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Site-specific preparation of 4-substituted-6-fluoro(carboalkoxyl)benzo[*b*]furans and benzo[*b*]thiophenes *via* base-catalyzed cyclization of enyne derivatives

Yi Wang, Donald J. Burton *

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

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This paper is dedicated to Professor Neil Bartlett on the occasion of his 75th birthday.

Abstract

A site-specific synthesis of 4-substituted-6-fluoro(carboalkoxyl)benzo[*b*]furans and benzo[*b*]thiophenes is described. The reactions of heterocyclic aromatic aldehydes with a Wittig reagent, followed by Sonogashira reaction with terminal alkynes, and subsequent base-catalyzed cyclization site-specifically provide 4-substituted-6-fluoro(carboalkoxyl)benzo[*b*]furans and benzo[*b*]thiophenes in good yields.

Keywords: Benzofurans; Benzothiophenes; Fluorine; Cyclization

1. Introduction

Benzo[*b*]furans and benzo[*b*]thiophenes represent many naturally occurring and designed molecules responsible for a diverse range of biological responses [1–6]. Recently, fluorinated benzofurans and benzothiophenes have also found application in liquid crystal displays [7]. Accordingly, there exists a wide selection of methods for the synthesis of these important structural motifs [8–11], including palladium-catalyzed cyclization, largely from the efforts of Larock and coworkers [12–15]. However, these methods often require expensive catalysts and/or multi-step synthesis. In addition, site-specific preparation of fluorinated benzofurans and benzothiophenes has been a challenging problem. Although Balz–Schiemann reactions [16,17] have been widely used for the preparation of fluorinated aromatic compounds, the starting diazonium salts are hazardous. In addition, electrophilic fluorination of aromatic compounds gives a mixture of regioisomers [18]. Barton and coworkers reported fluorination of benzofurans with trifluorofluorooxymethane (CF_3OF) to give CF_3O and F adducts [19]. Recently, we have developed a novel base-catalyzed cyclization to site-specifically prepare substituted naphthalenes and polycyclic aromatic hydrocarbons [20–23]. Herein, we wish to report the utilization of this base-catalyzed cyclization for the site-specific preparation of substituted heterocyclic compounds, such as benzo[*b*]furans and benzo[*b*]thiophenes.

2. Results and discussion

2.1. Preparation of 4-substituted-6-fluorobenzo[b]furans and benzo[b]thiophenes

Heteroaromatic aldehydes were employed as starting materials. The reaction of 2-thiophenecarboxaldehyde, Ph_3P (2 equiv) and $CFBr_3$ in refluxing THF gave 1-bromo-1-fluoroalkenes **1b** by the reported method [24,25]. However, this procedure could not be applied to the preparation of **1a**. Fortunately, the synthesis of **1a** was accomplished *via* an alternative procedure, wherein 1 equiv of activated zinc dust was used instead of the second equivalent of Ph_3P (debromination of the phosphonium salt gives a solution of a metal-stabilized ylide) [26–28]. The *Z*/*E* ratios of compounds **1a** and **1b** were determined from the ^{19}F NMR spectra of the products. The coupling constant of vicinal hydrogen and fluorine of the *E* isomer ($^3J_{trans(F,H)}$ = 13–52 Hz) is larger than that of the *Z* isomer ($^3J_{cis(F,H)}$ = 0–20 Hz) [29]. Subsequent Sonogashira

* Corresponding author.
E-mail address: donald-burton@uiowa.edu (D.J. Burton).

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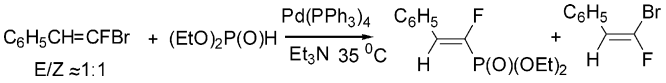
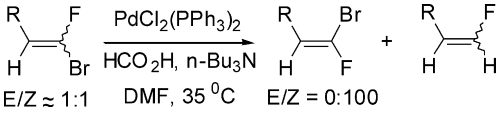
reaction [30] of the vinyl bromides **1a** and **1b** with terminal alkynes gave the corresponding monofluoroenynes, which were directly utilized as a mixture in the next step. The overall yields of the cyclized products can be improved by the utilization of pure (*Z*)-1-bromo-1-fluoroalkenes as precursors. The pure (*Z*)-alkenes can be prepared by the methodology developed in our laboratory and others. For example, pure (*Z*)-alkene can be prepared by the kinetic separation method reported by Zhang and Burton [31], which involves the selective preparation of (*E*)-1-fluorovinylphosphonates from the *E*/*Z* mixture of 1-bromo-1-fluoroolefins (Eq. (1)). The (*Z*)-1-bromo-1-fluoroalkene is easily recovered and can be utilized in pure form (if necessary).



