioselective,[13b,22f] and were not compatible with acid- and base-sensitive functional groups. Therefore, other methods have been developed starting from thiobenzyls[23] or thioanisole[24] derivatives along with useful catalytic routes via direct Heck type arylation of 2-unsubstituted benzo[*b*]-thiophenes[25−27] and iodine-induced intramolecular oxidative cyclization of *o*-acetylenic thiobenzyl derivatives.[19,28]

Our own interest in the synthesis of 2,3-substituted benzo[*b*] thiophenes derives from our longstanding experience in the synthesis of a wide range of substituted and fused five- and six-membered heterocycles utilizing polarized ketene dithioacetals as synthetic precursors.[29−32] During the course of these studies, we became interested in exploring intramolecular radical cyclizations of the appropriately substituted polarized ketene dithioacetals[33] and envisaged a general synthetic route for 2,3-substituted benzo[*b*]thiophenes through a tandem intramolecular attack of a carbon-centered aryl radical on a suitably located sulfur atom of bis(methylthio)methylene moiety of ketene dithioacetals and subsequent C−S bond cleavage.[34,35] Our literature survey at this stage revealed that Harrowven and co-workers in their pioneering studies have reported cascade radical transformations of few unpolarized cyclic (*o*-bromoarylidene) ketene dithioacetals yielding 2-(3-mercaptopropyl)/(tributylstannyl)-3-unsubstituted benzo[*b*] thiophenes as the major products along with few minor products by further cyclization of the initially formed radical intermediates.[36] However, these cyclic ketene dithioacetals have limitations for developing this reaction as a general concise approach for the synthesis of biologically important 2-aryl/heteroaryl-3-substituted benzo[*b*]thiophenes. We have realized this objective by subjecting either polarized ketene dithioacetals of the type **4** or the related 2-(2-bromoaryl)-3-methylthio-3-alkyl/aryl/heteroarylacrylonitrile analogues of the type **7** to radical cyclization affording 2-substituted-3-cyanobenzo[*b*]thiophenes in good yields (Schemes 1 and 2). We report the results of these studies in this paper.

Results and Discussion

The reaction of ketene dithioacetal **4a** derived from (2-bromophenyl)acetonitrile with TBTH was first examined

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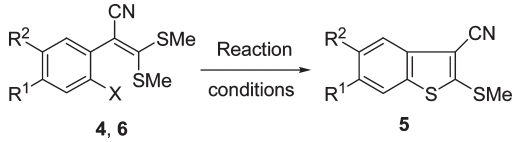
SCHEME 1. Synthesis of 3-Cyano-2-(methylthio)benzo[*b*]thiophenes 5



4, **6** **5**

TABLE 1. Synthesis of 3-Cyano-2-(methylthio)benzo[*b*]thiophenes 5

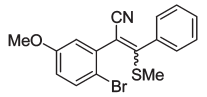
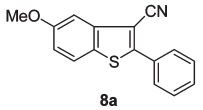
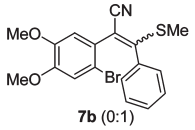
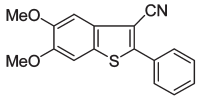
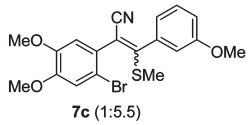
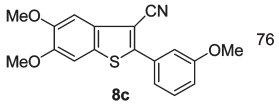
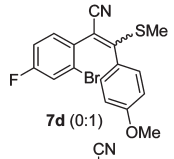
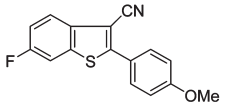
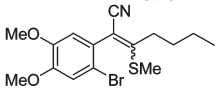
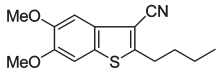
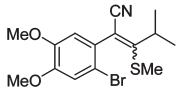
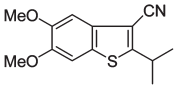
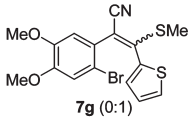
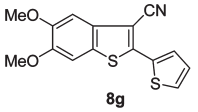
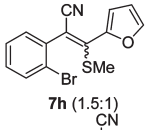
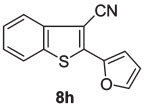
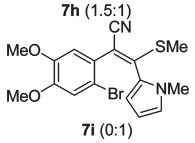
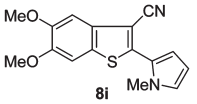
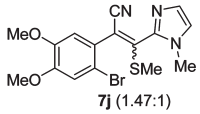
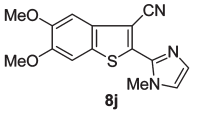
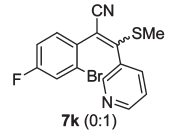
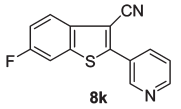
entry		X	R^1	R^2	**5**	% yield **5**
1	**4a**	Br	H	H	**5a**	25[a]
2	**4a**	Br	H	H	**5a**	59[b]
3	**6**	I	H	H	**5a**	61[b]
4	**4b**	Br	OMe	OMe	**5b**	68[b]
5	**4c**	Br	F	H	**5c**	59[b]

