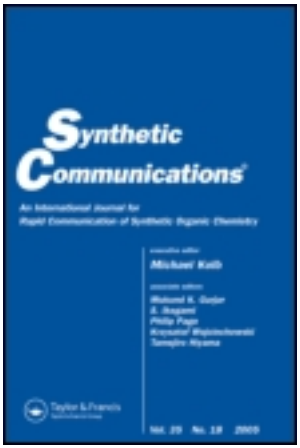

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Novel Route to 2-Trifluoromethylated Benzofurans

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Abstract: A novel route for the synthesis of a variety of 2-trifluoromethylbenzofurans is reported. By selection of solvents, the key intermediates, 2-chloro-3,3,3-trifluoropropenyl phenyl acetates, were cyclized either to give 2-trifluoromethyl-substituted benzofurans or to yield trifluoromethyl modified *o*-alkynylphenols. The latter intermediates could also be cyclized to give 3-iodo-2-trifluoromethyl-substituted benzofurans.

Keywords: *o*-Alkynylphenols, iodocyclization, phenyl acetates, trifluoromethyl-benzofurans

INTRODUCTION

Trifluoromethylated aromatic compounds have many applications in pharmaceuticals, dyes, liquid crystals, and polymers.[1] Benzofurans form the core of numerous natural products, and trifluoromethylated benzofurans have considerable pharmacological potential.[2] Even though the synthesis of benzofurans are well documented,[3] there are few reports for the synthesis of 2-trifluoromethyl-substituted benzofurans.[4] In these methods, the difficult handling of gaseous materials such as 3,3,3-trifluoropropyne[4b] and trifluoroiodomethane,[4c] the use of expensive palladium

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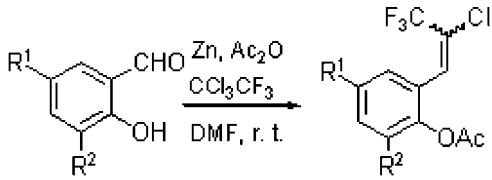
catalyst,[4d,e] the low yields, and poor selectivity have limited their application. Here we report a novel and convenient way to synthesize 2-trifluoromethylated benzofurans (**3a–e**) and 3-iodo-2-trifluoromethyl benzofurans (**6a–e**) from 2-chloro-3,3,3-trifluoropropenyl phenyl acetates (**2a–e**).

RESULTS AND DISCUSSION

In this study, phenyl acetates (**2**) were prepared by a method similar to that developed by Fujita et al.[5] Substituted salicylaldehydes (**1**) were treated with in situ generated organozinc reagent, 2,2,2-trifluorodichloroethylzinc chloride,[6]and acetic anhydride in N,N-dimethylformamide (DMF) to give **2** in moderate yield (Table 1). The configuration of **2** was studied by ^{1}H and ^{19}F NMR,[7] and the results indicated that the major configuration was Z (*cis*).[5,7]

A set of experiments were carried out using **2a** as model substrate. Under the conditions reported by Meazza and Zanardi,[8] treatment of **2a** with 1.2 equivalent of powdered KOH in dimethyl sulphoxide (DMSO) gave 2-(trifluoromethyl)benzofuran (**3a**) in 22% yield and recovered **2a** in 50%. The use of 1 equivalent of potassium *tert*-butoxide (*t*-BuOK) in DMF gave **3a** and **4a** in 26% and 23% yields respectively

Table 1. Synthesis of phenyl acetates (**2**) from substituted salicylaldehydes (**1**)



1 **2**

1	R^1	R^2	Yield of **2**[a] (%)
1a	H	H	50 (**2a**) [79/21][b]
1b	CH_3	H	40 (**2b**) [89/11]
1c	Cl	H	44 (**2c**) [93/7]
1d	Br	H	47 (**2d**) [95/5]
1e	H	OCH_3	46 (**2e**) [81/19]

[a]Isolated yield.
[b]The values in bracket are Z/E ratio of **2**.

after 27 h. Further increase of base loading led to an increase of the yield of **3a** (entry 2, Table 2). It was finally noticed that this parameter had a crucial influence on the outcome of the reaction. Base-induced cyclization of **2a** led to **3a** only when more than 2 equivalents of base were used (entries 3–5, Table 2). *t*-BuOK appeared to give best results among bases (NaH, KOH, and 1,8-diazabicyclo[5,4.0]-undec-7-ene [DBU]). Most curious was the impact of solvent. The effects of solvents such as acetonitrile (CH_3CN), dichloromethane (DCM), ether (Et_2O), toluene, tetrahydrofuran (THF), and tetrachloromethane (CCl_4) were investigated and are presented in Table 2. Dipolar solvents, such as DMF, DMSO, and acetonitrile, promoted intramolecular cyclization to form **3a** (entries 1, 9, and 10), whereas other solvents, such as DCM, ether, toluene, THF, and CCl_4, favored alkenyl elimination product 2-(3,3,3-trifluoroprop-1-ynyl)-phenol (**5a**) even when 3 equivalents of *t*-BuOK were used.