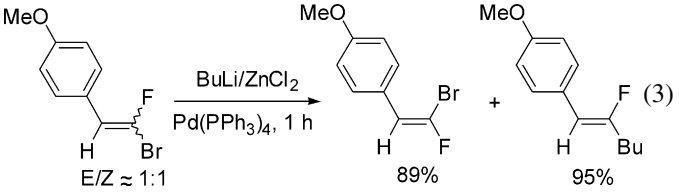
(1)

Alternatively, the (*E*)-1-bromo-1-fluoroalkene can be selectively reduced and the mixture of the (*Z*)-1-bromo-1-fluoroalkene and (*Z*)-1-fluoroalkene could be utilized in the cyclization reaction (Eq. (2)). The reduced olefin can be readily separated after the cyclization process has been completed [21,32,33].



(2)

Pannecoucke and coworkers employed a similar process to selectively remove the (*E*)-1-bromo-1-fluoroalkene *via* selective reaction of the (*E*)-alkene with BuLi/$ZnCl_2$ and Pd(0) catalyst [34]. Recovery of the (*Z*)-alkene provided the (*Z*)-1-bromo-1-fluoroalkene in 89% yield (Eq. (3)).



(3)

For demonstration purposes to illustrate that the cyclization process can be employed for the synthesis of site-specific fluorine-containing heterocycles, we have utilized the mixture of (*Z*)- and (*E*)-1-bromo-1-fluoroalkenes. Subsequently, the reaction of monofluoroenynes and DBU (0.2 equiv) in refluxing NMP readily afforded the cyclized products **2a**–**2c** within 6 h. The structural determination of the cyclized products was based on the fact that a long range coupling ($^5J_{H,H}$ = 1.0 Hz) between 3-H and 7-H was observed in both of compounds **2a** and **2b** [35]. These results are summarized in Table 1.

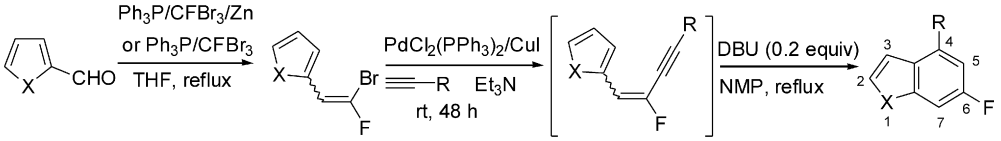
2.2. Preparation of 4-substituted-6-carboalkoxylbenzo[b]furans and benzo[b]thiophenes

Since we demonstrated that the base-catalyzed cyclization was not restricted to fluorinated enynes [22], we also extended this cyclization process to carboalkoxyl-substituted enynes. Starting from 2-furaldehyde or 2-thiophenecarboxaldehyde, the corresponding 4,6-disubstituted benzo[*b*]furan or benzo[*b*]thiophene derivative was obtained site-specifically in good yield from the reaction of the heterocyclic aromatic aldehyde and $Ph_3P{=}CBrCO_2Et$ [36] in CH_2Cl_2, followed by Sonogashira reaction and subsequent cyclization, respectively. These results are summarized in Table 2. The ratios of **3a** and **3b** were determined from their ^{1}H NMR spectra. The vinyl protons in the *Z* isomers appeared at lower field due to the deshielding effect from the ester group [37]. The yield of **4a** or **4b** in two steps was based on the amount of the corresponding *Z* isomer in the *Z*/*E* mixture **3a** or **3b**, respectively. Again, the structures of these cyclized products were established by the characteristic coupling between 2-H and 3-H ($^3J_{H,H}$ = 5.6 Hz), and long range coupling between 3-H and 7-H ($^5J_{H,H}$ = 1.0 Hz) in compound **4b** [38]. Unfortunately, our attempt to synthesize indole derivatives *via* a similar synthetic sequence from 1-methyl-2-pyrrolecarboxaldehyde was not successful. Although we were able to prepare the α-bromo-α,β-unsaturated ester from the Wittig reaction of 1-methyl-2-pyrrolecarboxaldehyde with $Ph_3P{=}CBrCO_2Et$, the subsequent Sonogashira reactions with terminal alkynes were not successful. Starting material was recovered after the reaction was carried out under similar conditions for 48 h at room temperature.