[a]TBTH (1.2 equiv)/AIBN (10 mol %)/toulene/Δ/12 h. [b]*n*-Bu_3SnCl (20 mol %), $NaCNBH_3$ (2 equiv)/AIBN (10% mol), *t*-BuOH/Δ/12 h.

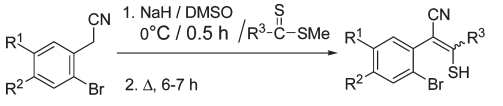
(Scheme 1). Thus, when **4a** was exposed to TBTH under standard radical-forming conditions (Table 1, entry 1), workup of the reaction mixture gave one product (25% yield) (along with unreacted **4a**), which was characterized as 3-cyano-2-(methylthio)benzo[*b*]thiophene **5a** on the basis of its spectral and analytical data (Table 1, entry 1).[37] The benzo[*b*]thiophene **5a** was obtained in increased and reproducible yield (59−60%), when **4a** was subjected to Stork's catalytic tin hydride conditions[38] using tributyltin chloride in the presence of $NaCNBH_3$ and AIBN in refluxing *tert*-butanol (Table 1, entry 2). Under identical conditions, the corresponding *o*-iodo derivative **6** furnished the 3-cyano-2-(methylthio)benzo[*b*]thiophene **5a** in comparable yield of 61% (Table 1, entry 3). Consequently, catalytic tributyltin chloride/$NaCNBH_3$ was used as the reagent of choice for all radical cyclizations described in the paper. The substrates bearing (*o*-bromoaryl) group were preferred over the corresponding (*o*-iodoaryl) analogues, because of the ease of preparation of the former by direct bromination of arylacetonitrile precursors. Ketene dithioacetals **4b**−**c** bearing electron-donating (**4b**) and electron-withdrawing (**4c**) substituents were also subjected to radical cyclization under identical conditions affording 2-(methylthio)-3-cyano-5,6-substituted benzo[*b*]thiophenes **5b**−**c** in 68% and 59% yields, respectively (Table 1, entries 4 and 5).

To further explore the generality and scope of this reaction, especially for the synthesis of 2-aryl/heteroarylbenzo[*b*]-thiophenes, we next examined analogous radical cyclization of the corresponding 3-(methylthio)-3-(aryl/heteroaryl/alkyl)-2-(2-bromoaryl)acrylonitriles **7** under identical conditions (Scheme 2, Table 2). We have previously developed a general synthetic protocol for these intermediates via

TABLE 2. Synthesis of 3-Cyano-2-aryl/alkyl/heteroarylbenzo[*b*]thiophenes 8

Entry	**7** (*E*/*Z*)	Reflux Time (h)	**8**	% Yield of **8**
1	 **7a** (1:2.3)	7	 **8a**	81
2	 **7b** (0:1)	8	 **8b**	74
3	 **7c** (1:5.5)	6	 **8c**	76
4	 **7d** (0:1)	7	 **8d**	78
5	 **7e** (1.14:1)	6	 **8e**	63
6	 **7f** (1:1)	8	 **8f**	55
7	 **7g** (0:1)	5	 **8g**	73
8	 **7h** (1.5:1)	5	 **8h**	68
9	 **7i** (0:1)	5	 **8i**	78
10	 **7j** (1.47:1)	7	 **8j**	52
11	 **7k** (0:1)	8	 **8k**	74