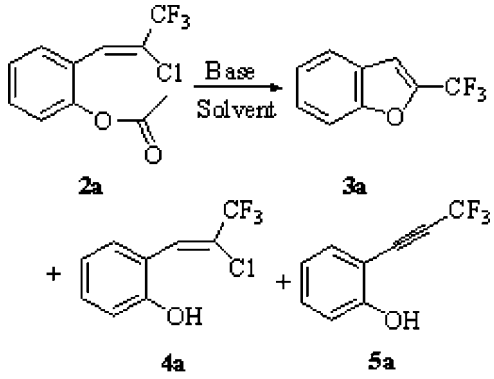
We could detected **5a** when **4a** was treated with *t*-BuOK (Fig. 1). We found that when **4a** was treated with 2 equivalents of *t*-BuOK, it would converted to **3a** completely.

The process of **2a** converting to **3a** was presumed as follows (Scheme 1): when **2a** was treated with *t*-BuOK, firstly it deacetylated to get **7**, with more *t*-BuOK, then 1 mol HCl was eliminated from **7** to get **8** which was transformed into **3a** by a intramolecular cyclization.

The optimized reaction conditions, 3 equivalents of *t*-BuOK as alkali and DMF or Et_2O as solvents, were applied to convert **2** into **3** and **5**, respectively. The results are summarized in Table 3. Under these conditions, **2a–e** were transformed to **3a–e** and **5a–e** in good to excellent yields. No spectacular electronic effects were observed, and a variety of functional groups was tolerated.

o-Alkynylphenols could be cyclized by a base, such as sodium ethanolate,[9a] pypridine,[4b] and cesium hydroxide,[9b] to form benzofunans. They could also be converted into 3-iodobenzofurans by iodocyclization.[10] Under the standard condition reported by Arcadi (3 equivalents of sodium bicarbonate, 3 equivalents of iodine in acetonitrile at room temperature), trifluoromethylated *o*-alkynylphenol **5a** was transformed into expected 3-iodobenzofuran **6a** in a low yield of 10%. Other bases (such as sodium carbonate, potassium carbonate, cesium carbonate, potassium phosphate, sodium hydrogen phosphate, sodium dihydrogen phosphate, and sodium acetate) and solvents (such as 1,4-dioxane, THF, CH_2Cl_2, $CHCl_3$, CCl_4, MeOH, and hexane) were investigated. We finally found **5a–d** can be converted into **6a–d** in moderate yield when sodium carbonate was used as base and the reaction was performed in CCl_4 at 70 °C (Table 4). However, even under this optimized condition, **6e** was obtained in a low yield of 5%. Maybe the electronic effect of substituted groups on the phenyl ring plays a controlling role in this iodocyclization.

Table 2. Cyclization of 2-(2-chloro-3,3,3-trifluoroprop-1-enyl)phenyl acetate **2a** into 2-(trifluoromethyl)benxofuran **3a**[a]



Entry	Base (equivalent)	Solvent	Time (h)	Yield[b] (%)
				3a/**4a**/**5a**
1	*t*-BuOK (1.0)	DMF	27	26/23/0
2	*t*-BuOK (1.7)	DMF	27	55/44/0
3	*t*-BuOK (2.2)	DMF	27	100/0/0
4	*t*-BuOK (2.7)	DMF	27	100/0/0
5	*t*-BuOK (3.0)	DMF	1	100/0/0
6	NaH (5.0)	DMF	1	44/44/0
			6	99/0/0
7	KOH (3.0)	DMF	1	75/0/0
			3	100/0/0
8	DBU (3.0)	DMF	1	24/18/18
			27	99/0/0
9	*t*-BuOK (3.0)	DMSO	1	100/0/0
10	*t*-BuOK (3.0)	CH_3CN	3	99/0/0
11	*t*-BuOK (3.0)	DCM	3	19/0/78
12	*t*-BuOK (3.0)	Et_2O	3	0/0/99
13	*t*-BuOK (3.0)	Toluene	3	10/0/85
14	*t*-BuOK (3.0)	THF	3	17/0/75
15	*t*-BuOK (3.0)	CCl_4	3	0/0/93

[a] Reaction conditions: **2a** (0.5 mmol) dissolved in 2 mL solvent, the base was added and the reaction was performed at room temperature.

[b] GC yield.