2.3. Preparation of compound 7

This base-catalyzed cyclization could be further utilized for the preparation of more complex heterocyclic aromatic

Table 1
Preparation of **2a**–**2c**



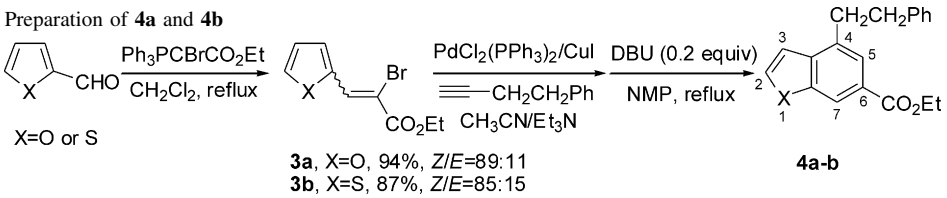
1a, X=O, *Z*/*E*=39:61, 38%
1b, X=S, *Z*/*E*=31:69, 35%

2a-2c

Entry	X	R	Time (h)	Product	Isolated yield[a] (%)
1	O	*n*-C_4H_9	6	**2a**	83
2	O	*n*-CH_2CH_2Ph	5	**2b**	71
3	S	*n*-C_4H_9	5	**2c**	76

[a] Yields are calculated in two steps based on the percentage of the *Z* isomers in the starting mixture of the 1-bromo-1-fluoroethenes.

Table 2
Preparation of **4a** and **4b**



3a, X=O, 94%, *Z*/*E*=89:11
3b, X=S, 87%, *Z*/*E*=85:15

4a-b

Entry	X	Time (h)	Product	Isolated yield[a] (%)
1	O	3	**4a**	52
2	S	3	**4b**	61

[a] Yields are calculated in two steps based on the percentage of the *Z* isomers in the starting mixture of the α-bromoacrylates.

compounds, as illustrated in Scheme 1. The Sonogashira reaction of compound **5** [39] with 2-thienylboronic acid under Suzuki reaction [40] conditions gave the precursor for cyclization, compound **6**, in good yield. Under our normal reaction conditions, the reaction of **6** and 0.2 equiv of DBU in refluxing NMP afforded compound **7** in 60% isolated yield.

2.4. Mechanism

Similar to the mechanism proposed in our previous reports [20–23], the reaction pathway is illustrated in Scheme 2. First, the base catalyzes the isomerization of the enyne to the allene intermediate, which undergoes 6π cycloaddition to form the two-ring system. Subsequent isomerization gives the final product.