(37) 2-(Methylthio)-3-cyanobenzo[b]thiophene (**5a**) is reported to be formed in 86% yield on treatment of 2-bromophenylacetonitrile with carbon disulfide in the presence of NaH in DMSO and subsequent warming and alkylation with methyl iodide: Rudorf, W.-D; Schierhorn, A.; Augustin, M. *J. Prakt. Chem.* **1979**, *321*, 1021. However, we could isolate **5a** in only 28% yield under these conditions. Similarly, the benzothiophenes **5b** and **5c** were obtained in 30% and 32% yields, respectively, when the corresponding 2-bromo-4,5-dimethoxy- and 2-bromo-4-fluorophenylacetonitriles **20a** and **20b** were reacted with carbon disulfide and methyliodide under Rudorf's conditions. On the otherhand, treatment of **20a** and **20b** with either methyl 2-thienyl- or 4-(methoxyphenyl)dithioates in the presence of NaH/DMSO under these conditions furnished only the acyclic compounds **21a** and **21b** in 34% and 36% yields, respectively, and no trace of benzothiophenes **8g** or **8d** could be isolated from the reaction mixture.

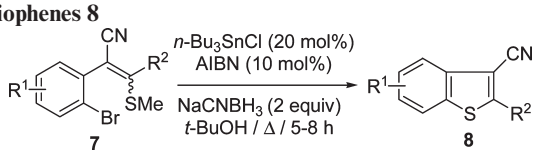


20a, $R^1 = R^2 =$ OMe **21a**, $R^1 = R^2 =$ OMe, R^3 = thienyl; 34%

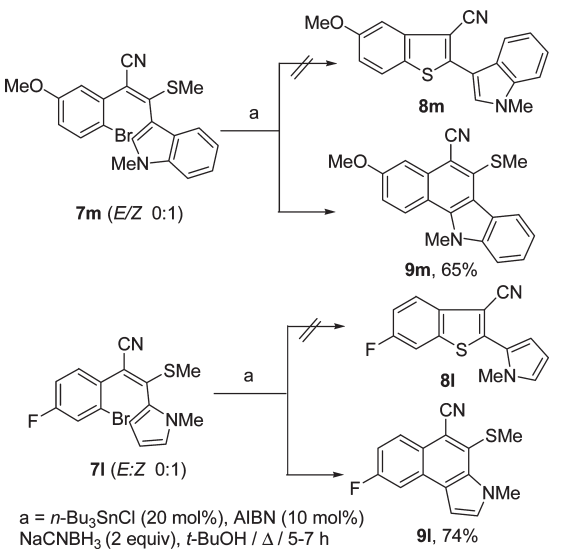
20b, R^1 = H; R^2 = F **21b**, R^1 = H; R^2 = F, 4-$MeOC_6H_4$; 36%

(38) (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (b) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

SCHEME 2. Synthesis of 3-Cyano-2-alkyl/aryl/heteroarylbenzo-[*b*]thiophenes 8



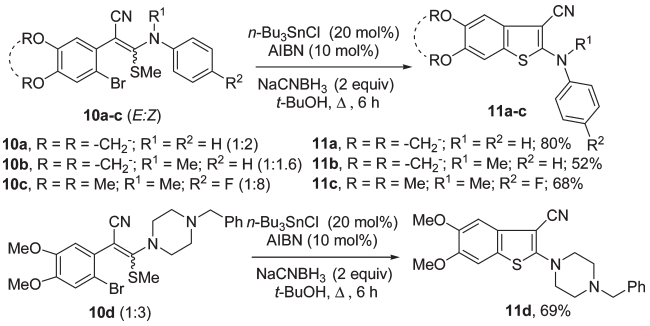
SCHEME 3. Radical Cyclization of 7l and 7m