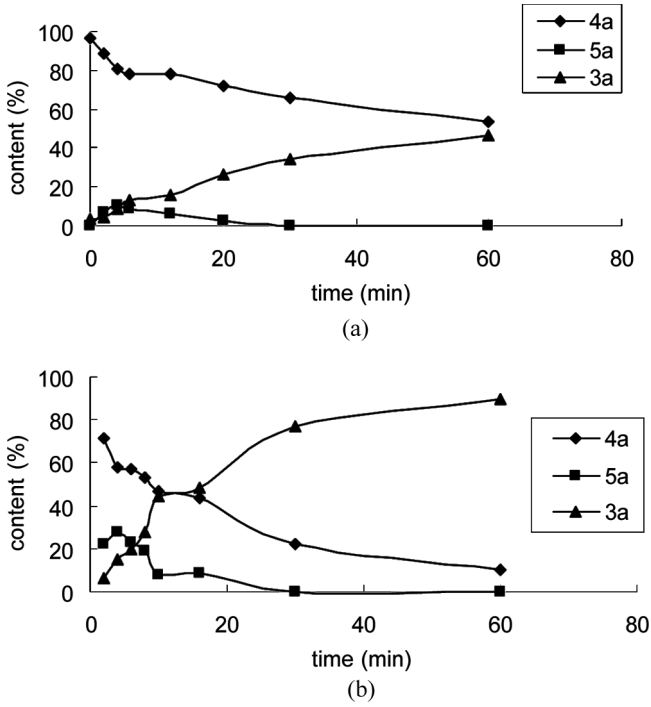


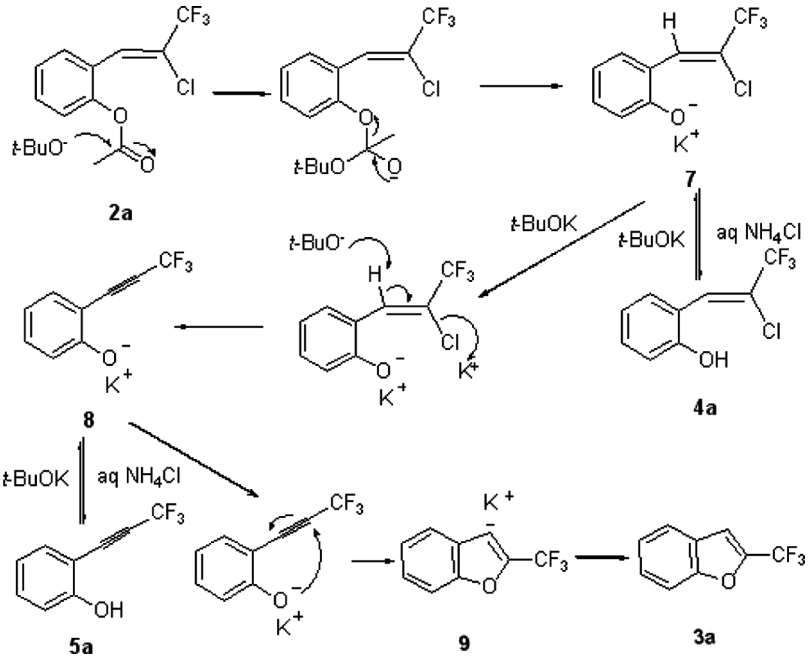
Figure 1. (a) **4a** treated with 1.2 equivalent of *t*-BuOK; (b) **4a** treated with 2 equivalent of *t*-BuOK.

In conclusion, a novel and convenient method for the synthesis of 2-trifluoromethylated benzofurans and 3-iodo-2-trifluoromethyl benzofurans has been developed. In this method, 1,1,1-trichloro-2,2,2-trifluoro-ethane was used to introduce the trifluoromethyl group; 2-chloro-3,3,3-trifluoro-propenyl phenyl acetates were treated with potassium *tert*-butoxide to give 2-(trifluoromethyl)benzofurans in DMF and o-alkynylphenols in Et_2O respectively with good to excellent yields; and iodine induced iodocyclization of *o*-alkynylphenols to give 3-iodo-2-trifluoromethyl benzofurans with moderate yields.

EXPERIMENTAL

Methods

^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-300, Bruker Varian-400, and Bruker Varian-600 spectrometers in $CDCl_3$ with



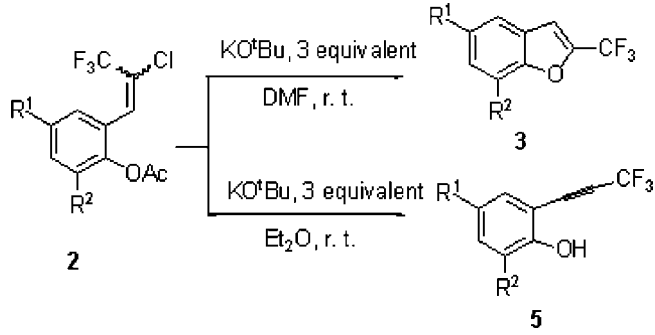
Scheme 1. The process of conversion of **2a** to **3a**.

TMS as an internal standard. ^{19}F NMR spectra were recorded on a Bruker Avance-300 spectrometer using trifluoroacetic acid as external standard. All chemical shifts (δ) were expressed in parts per million (ppm); coupling constants (*J*) were given in hertz. IR spectra were obtained with a Bruker Vertex 70 FTIR spectrometer. Gas chromatography–mass spectra (GC-MS) were recorded on an Agilent 6890N-5975 spectrometer. High-resolution mass spectra (HRMS) were done on an IonSpec HiRes. All reagents were purchased from commercial sources and used without treatment (purification) unless otherwise indicated. The products were purified by column chromatography over silica gel.