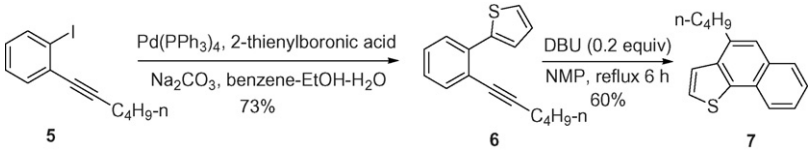
3. Experimental

3.1. General procedures

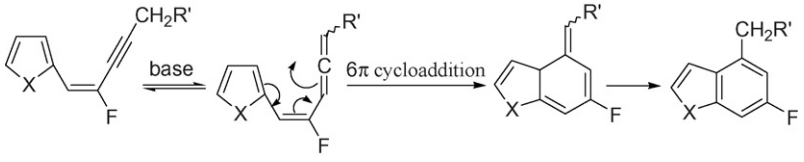
^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 or 400 MHz Spectrometer. Chemical shifts have been reported in ppm relative to internal tetramethylsilane and $CFCl_3$, respectively. Unless noted otherwise, $CDCl_3$ was used as the NMR lock solvent. High resolution mass spectra (HRMS) were obtained by the University of Iowa High Resolution Mass Spectrometry Facility. Column chromatography was carried out using silica gel (silica gel 60, particle size 0.063–0.200 mm, 70–230 mesh ASTM). Thin layer chromatography was carried out using 40 mm × 80 mm PolyGram Sil G/UV_{254} plates. All melting points were obtained in a 1.2 mm capillary tube and were not corrected. All solvents were stored in a brown bottles capped with rubber septa and sealed with copper wire and Para film. NMP was dried over CaH_2 overnight, and then distilled at reduced pressure. Zinc dust was stirred in 2% HCl for 1 min, and washed with 2% HCl, distilled water, ethanol, and finally with absolute ether. The material was then dried thoroughly. Tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl under N_2 atmosphere. $PdCl_2(PPh_3)_2$ was prepared by Negishi's procedure [41]. CuI was purified by the literature procedure [42]. All aldehydes were used directly as purchased from vendors. N_2 was used without further purification.

3.2. 2-[(Z)- and (E)-2-bromo-2-fluorovinyl]furan (*1a*)

An oven dried 50 mL round bottom flask equipped with a stirring bar and a cold water condenser was charged with PPh_3 (5.24 g, 20 mmol), 20 mL of freshly distilled THF and $CFBr_3$ (2.20 mL, 22 mmol). The solution was stirred at room temperature for 1 h. Then furan-2-aldehyde (1.65 mL, 20 mmol) was added, followed by the addition of acid-activated zinc (1.30 g, 20 mmol). The mixture was refluxed for about 6 h. After the reaction was completed, the mixture was cooled to room temperature, poured into 100 mL of hexanes and filtered. The filtrate was evaporated under vacuum and the residue was subjected to column chromatography. A colorless oil (1.45 g) was obtained (38% yield), *Z*/*E* = 39:61. ^{19}F NMR



Scheme 1. Preparation of **7**.



Scheme 2. Proposed mechanism for the formation of **2a**–**2c**.

($CDCl_3$, 282 MHz) δ −66.9 (d, J = 32.3 Hz, F in *E* isomer), −70.2 (d, J = 14.1 Hz, F in *Z* isomer) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (dd, J = 1.9, 0.4 Hz, 5-H in *Z* isomer), 7.36 (dd, J = 1.8, 0.8 Hz, 5-H in *E* isomer), 6.69 (dd, J = 3.5, 0.6 Hz, 3-H in *Z* isomer), 6.63 (d, J = 13.0 Hz, vinyl H in *Z* isomer), 6.48 (ddd, J = 3.9, 1.0, 0.4 Hz, 3-H in *E* isomer), 6.44 (dd, J = 3.5, 1.8 Hz, 4-H in *Z* isomer), 6.42 (dd, J = 3.6, 1.8 Hz, 4-H in *E* isomer), 6.03 (d, J = 31.6 Hz, vinyl H in *E* isomer) ppm. No further data were obtained due to decomposition of this compound.

3.3. 2-[(Z)- and (E)-2-bromo-2-fluorovinyl]thiophene (**1b**)

Similarly, reaction of 2-thiophene-2-carboxaldehyde (0.92 mL, 10 mmol), PPh_3 (5.24 g, 20 mmol), $CFBr_3$ (1.20 mL, 12 mmol) and 15 mL of THF gave 0.72 g of colorless oil (35% yield), *Z*/*E* = 31:69. ^{19}F NMR ($CDCl_3$, 282 MHz) δ −68.1 (d, J = 31.8 Hz, F in *E* isomer), −71.2 (d, J = 14.9 Hz, F in *Z* isomer) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.29 (m), 7.19–7.17 (m), 7.07–6.97 (m), 6.90 (d, J = 13.6 Hz, vinyl H in *Z* isomer), 6.24 (d, J = 32.5 Hz, vinyl H in *E* isomer) ppm. No further data were obtained due to decomposition of this compound.