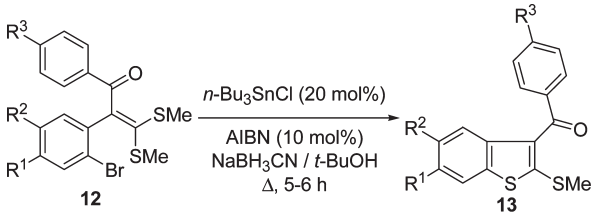
base-induced condensation of the substituted (*o*-bromo) arylacetonitriles with the corresponding aryl/heteroaryl/alkyl dithioesters followed by in situ S-methylation of the resulting enethiolate salts with methyl iodide.[39] With a number of substrates in hand, we first subjected the representative 3-methylthio-3-phenylacrylonitrile **7a** to radical cyclization under previously described conditions, and we were pleased to observe that the anticipated 3-cyano-5-methoxy-2-phenylbenzo[*b*]thiophene **8a** was obtained in 81% yield (Table 2, entry 1). The other substituted 2-aryl-3-cyanobenzo[*b*]thiophenes **8b**−**d** were similarly obtained in high yields from the respective 3-aryl-3-(methylthio)acrylonitrile precursors **7b**−**d** (Table 2, entries 2−4). The methodology could also be extended successfully for the synthesis of 2-alkyl-3-cyanobenzo[*b*]thiophenes **8e**−**f** in reasonably good yields from the appropriate 3-alkyl-3-(methylthio)acrylonitrile precursors **7e**−**f** (Table 2, entries 5 and 6). Similarly, we were further delighted to find that the corresponding 3-(heteroaryl)-3-(methylthio)acrylonitriles **7g**−**k** also underwent facile cyclization under identical radical-mediated conditions providing the novel hitherto unreported 2-(2-thienyl)-, 2-(2-furyl), 2-(2-*N*-methylpyrrolyl), 2-(2-*N*-methylimidazolyl), and 2-(3-pyridyl)-3-cyanobenzo[*b*]thiophenes **8g**−**k** in high yields (except **8j**) (Table 2, entries 7−11).

Interestingly, the radical cyclization of the corresponding 3-methylthio-3-(3-indolyl)acrylonitrile **7m** under similar reaction conditions did not follow the expected protocol to afford the desired 2-(3-indolyl)-3-cyanobenzo[*b*]thiophene **8m**, and the product isolated (65%) was found to be benzo [1,2-*a*]carbazole derivative **9m** (Scheme 3). The corresponding 3-(methylthio)-3-(2-pyrrolyl) derivative **7l** bearing electron-withdrawing fluorine on the phenyl ring also behaved in the similar fashion (unlike its electron-rich counterpart **7i**) (Table 2, entry 9) yielding the substituted benzo[*e*]indole **9l** instead of the anticipated 2-(2-pyrrolyl)-3-cyano-6-fluorobenzo[*b*]thiophene **8l** (Scheme 3).

SCHEME 4. Synthesis of 2-Anilino/cycloamino-3-cyanobenzo[*b*]-thiophenes 11a−d



SCHEME 5. Attempted Synthesis of 2-Methylthio-3-aroylbenzo-[*b*]thiophenes 13

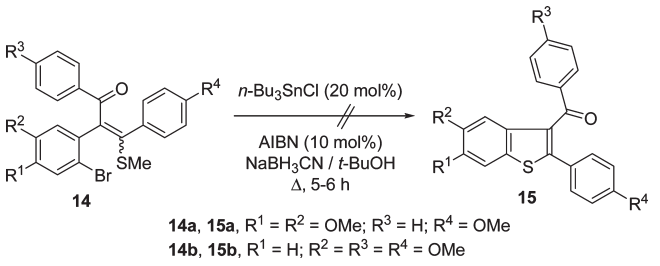


After successful synthesis of various 2-aryl/heteroaryl/alkyl-3-cyanobenzo[*b*]thiophenes, we next extended this radical cyclization protocol to few *N*,*S*-acetals **10a**−**d** derived from (*o*-bromoaryl)acetonitriles and primary/secondary amines (Scheme 4). The resulting 2-(cycloamino/arylamino)-3-cyanobenzo[*b*]thiophenes **11a**−**d** are useful substrates for further synthetic elaboration.[21a] Thus, when **10a**−**d** were exposed to *n*-$Bu_3SnCl/NaCNBH_3$ under earlier reported conditions, the reaction proceeded as expected yielding 2-*N*-anilino and 2-(*N*-methylanilino)- and 2-(*N*-benzylpiperazino)-3-cyanobenzo-[*b*]thiophenes **11a**−**d** in moderate to good yields (Scheme 4).