Typical Procedure for the Synthesis of Substituted 2-(2-Chloro-3,3, 3-trifluoroprop-1-enyl)phenyl Acetates (2)

Five equivalents of zinc powder (washed with 2% HCl, water, 95% ethanol and ether, then dryed with vacuum) and 3 equivalents of acetic anhydride were added into a solution of substituted salicylaldehyde (**1**, 10 mmol) in DMF (20 mL, dried by 4Å molecular sieve) in an argon atmosphere at room temperature. Then 3 equivalents of 1,1,1-trichloro-2,

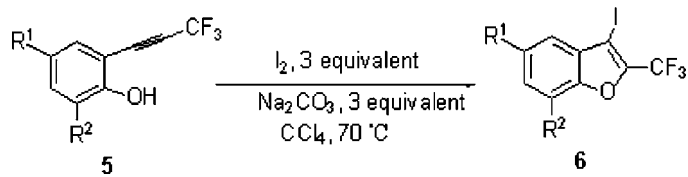
Table 3. Solvents selected formation of benzofurans **3** and *o*-alkynylphenols **5** from phenyl acetates **2**



2	R^1	R^2	Yield of **3**[a] (%)	Yield of **5**[a] (%)
2a	H	H	86 (**3a**)	62 (**5a**)
2b	CH_3	H	82 (**3b**)	70 (**5b**)
2c	Cl	H	95 (**3c**)	72 (**5c**)
2d	Br	H	94 (**3d**)	80 (**5d**)
2e	H	OCH_3	94 (**3e**)	88 (**5e**)

[a]Isolated yield.

Table 4. Iodine cyclization of *o*-alkynylphenols **5**



5	R^1	R^2	Yield of **6**[a] (%)
5a	H	H	63 (**6a**)
5b	CH_3	H	54 (**6b**)
5c	Cl	H	80 (**6c**)
5d	Br	H	62 (**6d**)
5e	H	OCH_3	5 (**6e**)

[a]Isolated yield.

2,2-trifluoroethane were dripped into this system in 10 min with fierce stirring using a magnetic bar. The reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was treated with saturated ammonium chloride solution (150 mL) and extracted with diethyl ether (3×50 mL). The organic phase was dried with magnesium sulfate, filtered, and concentrated to get the crude product, which was purified by column chromatography (hexane–ethyl acetate) over silica gel to provide phenyl acetates **2**.

Compound 2a

This compound was obtained as a mixture of Z–E isomers in a ratio of 79/21 (after purification); light yellow oil. IR (film) (ν, cm^{-1}): 1652 (C = C), 1772 (C = O). Z isomer: ^1H NMR ($CDCl_3$, 600 MHz): δ 2.327 (s, 3H), 7.172 (d, $J = 8.4$ Hz, 1H), 7.317 (t, $J = 7.5$ Hz, 2H), 7.446 (t, $J = 7.8$ Hz, 1H), 7.867 (d, $J = 7.8$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH as external standard): 8.734 (s). E isomer: ^1H NMR ($CDCl_3$, 600 MHz): δ 2.305 (s, 3H), 7.097 (s, 1H), 7.134 (d, $J = 8.4$ Hz, 1H), 7.244–7.277 (m, 2H), 7.393 (t, $J = 7.5$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH as external standard): 14.171 (s). ^{13}C NMR ($CDCl_3$, 75 MHz) for Z–E mixtures: δ 21.01, 119.23 (q, $^1J_{C,F} = 272.5$ Hz), 122.34 (q, $^2J_{C,F} = 37.0$ Hz), 122.65, 123.05, 124.92, 125.95 (d, $^3J_{C,F} = 4.5$ Hz), 126.17, 126.27, 129.98, 130.67, 131.30, 132.09, 148.25, 149.38, 169.04. GC-MS: t = 9.279 min (21%), t = 9.402 min (79%), m/z 264 (M^+, 15), 266 (M^+, 5), 222 (98), 224 (33), 167 (100), 43 (80). HRMS (ESI) m/z : calcd. for $C_{11}H_8ClF_3O$, [M + Na] 287.00627; found 287.00746.

Compound 2b

This compound was obtained as a mixture of Z–E isomers in a ratio of 89/11 (after purification); light yellow oil. Z isomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H), 2.38 (s, 1H), 7.04 (d, $J = 8.40$ Hz, 1H), 7.22 (dd, $J = 8.40$ Hz, 1.20 Hz, 1H), 7.27 (s, 1H), 7.65 (s, 1H). ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 8.778 (s). E isomer: ^1H NMR: δ 2.28 (s, 3H), 2.34 (s, 3H), 6.98 (d, $J = 8.00$ Hz, 1H), 7.17 (d, $J = 8.40$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 14.067 (s). ^{13}C NMR ($CDCl_3$, 75.48 MHz) for Z–E mixture: δ 20.97, 21.24, 119.26 (q, $^1J_{CF} = 272.46$ Hz), 122.08 (q, $^2J_{CF} = 36.98$ Hz), 122.31, 122.71, 124.54, 126.12 (d, $^3J_{CF} = 3.77$ Hz), 130.24, 131.26, 131.95, 132.24, 136.08, 147.19, 169.27. GC-MS: t = 8.211 min (11%), t = 8.284 min (89%), m/z (%): 278 (M^+, 11), 280 (M^+, 4), 236 (98), 238 (31), 181 (100), 43 (67).