3.4. General procedure for the Sonogashira reaction of 1-bromo-fluoroalkenes with terminal alkynes

Under N_2, a mixture of $PdCl_2(PPh_3)_2$ (40 mg, 0.05 mmol) and CuI (20 mg, 0.10 mmol) was added into a flask. Then 4 mL of CH_3CN, 1-bromo-1-fluoroalkenes (1 mmol) and terminal alkyne (1.2 mmol) were added sequentially. Then the mixture was stirred at room temperature for 48 h. The mixture was poured into 50 mL of hexanes and filtered. The filtrate was concentrated and the residue was purified on silica gel to give the product. The mixture of (*Z*)- and (*E*)-enynes was used directly in the next step without further characterization.

3.5. General procedure for the cyclization of enynes

The solution of 1 mmol of enyne, DBU (0.03 mL, 0.2 mmol) in 4 mL of NMP was refluxed. After the reaction was completed, the reaction mixture was cooled to room temperature and poured onto silica gel for further purification.

3.6. 4-Butyl-6-fluoro-1-benzofuran (**2a**)

Colorless oil; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −118.8 (t, J = 10.1 Hz) ppm; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.8, 1.8 Hz, 1H), 6.84 (dd, J = 10.4, 1.8 Hz, 1H), 6.75 (dd, J = 2.2, 1.0 Hz, 1H), 2.82 (t, J = 7.7 Hz, 2H), 1.72–1.64 (m, 2H), 1.43–1.37 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6 (d, J = 234.0 Hz), 157.4 (d, J = 14.3 Hz), 147.5 (d, J = 4.1 Hz), 139.8 (d, J = 9.2 Hz), 125.6 (d, J = 1.4 Hz), 113.1 (d, J = 23.6 Hz), 107.7 (d, J = 1.1 Hz), 99.1 (d, J = 26.6 Hz), 35.5 (d, J = 1.6 Hz), 35.2, 25.1, 16.6 ppm; GC–MS *m*/*z* (relative intensity): 101 (29), 149 (100), 192 (40); HRMS calcd. 192.0950 for $C_{12}H_{13}FO$, found 192.0951.

3.7. 4-(2-Phenylethyl)-6-fluorobenzofuran (**2b**)

Yellow oil; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −118.5 (t, J = 9.4 Hz) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 2.1 Hz, 1H), 7.32–7.17 (m, 5H), 7.08 (ddd, J = 8.8, 2.2, 1.0 Hz, 1H), 6.83 (dd, J = 10.5, 2.2 Hz, 1H), 6.70 (dd, J = 2.3, 1.0 Hz, 1H), 3.12 (m, 2H), 3.00 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9 (d, J = 240.0 Hz), 154.7 (d, J = 14.2 Hz), 145.02, 144.98, 141.2, 135.8 (d, J = 9.3 Hz), 128.4 (d, J = 6.8 Hz), 126.2, 123.0 (d, J = 1.5 Hz), 110.6 (d, J = 23.8 Hz), 104.8, 96.9 (d, J = 26.5 Hz), 36.7, 35.2 (d, J = 1.6 Hz) ppm; HRMS calcd. 240.0950 for $C_{16}H_{13}FO$, found 240.0954.

3.8. 4-Butyl-6-fluorobenzothiophene (**2c**)

Colorless oil; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −118.8 (t, J = 9.6 Hz) ppm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (dd, J = 8.6, 2.4 Hz, 1H), 7.36 (s, 2H), 6.93 (dd, J = 10.0, 2.4 Hz, 1H), 2.91 (t, J = 7.7 Hz, 2H), 1.74–1.64 (m, 2H), 1.47–1.37 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6 (d, J = 242.0 Hz), 140.7 (d, J = 10.7 Hz), 139.6 (d, J = 8.4 Hz), 135.2 (d, J = 1.3 Hz), 125.1 (d, J = 3.8 Hz), 121.4 (d, J = 0.6 Hz), 112.7 (d, J = 23.8 Hz), 105.8 (d, J = 25.1 Hz), 33.6 (d, J = 1.4 Hz), 32.6, 22.6, 13.9 ppm; HRMS calcd. 208.0722 for $C_{12}H_{13}FS$, found 208.0722.