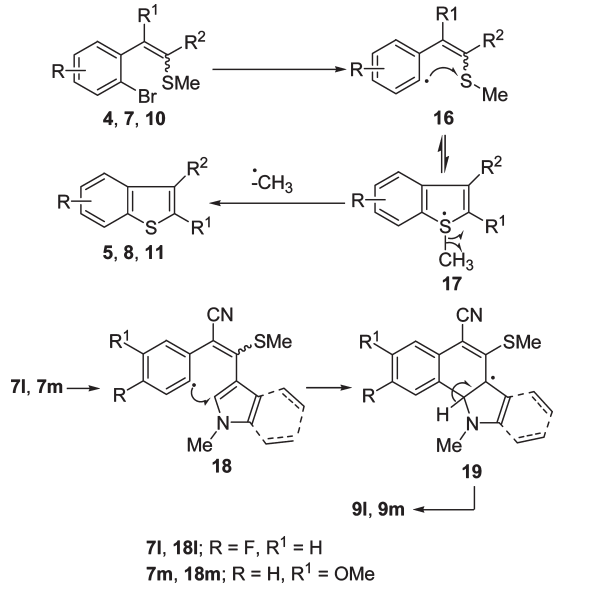
After successfully achieving the synthesis of 2-substituted-3-cyanobenzo[*b*]thiophenes via radical-mediated cyclization, we next focused our attention toward creating functional group diversity at the 3-position of benzo[*b*]thiophenes and therefore examined the intramolecular radical cyclization of ketene dithioacetals **12a**−**c** derived from (*o*-bromoaryl)desoxybenzoins and the related 3-aryl analogues **14** (Schemes 5 and 6). The resulting 3-aroylbenzo[*b*]thiophenes **13** and **15** are structural analogues of few therapeutically important benzo[*b*]thiophenes such as Raloxifene **1** and tubulin-binding agents such as **3**. Thus, when the ketene dithioacetal **12a** was subjected to radical cyclization under earlier reported conditions (*n*-$Bu_3SnCl/NaCNBH_3$), the desired 3-benzoyl-2-(methylthio) benzo[*b*]thiophene **13a** was isolated in 62% yield (Scheme 5). However, the reaction of the related ketene dithioacetals **12b**−**c** from methoxy/fluoro substituted desoxybenzoins yielded only

(39) Kumar, S.; Peruncheralathan, S; Ila, H.; Junjappa, H. *Org. Lett.* **2008**, *10*, 965.

SCHEME 6. Attempted Synthesis of 2-Aryl-3-aroylbenzo[*b*]thiophenes 15



SCHEME 7. Probable Mechanism for Formation of Benzo[*b*]thiophenes 5, 8, 11, and 9l−m



unreacted starting materials under these conditions due to the insolubility of **12b−c** in *tert*-butanol. Similarly, the attempted radical cyclization of the newly synthesized 3-aryl-3-methylthio-2-(2-bromoaryl)-1-arylpropenones **14a−b** to the desired 2-aryl-3-aroylbenzo[*b*]thiophenes under identical conditions or by varying the solvent or reagent (toluene or TBTH/toluene) did not meet with any success and yielded only unreacted **14a−b** without any trace of **15** (Scheme 6).

The probable mechanism for the formation of various substituted benzo[*b*]thiophenes from the respective precursors is shown in Scheme 7. Thus, the initially formed 2-(*o*-aryl) radical species **16** attacks intramolecularly the sulfur atom of methylthio group of either ketene dithioacetals **4** or of 3-(methylthio) moiety of acrylonitriles **7** or *N*,*S*-acetals **10** to give the cyclized radical intermediate **17**, which on homolytic C−S bond cleavage affords the product benzo[*b*]thiophenes **5**, **8**, or **11** in good yields (Scheme 7).