Compound 2c

This compound was obtained as a mixture of Z–E isomers in a ratio of 93/7 (after purification); light yellow oil. IR (film) (ν, cm^{-1}): 1653 (C = C), 1771 (C = O). Z isomer: ^1H NMR ($CDCl_3$, 600 MHz): δ 2.322 (s, 3H), 7.129 (d, $J = 8.40$ Hz, 1H), 7.241 (s, 1H), 7.400 (d, $J = 9.00$ Hz, 1H), 7.837 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 20.92, 118.99 (q, $^1J_{CF} = 272.46$ Hz), 123.55(q, $^2J_{CF} = 36.23$ Hz), 124.36, 124.89 (d, $^3J_{CF} = 4.53$ Hz), 126.36, 129.70, 131.15, 131.78, 147.79, 168.75. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 8.578 (s). E isomer: ^1H NMR: δ 2.295 (s, 3H), 7.005 (s, 1H), 7.075 (d, $J = 9.00$ Hz, 1H), 7.348 (d, $J = 8.40$ Hz, 1H).^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 13.879 (s). GC-MS: t = 8.710 min, m/z (%): 298 (M^+, 5), 300 (M^+, 3), 256 (68), 258 (45), 260 (6), 201 (56), 203 (19), 43 (100).

Compound 2d

This compound was obtained as a mixture of Z–E isomers in a ratio of 95/5 (after purification); light yellow solid. IR (KBr) (ν, cm^{-1}): 1651 (C = C), 1765 (C = O). Z isomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 2.316 (s, 3H), 7.067 (d, $J = 8.40$ Hz, 1H), 7.237 (s, 1H), 7.537–7.565 (dd, $J = 8.80$, 2.40 Hz, 1H), 7.968 (d, $J = 2.00$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 20.95, 118.99 (q, $^1J_{CF} = 272.47$ Hz), 119.30, 123.55 (q, $^2J_{CF} = 37.74$ Hz), 124.70, 124.84 (d, $^3J_{CF} = 4.53$ Hz), 126.75, 132.62, 134.12, 148.32, 168.65. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 8.606 (s). E isomer: ^1H NMR: δ 2.291 (s, 3H), 7.005 (s, 1H), 7.014 (d, $J = 8.80$ Hz, 1H), 7.394 (d, $J = 1.60$ Hz, 1H), 7.486–7.513 (dd, $J = 8.40$ Hz, 2.00 Hz, 1H). ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 13.899 (s). GC-MS: t = 9.374 min, m/z (%): 342 (M^+, 4), 344 (M^+, 6), 346 (M^+, 1), 300 (46), 302 (59), 304 (15), 245 (32), 247 (32), 43 (100).

Compound 2e

This compound was obtained as a mixture of Z–E isomers in a ratio of 81/19 (after purification); light yellow solid. Recyclization from n-hexane gave a colorless sheet crystal. IR (KBr) (ν, cm^{-1}): 1653 (C = C), 1770 (C = O). Z isomer: ^1H NMR ($CDCl_3$, 300 MHz): δ 2.3356 (s, 3H), 3.8500 (s, 3H), 7.0138 (d, $J = 8.22$ Hz, 1H), 7.2398 (d, $J = 8.10$ Hz, 1H), 7.2936 (s, 1H), 7.4601 (d, $J = 7.89$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 20.53, 56.37, 114.13, 119.25 (q, $^1J_{CF} = 272.47$ Hz), 121.20, 122.39 (q,

$^{2}J_{CF} = 35.47$ Hz), 125.76 (d, $^{3}J_{CF} = 3.77$ Hz), 126.22, 126.73 139.07, 151.82, 168.56. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 8.755 (s). E isomer: ^{1}H NMR: δ 2.3167 (s, 3H), 3.8351 (s, 3H), 6.863 (d, $J = 7.80$ Hz, 1H), 6.987 (d, $J = 7.80$ Hz, 1H), 7.072 (s, 1H), 7.190 (d, $J = 7.80$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 14.424 (s). GC-MS: t = 9.091 min, m/z (%): 294 (M^+, 3), 252 (100), 232 (9), 216 (11), 197 (45), 145 (11), 43 (53). HRMS (ESI) calcd. for $C_{12}H_{10}ClF_3O_3$, [M + H] 295.03488, [M + Na] 317.01683, 319.01388, [M + K] 332.99077, 334.98782; found 295.03459, 317.01538, 319.01273, 332.99004, 334.98717.

Typical Procedure for the Synthesis of Substituted 2-(Trifluoromethyl)benzofurans (3)

t-BuOK (6 mmol) was added to a solution of **2** (2 mmol) in 4 mL of DMF. The mixture was stirred at room temperature and monitored by TLC. After completion, the reaction mixture was treated with saturated ammonium chloride solution (30 mL) and extracted with diethyl ether (3 × 15 mL). The organic layer was dried with magnesium sulfate and filtered. The solvent was distilled, and the residue was purified by column chromatography and eluted with n-pentane to obtain product **3**.