3.9. General procedure for the preparation of ethyl α-bromoacrylates (**3a** and **3b**)

A solution of aromatic aldehyde (5.0 mmol), $Ph_3P{=}CBrCO_2Et$ (3.20 g, 7.5 mmol) in 20 mL of CH_2Cl_2 was refluxed. The progress of the reaction was monitored by TLC. When the reaction was completed, the solution was cooled to room temperature and the solvent was evaporated. The residue was rinsed with hexane and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel. The *Z*/*E* ratio of olefins was determined by ^{1}H NMR.

3.9.1. Ethyl (Z)-2-bromo-3-(2-furyl)acrylate and ethyl (E)-2-bromo-3-(2-furyl)acrylate (**3a**) [43]

Colorless oil; ^{1}H NMR of the mixture ($CDCl_3$, 300 MHz) δ 8.16 (t, J = 0.6 Hz, vinyl H in *Z* isomer), 7.61 (dd, J = 1.8, 0.7 Hz, 5-H in *Z* isomer), 7.46–7.44 (m, 3-H in *Z* isomer and 5-H in *E* isomer), 7.19 (s, vinyl H in *E* isomer), 7.02 (dt, J = 3.6, 0.7 Hz, 3-H in *E* isomer), 6.58 (ddd, J = 3.6, 1.8, 0.6 Hz, 4-H in *Z* isomer), 6.46 (ddd, J = 3.5, 1.8, 0.4 Hz, 4-H in *E* isomer), 4.34 (q, J = 7.2 Hz, CH_2CH_3 in *E* isomer), 4.33 (q, J = 7.2 Hz, CH_2CH_3 in *Z* isomer), 1.37 (t, J = 7.2 Hz, CH_2CH_3 in *Z* isomer), 1.36 (t, J = 7.1 Hz, CH_2CH_3 in *E* isomer) ppm; ^{13}C NMR of the mixture ($CDCl_3$, 100 MHz) δ 163.7, 163.0, 150.0, 149.3, 144.9, 144.1, 129.6, 128.4, 116.7, 114.9, 112.5, 112.2, 109.6, 107.6, 62.6, 62.2, 14.2, 14.0 ppm (loss of two peaks due to overlap); HRMS calcd. 243.9735 for $C_9H_9{}^{79}BrO_3$, found 243.9736.

3.9.2. Ethyl (Z)-2-bromo-3-(2-thienyl)acrylate and ethyl (E)-2-bromo-3-(2-thienyl)acrylate (**3b**) [44]

Pale oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, vinyl H in *Z* isomer), 7.64 (s, vinyl H in *E* isomer), 7.62–7.60 (m, 5-H in *Z* isomer), 7.58–7.56 (m, 3-H in *Z* isomer), 7.51–7.49 (m, 5-H in *E* isomer), 7.32–7.30 (m, 3-H in *E* isomer), 7.17 (dd, J = 5.1, 3.9 Hz, 4-H in *Z* isomer), 7.04 (dd, J = 5.2, 3.6 Hz, 4-H in *E* isomer), 4.35 (q, J = 7.1 Hz, CH_2CH_3 in *E* isomer), 4.34 (q, J = 7.1 Hz, CH_2CH_3 in *Z* isomer), 1.38 (t, J = 7.1 Hz, CH_2CH_3 in both isomers) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 137.6, 136.6, 134.9, 134.7, 134.4, 131.4, 131.1, 127.0, 126.7, 110.0, 107.2, 62.6, 62.4, 14.2, 14.1 ppm; HRMS calcd. $C_9H_9{}^{81}BrO_2S$ 261.9486, found 261.9495.

3.10. General procedure for the Sonogashira reaction of ethyl α-bromoacrylates with terminal alkynes

Under N_2, a mixture of $PdCl_2(PPh_3)_2$ (40 mg, 0.05 mmol) and CuI (20 mg, 0.10 mmol) was added into a flask. Then 4 mL of CH_3CN, α-bromoacrylate (1 mmol) and terminal alkyne (1.2 mmol) were added sequentially. Then the mixture was stirred at room temperature for 48 h. The mixture was poured into 50 mL of hexanes and filtered. The filtrate was concentrated and the residue was purified on silica gel to give the product. The mixture of (*Z*)- and (*E*)-enynes was used directly in the next step without further characterization.