In the case of 3-(2-*N*-methylpyrrolyl) and 3-(3-*N*-methylindolyl)acrylonitriles **7l−m**, the initially formed aryl radical in intermediate **18** attacks intramolecularly either 3-position of pyrrole **7l** or 2-position of indole **7m** rather than the methylthio group, yielding the products benzo[*e*]indole **9l** or the corresponding benzo[*a*]carbazole **9m** instead of the expected benzo[*b*]thiophenes **8l−m** (Scheme 4). Failure of the corresponding 1-(methylthio)-1,2,3-triarylpropen-3-ones **14a−b** or **12b−c** to undergo radical-mediated cyclization to give the desired 3-aroylbenzo[*b*]thiophenes **15a−b** or **13b−c** (Schemes 5 and 6) appears to be due to insolubility of starting compounds **14a−b** and **12b−c** in the reaction solvents and also due to steric crowding in these precursors (**14a−b** and **12b−c**), thus resisting the abstraction of bromine by bulkier tributyltin radical in the initial step (Scheme 7).

Interestingly, the X-ray diffraction data of pure stereoisomers **7b**, **7d**, **7g**, **7k**, and **7m** showed that they exist in *Z* form with *o*-bromoaryl and SMe groups being *trans* to each other.[41] Thus, the facile cyclization of *Z* isomers of **7** to benzo[*b*]thiophenes appears to proceed via a *cis*−*trans* isomerization of the double bond in **7** involving either an addition−elimination of tributytin radical[42,43] or a thermal isomerization to *E* isomers, under the present reaction conditions, for their favorable cyclization to **8**.[44]

Conclusion

In summary, we have demonstrated that the appropriately substituted polarized ketene dithioacetals derived from *o*-bromoarylacetonitriles or the corresponding 3-(methylthio)-3-aryl/heteroarylacrylonitrile analogues are useful substrates for the synthesis of 2,3-substituted benzo[*b*]thiophenes via an intramolecular radical cyclization protocol involving tandem attack of a carbon-centered radical on sulfur and subsequent C−S bond cleavage. This new methodology allows direct one-step access to 2-substituted-3-cyanobenzo[*b*]thiophenes with potential biological activity. Also, this versatile methodology will be a good alternative for the synthesis of Raloxifene analogues despite our initial unsuccessful attempts, and further efforts in this direction and to study scope and limitations of this methodology are in progress.

Experimental Section

General details are described in Supporting Information. The known *S*,*S*-acetals **4a−c**, **6**, **7b−c**, and **7g−i** and the unknown **7a**, **7d−f**, **7j−k**, and **7l−m** were prepared according to the our earlier reported procedure.[39,45] Similarly, the unknown *S*,*S*-acetals **12a−c** and **14a−b** were prepared from the appropriate desoxybenzoins.[29a,39,45] The unknown *N*,*S*-acetals **10a−d** were obtained either by arylisothiocyanate method[29a,46] (**10a−c**) or by direct displacement on the ketene dithioacetals by amine (**10d**).[29a,46]

General Procedure for Radical Cyclization of 2-(2-Bromoaryl-3-(alkyl/aryl/heteroaryl)-3-(methylthio)-2-propenenitriles 4, 6, 7, 10, 12, and 14. To a solution of corresponding 2-(2-bromoaryl)

(40) Branum, S. T.; Colburn, R. W.; Dax, S. L.; Flores, C. M.; Jetter, M. C.; Liu, Y.; Ludovici, D.; Macielag, M. J.; Matthews, J. M.; Mcnally, J. J. *PCT Int. Appl.* **2009**, WO 2009012430 A1 20090122; *Chem. Abstr.* **2009**, *150*, 168153.

(41) The stereochemical assignments for **7a**, **7c**, **7e**, **7f**, **7h**, and **7j** existing as *E*/*Z* mixtures are based on the chemical shift value of the SMe signal that appears at higher δ value (δ 2.05−2.45) in *Z* isomers (also in pure *Z* isomers **7b**, **7d**, **7g**, **7i**, **7k**, **7l** and **7m**) in comparison to *E* isomers (δ 1.8−2.11) probably due to shielding by the *cis* (*o*-bromoaryl group) in *E* isomers.