Compound 3a

This compound was obtained as colorless volatile oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.167 (d, $J = 0.9$ Hz, 1H), 7.328 (t, $J = 7.5$ Hz, 1H), 7.444 (t, $J = 8.4$ Hz, 1H), 7.558 (d, $J = 8.4$ Hz, 1H), 7.656 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 108.50 (d, $^{3}J_{C,F} = 3.0$ Hz), 112.49, 119.75 (q, $^{1}J_{C,F} = 267.9$ Hz), 122.88, 124.37, 126.42, 127.32, 143.93 (q, $^{2}J_{C,F} = 41.5$ Hz), 155.58. ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH as external standard): 12.885 (s). HRMS (ESI) m/z: calcd. for $C_9H_5F_3O$, [M − H] 185.02142; found 185.02191.

Compound 3b

This compound was obtained as light yellow volatile oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.455 (s, 3H), 7.080 (s, 1H), 7.232 (m, 1H), 7.429 (s, 1H), 7.442 (d, $J = 7.80$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 21.15, 107.84, 111.52, 118.56 (q, $^{1}J_{CF} = 267.13$ Hz), 122.06, 126.13, 128.31, 133.63, 143.39 (q, $^{2}J_{CF} = 42.26$ Hz), 153.68. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 12.891 (s). GC-MS:

t = 2.362 min, *m/z* (%): 200 (M^+, 99), 199 (100), 181 (18), 151 (18), 131 (47), 103 (20), 77 (17), 51(16).

Compound 3c

This compound was obtained as light yellow oil. IR (film) (ν, cm^{-1}): 1609, 1585, 1449, 1439, 1359, 1350, 1315, 1278, 1259, 1216, 1181, 1167, 1144, 1076, 1063, 934, 873, 806, 733, 698, 587, 480, 438, 419. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.1219 (s, 1H), 7.3851 (dd, $J = 8.88$, 2.07 Hz, 1H), 7.4867 (d, $J = 8.82$ Hz, 1H), 7.6428 (d, $J = 2.07$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 107.64, 113.19, 118.10 (q, $^1J_{CF} = 267.13$ Hz), 122.03, 127.31, 127.39, 129.76, 144.74 (q, $^2J_{CF} = 42.26$ Hz), 153.50. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 12.680 (s). GC-MS: t = 11.683 min, *m/z* (%): 220 (M^+, 100), 222 (M^+, 33), 201 (15), 170 (29), 157 (10), 137 (8), 123 (9), 107 (8), 87 (9), 62 (8). HRMS (ESI) *m/z*: calcd. for $C_9H_4ClF_3O$, [M − H] 218.98245; found 218.98232.

Compound 3d

This compound was obtained as light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.1223 (s, 1 H), 7.4385 (d, $J = 8.88$, 1.89 Hz, 1H), 7.8079 (d, $J = 1.86$ Hz, 1H), 7.6428 (d, $J = 2.07$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.58 MHz): δ 107.46 (d, $^3J_{CF} = 2.01$ Hz), 113.59, 117.11, 117.63 (q, $^1J_{CF} = 268.54$ Hz), 125.12, 127.91, 144.50 (q, $^2J_{CF} = 42.24$ Hz), 153.87. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 12.697 (s). GC-MS: t = 3.442 min, *m/z* (%): 264 (M^+, 100), 266, (M^+, 97), 245 (10), 247(10), 214 (17), 216 (17), 185 (13), 157 (24), 137 (22), 87 (15), 62 (15). HRMS (ESI) *m/z*: calcd. for $C_9H_4BrF_3O$, [M−H] 262.93194, 264.92989; found 262.93200, 264.92996.

Compound 3e

This compound was obtained as light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.028 (s, 3H), 6.896–6.955 (m, 1H), 7.155 (d, $J = 0.90$ Hz, 1H), 7.234 (s, 1H), 7.246–7.256 (m, 1H). ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 56.02, 108.46, 108.55, 114.28, 118.36 (q, $^1J_{CF} =$ 268.64 Hz), 124.75, 127.66, 143.42 (q, $^2J_{CF} = 42.23$ Hz), 144.75, 145.79. ^{19}F NMR ($CDCl_3$, 282.4 MHz, CF_3COOH as external standard): δ 13.128 (s). GC-MS: t = 12.707 min, *m/z* (%): 216 (M^+, 100), 201 (33), 197 (11), 186 (8), 173 (41), 145 (37), 125 (10).