3.11. General procedure for the cyclization of enynes

The solution of 1 mmol of enyne, DBU (0.03 mL, 0.2 mmol) in 4 mL of NMP was refluxed. After the reaction was completed, the reaction mixture was cooled to room temperature and poured onto silica gel for further purification.

3.12. Ethyl 4-(2-phenylethyl)benzofuran-6-carboxylate (**4a**)

Pale oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (m, 1H), 7.82 (m, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.33–7.20 (m, 5H), 6.75 (dd, J = 2.3, 1.0 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.22–3.16 (m, 2H), 3.05–3.00 (m, 2H), 1.43 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 154.3, 147.3, 141.4, 134.7, 131.1, 128.42, 128.38, 126.7, 126.1, 123.3, 111.0, 105.2, 61.0, 36.9, 35.2, 14.4 ppm; HRMS calcd. 294.1256 for $C_{19}H_{18}O_3$, found 294.1255.

3.13. Ethyl 4-(2-phenylethyl)benzothiophene-6-carboxylate (**4b**)

Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (m, 1H), 7.88 (m, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.45 (dd, J = 5.6, 1.0 Hz, 1H), 7.33–7.23 (m, 5H), 4.43 (q, J = 7.1 Hz, 2H), 3.32–3.27 (m, 2H), 3.07–3.03 (m, 2H), 1.44 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 141.9, 141.4, 139.6, 136.6, 129.9, 128.5, 128.4, 126.5, 126.1, 124.5, 122.6, 121.7, 61.0, 37.0, 36.0, 14.4 ppm; HRMS calcd. for $C_{19}H_{18}O_2S$ 310.1028, found 310.1031.

3.14. 2-(2-Hexynylphenyl)thiophene (**6**)

In a 50 mL flask were placed compound **5** (0.57 g, 2 mmol), 2-thienylboronic acid (0.31 g, 2.4 mmol), Na_2CO_3 (0.53 g, 5 mmol), $Pd(PPh_3)_4$ (0.11 g, 0.10 mmol), water (2 mL), benzene (10 mL) and ethanol (2 mL) sequentially. The mixture was refluxed for 24 h. After the mixture was allowed to cool to room temperature, it was diluted with ether (50 mL). The organic phase was washed with water (10 mL), and then dried over Na_2SO_4. After the solvent was removed, the residue was subjected to column chromatography to give 0.35 g of a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (dd, J = 3.6, 1.4 Hz, 1H), 7.54 (ddd, J = 7.7, 1.5, 0.5 Hz, 1H), 7.50 (dd, J = 7.7, 1.2 Hz, 1H), 7.33 (dd, J = 5.1, 1.1 Hz, 1H), 7.28 (td, J = 7.5, 1.6 Hz, 1H), 7.22 (td, J = 7.5, 1.5 Hz, 1H), 7.09 (dd, J = 5.2, 3.7 Hz, 1H), 2.43 (t, J = 7.0 Hz, 2H), 1.64–1.38 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.4, 135.6, 133.8, 128.8, 127.8, 127.0, 126.9, 126.4, 125.4, 121.4, 95.3, 80.3, 30.4, 22.0, 19.4, 13.6 ppm; HRMS calcd. for $C_{16}H_{16}S$ 240.0973, found 240.0975.

3.15. 4-n-Butylnaphtho[1,2-b]thiophene (**7**)

Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11–8.08 (m, 1H), 7.86–7.83 (m, 1H), 7.55–7.44 (m, 5H), 3.03 (t, J = 7.7 Hz, 2H), 1.82–1.72 (m, 2H), 1.52–1.39 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 137.5, 136.0, 131.3, 128.2, 127.8, 125.7, 125.6, 124.7, 123.6, 123.4, 123.2, 33.9, 32.6, 22.7, 14.0 ppm; HRMS calcd. for $C_{16}H_{16}S$ 240.0973, found 240.0970.

4. Conclusion

We have demonstrated that 4-substituted-6-fluoro(carboalkoxyl)benzo[*b*]furans and benzo[*b*]thiophenes can be prepared site-specifically *via* base-catalyzed cyclization from the corresponding substituted enynes. Our work continues to explore new applications of this base-catalyzed cyclization in organic chemistry.

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