(42) (a) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 3185. (b) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557. (c) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795.

(43) A detailed analysis of reaction mixtures from **7a−k** showed exclusive formation of benzo[b]thiophene products **8a−k** with no trace of fused products such as **9l−m**.

(44) We are thankful to one of the reviewers for this suggestion and in fact, when **7a** (*E*/*Z* 1:2.3) was refluxed in *t*-BuOH for 10 h in the absence of *n*-Bu_3SnCl/AIBN/$NaCNBH_3$, the *E*/*Z* ratio was found to change to 18:1 (estimated by ^1H NMR spectrum).

(45) Chauhan, S. M. S.; Junjappa, H. *Tetrahedron Lett.* **1976**, *32*, 1779.

(46) Kumar, A.; Aggarwal, V.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 784.

acrylonitriles **4**, **6**, **7**, **10**, **12**, or **14** (0.25 mmol), AIBN (10 mol %), and $NaCNBH_3$ (0.50 mmol) in degassed *t*-BuOH (15 mL) was added *n*-Bu_3SnCl (20 mol %), and the reaction mixture was refluxed for 5−8 h. It was then cooled to room temperature, and solvent was evaporated followed by addition of water (25 mL). It was extracted with ethylacetate (3 × 15 mL), and the combined organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to afford crude product, which was purified by column chromatography over silica gel using EtOAc−hexane as eluent to give pure benzo[*b*]thiophenes **5**, **8**, **11**, or **13** and **9l**−**m**.

2-Methylthiobenzo[*b*]thiophene-3-carbonitrile (5a)[37]. White solid; yield 59% (0.31 g); mp 79−80 °C; R_f 0.63 (1:19 EtOAc/hexane); IR (KBr) 2923, 2207, 1456, 1419, 747, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.3, 137.6, 126.1, 125.3, 121.9, 121.4, 113.7, 104.8, 18.9; MS (FAB) *m*/*z* (%) 206 ($M + H^+$, 90), 205 (M^+, 100); HRMS (ESI) *m*/*z* calcd for $C_{10}H_8NS_2$ ($M^+ + H$) 206.0098, found 206.0093.

5,6-Dimethoxy-2-phenyl-benzo[*b*]thiophene-3-carbonitrile (8b). White solid; yield 74% (0.55 g); mp 179−180 °C; R_f 0.45 (1:9 EtOAc/hexane); IR (KBr) 2933, 2217, 1520, 1492, 1437, 1359, 1264, 1251, 1035, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.83 (m, 2H), 7.52−7.45 (m, 3H), 7.32 (s, 1H), 7.24 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 149.6, 149.6, 133.1, 131.8, 130.3, 130.1, 129.4, 127.9, 115.7, 103.6, 103.5, 101.5, 56.4, 56.3; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{14}NSO_2$ ($M^+ + H$) 296.0745, found 296.0746.

2-Isopropyl-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (8f). Viscous liquid; yield 55% (0.36 g); R_f 0.48 (1:9 EtOAc/hexane); IR (CH_2Cl_2) 2936, 2239, 1517, 1464, 1263, 1227, 1145, 1026, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.77 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.80−3.75 (m, 1H), 1.55 (d, J = 9.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 148.8, 129.6, 121.9, 119.0, 111.5, 109.8, 56.1, 56.1, 30.9, 21.6; MS (FAB) *m*/*z* (%) 261 (M^+ 100), 232 (75%); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{15}NSO_2$ (M^+) 261.0823, found 261.0826.

5,6-Dimethoxy-2-(1-methyl-1*H*-pyrrol-2-yl)benzo[*b*]thiophene-3-carbonitrile (8i). White solid; yield 78% (0.58 g); mp 139−140 °C; R_f 0.42 (1:9 EtOAc/hexane); IR (KBr) 3010, 2932, 2213, 1601, 1521, 1468, 1285, 1235, 1206, 1030, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.16 (s, 1H), 6.78 (t, J = 2.2 Hz, 1H), 6.65 (dd, J = 6.3 Hz, 1.7 Hz, 1H), 6.20 (t, J = 3.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 149.2, 143.4, 132.1, 130.2, 126.8, 123.9, 115.6, 113.8, 109.0, 103.3, 103.1, 102.5, 56.3, 56.2, 35.7; MS (ESI) *m*/*z* (%) 299 ($M^+ + 1$, 100); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}N_2O_2S$ ($M^+ + H$) 299.0854, found 299.0858.