Procedure for the Synthesis of 2-(2-Chloro-3,3,3-trifluoroprop-1-enyl)phenol (4a)

t-BuOK (0.336 g, 3 mmol) was added into a solution of **2a** (0.528 g, 2 mmol) in 4 mL of DMF. The mixture was stirred at room temperature for 1 h. Then the reaction mixture was treated with saturated ammonium chloride solution (30 mL) and extracted with diethyl ether (3×15 mL). The organic layer was dried with magnesium sulfate and filtered. The solvent was distilled, and the residue was purified by column chromatography to obtain 0.112 g of product **4a**. It was a mixture of Z–E isomers in a ratio of 79/21 (after purification); light yellow oil. Z isomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.112 (s, 1H), 6.808 (d, $J = 8.1$ Hz, 1H), 7.003 (t, $J = 7.8$ Hz, 1H), 7.257 (d, $J = 8.7$ Hz, 1H), 7.618 (s, 1H), 7.891 (d, $J = 7.8$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH as external standard): 9.191 (s). E isomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.996 (s, 1H), 6.780 (s, 1H), 6.977 (t, $J = 8.7$ Hz, 1H), 7.187 (d, $J = 8.7$ Hz, 1H), 7.306 (d, $J = 1.5$ Hz, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz, CF_3COOH as external standard): 15.149 (s). ^{13}C NMR ($CDCl_3$, 75 MHz) for Z-E mixture: δ 115.41, 115.67, 119.04, 119.13, 119.73 (q, $^1J_{C,F} = 272.5$ Hz), 119.81 (q, $^2J_{C,F} = 38.4$ Hz), 120.22, 125.56 (d, $^3J_{C,F} = 4.5$ Hz), 129.79, 130.08, 130.73, 131.32, 132.57, 152.74, 153.95. GC-MS: t = 5.06 min and 5.26 min, m/z 222 (M^+, 38), 224 (M^+, 13), 203 (3), 186 (4), 167 (100), 139 (10), 119 (10), 109 (8), 101(8), 89 (13), 63 (10), 39 (7). HRMS (ESI) m/z: calcd. for $C_9H_6ClF_3O$, [M − H] 220.99810, 222.99515; found 220.99824, 222.99531.

Typical Procedure for the Synthesis of Substituted 2-(3,3,3-Trifluoroprop-1-ynyl)phenols (5)

t-BuOK (30 mmol) was added into a solution of **2** (10 mmol) in 30 mL of ether. The mixture was stirred at room temperature and monitored by TLC. After completion, the reaction mixture was treated with sat aqueous ammonium chloride solution (150 mL) and extracted with diethyl ether (3×50 mL). The organic layer was dried with magnesium sulfate and filtered. The solvent was distilled, and the residue was purified by column chromatography (ether/n-pentane) to give the desired product **5**.

Compound 5a

This compound was obtained as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.496 (s, 1H), 6.927–6.988 (m, 2H), 7.361–7.459 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 80.68 (q, $^2J_{C,F} = 53.3$ Hz), 82.58 (d, $^3J_{C,F} = 6.0$ Hz), 105.29, 113.53 (q, $^1J_{C,F} = 257.5$ Hz), 115.83, 120.61, 132.82, 133.27, 158.07. GC-MS m/z : 186 (M^+, 100), 166 (59), 158 (50), 138 (70), 107 (18), 89 (26), 69 (17), 63 (26), 39 (16), 28 (7). HRMS (ESI) m/z: calcd. for $C_9H_5F_3O$, [M – H] 185.02142; found 185.02199.

Compound 5b

This compound was obtained as light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.273 (s, 3H), 5.315 (s, 1H), 6.850 (d, $J = 8.40$ Hz, 1H), 7.167 (dd, $J = 8.40$ Hz, 1.80 Hz, 1H), 7.281 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 20.54, 81.47 (q, $^2J_{CF} = 45.29$ Hz), 82.77 (d, $^3J_{CF} = 6.79$ Hz), 105.06, 113.47 (q, $^1J_{CF} = 257.39$ Hz), 116.07, 130.74, 133.29, 134.35, 156.13.

Compound 5c

This compound was obtained as a dark red oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.474 (s, 1H), 6.912 (d, $J = 8.70$ Hz, 1H), 7.324 (dd, $J = 8.70$ Hz, 2.70 Hz, 1H), 7.420 (d, $J = 2.70$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 80.87 (d, $^3J_{CF} = 6.79$ Hz), 82.38 (q, $^2J_{CF} = 53.59$ Hz), 106.88, 113.21 (q, $^1J_{CF} = 258.13$ Hz), 117.69, 126.13, 132.57, 133.56, 156.80. GC-MS: t = 5.092 min, m/z (%): 220 (M^+, 94), 222 (M^+, 31), 200 (100), 202 (34), 192 (21), 194 (8), 172 (59), 174 (19), 157 (37), 137 (27), 123 (23), 87 (21).

Compound 5d

This compound was obtained as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5253 (s, 1H), 6.8587 (d, $J = 8.79$ Hz, 1H), 7.4583 (dd, $J = 8.82$ Hz, 2.40 Hz, 1H), 7.5632 (d, $J = 2.37$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 80.73 (d, $^3J_{CF} = 6.04$ Hz), 82.53 (q, $^2J_{CF} = 53.59$ Hz), 107.43, 112.89, 113.20 (q, $^1J_{CF} = 258.13$ Hz), 118.05, 135.48, 136.41, 157.24. GC-MS: t = 5.678 min, m/z (%): 264 (M^+, 100), 266 (M^+, 100), 244 (82), 246 (82), 236 (16), 238 (16), 216 (39), 218 (37), 179 (7), 181 (7), 167 (7), 169 (7), 157 (41), 137 (70), 107 (16), 87 (37), 69 (16), 62 (18).