6-Fluoro-2-(pyridin-3-yl)benzo[*b*]thiophene-3-carbonitrile (8k). White solid; yield 74% (0.47 g); mp 187−188 °C; R_f 0.60 (1:4 EtOAc/hexane); IR (KBr) 2924, 2219, 1564, 1468, 1416, 1192, 1133, 900, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (brs, 1H), 8.76 (brs, 1H), 8.25 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.96 (dd, J = 8.8 Hz, 4.8 Hz, 1H), 7.60 (dd, J = 8.0 Hz, 2.2 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 4.9 Hz, 1H), 7.35−7.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (d, J = 248.0 Hz), 151.4, 150.6, 148.9, 138.73 (d, J = 10.7 Hz), 135.4, 135.2, 127.7, 124.4, 124.09, 115.84 (d, J = 23.8 Hz), 114.4, 109.0 (d, J = 26.2 Hz), 103.3; HRMS (ESI) *m*/*z* calcd for $C_{14}H_8FN_2S$ ($M^+ + H$) 255.0396, found 255.0391.

3-Methoxy-11-*N*-methyl-6-methylthiobenzo[*a*]carbazole-5-carbonitrile (9m). Light yellow solid; yield 65% (0.24 g); mp 203−204 °C; R_f 0.56 (1:6 EtOAc/hexane); IR (KBr) 2916, 2200, 1618, 1564, 1467, 1224, 1047, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, J = 8.1 Hz, 1H), 8.61 (d, J = 9.5 Hz, 1H), 7.71−7.70 (m, 1H), 7.57−7.55 (m, 2H), 7.42−7.38 (m, 1H), 7.32−7.29 (m, 1H), 4.35 (s, 3H), 4.01 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 141.2, 138.5, 138.1, 134.7, 125.7, 124.4, 123.1, 122.5, 121.2, 118.8, 118.5, 118.2, 116.3, 109.1, 107.1, 105.5, 55.6, 34.4, 19.6; MS (FAB) (*m*/*z*, %) 333 (M + 1, 88), 332 (M^+, 100); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{17}N_2OS$ ($M^+ + H$) 333.1062, found 333.1068.

6-Phenylamino-1,3-dioxa-5-thia-*s*-indacene-7-carbonitrile (11a). White solid; yield 80% (0.58 g); mp 221−222 °C; R_f 0.70 (1:9 EtOAc/hexane); IR (KBr) 3251, 2886, 2203, 1597, 1559, 1498, 1472, 1446, 1294, 1217, 1050, 1038, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 7.04 (brs, 1H), 6.99 (s, 1H), 6.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 147.7, 145.7, 140.1, 130.5, 129.8, 124.6, 121.5, 119.4, 115.1, 101.8, 101.5, 99.9, 85.0; MS (FAB) *m*/*z* (%) 294 (M^+, 100); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{10}N_2O_2S$ (M^+) 294.0463, found 294.0482.

(2-Methylthiobenzo[*b*]thiophen-3-yl)-phenylmethanone (13a). Yellow liquid; yield 62% (0.44 g); R_f 0.28 (1:9 EtOAc/hexane); IR (KBr) 3057, 2924, 1638, 1557, 1464, 1434, 1347, 1316, 1250, 1076, 1026, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.1 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.46−7.42 (m, 1H), 7.38−7.28 (m, 3H), 7.19−7.14 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 151.9, 138.5, 136.9, 132.9, 131.7, 131.5, 129.8, 129.3, 128.7, 128.1, 127.5, 123.5, 17.8; MS (FAB) *m*/*z* (%) 284 (M^+ 100); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{12}OS_2$ (M^+) 284.0330, found 284.0348.

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Supporting Information Available: General experimental procedures, characterization data and copies of ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.