Compound 5e

This compound was obtained as light yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.0699 (s, 1H), 6.8159 (t, $J = 7.92$ Hz, 1H), 6.9299 (dd,

$J = 8.13$ Hz, 1.44 Hz, 1H), 7.0322 (dd, $J = 7.80$ Hz, 1.32 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 56.56, 79.62 (q, $^2J_{CF} = 52.84$ Hz), 83.19 (d, $^3J_{CF} = 6.79$ Hz), 105.31, 113.53, 113.66 (q, $^1J_{CF} = 256.63$ Hz), 120.40, 125.53, 146.98, 149.00. GC-MS: t = 5.015 min, m/z (%): 216 (M^+, 100), 197 (21), 186 (6), 173 (9), 167 (17), 153 (9), 145 (76), 138 (17), 125 (29), 119 (17), 99 (18), 91 (11), 75 (17), 69 (12).

Typical Procedure for the Synthesis of Substituted 3-Iodo-2-(trifluoromethyl)benzofurans (6)

One hundred mg of **5** was dissolved in 1 mL CCl_4, then 3 equivalents of iodine and 3 equivalents of Na_2CO_3 were added into this solution. It was flushed with argon, sealed with rubber, then stirred at 70 °C, and monitored by gas chromatography. When the reactant disappeared, the reaction mixture was quenched with 2 mL saturated sodium thiosulphate solution, extracted with ethyl acetate (3 × 3 mL), and filtered through a silica-gel pad. The filtrate was evaporated and purified by preparative TLC to obtain **6**.

Compound 6a

This compound was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.383–7.436 (m, 1H), 7.487–7.565 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.15, 112.08, 118.08 (q, $^1J_{C,F} = 270.6$ Hz), 123.06, 124.57, 128.16, 130.08, 142.69 (d, $^2J_{C,F} = 40.2$ Hz), 153.89. GC-MS m/z: 312 (M^+, 100), 293 (8), 262 (8), 185 (11), 157 (28), 137 (23), 107 (11), 87 (8), 62 (7).

Compound 6b

This compound was obtained as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.50 (s, 3H), 7.28 (s, 1H), 7.29 (d, $J = 8.40$ Hz, 1H), 7.40 (d, $J = 8.40$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.58 MHz): δ 21.26, 65.89, 111.62, 118.11 (q, $^1J_{CF} = 269.55$ Hz), 122.58, 129.59, 130.05, 134.47, 142.67 (q, $^2J_{CF} = 40.23$ Hz), 152.35. GC-MS: t = 7.478 min, m/z (%): 326 (M^+, 100), 307 (7), 257 (8), 199 (11), 169 (7), 151 (26), 102 (8),75 (6), 51 (5).

Compound 6c

This compound was obtained as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.453–7.482 (m, 2H), 7.502–7.518 (m, 1 H). ^{13}C NMR

($CDCl_3$, 100.58 MHz) δ 65.06, 112.91, 117.73 (q, $^1J_{CF} = 270.56$ Hz), 122.75, 128.63, 130.60, 131.50, 144.05 (q, $^2J_{CF} = 40.23$ Hz), 152.28. GC-MS: t = 8.185 min, m/z (%): 346 (M^+, 100), 348 (M^+, 35), 327 (5), 296 (3), 219 (28), 221 (10), 191(20), 193 (7), 173 (5), 156 (32), 141 (5), 105 (5).

Compound 6d

This compound was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.424 (d, $J = 8.70$ Hz, 1H), 7.591 (dd, $J = 8.70$ Hz, 1.80 Hz, 1H), 7.672 (d, $J = 2.10$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 65.29, 114.07, 117.65 (q, $^1J_{CF} = 270.22$ Hz), 118.27, 126.27, 131.73, 132.43, 144.20 (q, $^2J_{CF} = 40.00$ Hz), 153.09. GC-MS: t = 9.017 min, m/z (%): 390 (M^+, 100), 392 (M^+, 100), 371 (5), 373 (5), 340 (1), 342 (1), 263 (25), 265 (25), 235 (19), 237 (19), 216 (1), 218 (1), 184 (10), 156 (48), 105 (10), 87 (22).

Compound 6e

This compound was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.031 (s, 3H), 6.981 (d, $J = 7.95$Hz, 1H), 7.086 (dd, $J = 8.01$ Hz, 0.72 Hz, 1H), 7.3286 (t, $J = 8.01$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.48 MHz) δ 56.71, 66.66 (d, $^3J_{CF} = 3.02$ Hz), 109.96, 115.18, 117.91 (q, $^1J_{CF} = 270.22$ Hz), 125.58, 132.13, 143.16 (q, $^2J_{CF} = 40.76$ Hz), 143.93, 145.94. GC-MS: t = 6.019 min, m/z (%): 342 (M^+, 100), 327 (17), 299 (5), 271 (7), 172 (9), 144 (19), 28 (59).

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