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$Rh_2(OAc)_4$ catalyzed formation of fluorine-containing polysubstituted furans from diazocompounds and aromatic alkynes

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ABSTRACT

A new building block strategy for the synthesis of fluorine-containing 1,2,4-trisubstituted furan was reported. The 1,2,4-trisubstituted furan was constructed through [3+2] cycloaddition reaction of fluoroacetyl-containing diazocompound and aromatic alkyne, catalyzed by $Rh_2(OAc)_4$.

1. Introduction

Polysubstituted furan derivatives are a class of compounds with fundamentally important heterocyclic molecules as well as having practical utility as recurring unit in many natural molecules and medicinal molecules.[1] As well known, the introduction of fluorine atoms into a medicinal molecule can often bring some unpredictable huge influence on its bioactivity.[2] Due to the importance and increasing concern of polysubstituted furan in pharmaceutical and biological field, fluorine-containing polysubstituted furans also attracted the great interests of chemists and biochemists. However, how to efficiently and selectively introduce the fluorine atom into the furan structure is an often met problem.[3]

Of all kinds of methods to synthesize polysubstituted furans, transitional metal-catalyzed [3+2] cycloaddition of α-carbonyl diazocompounds with alkynes was considered one of the most versatile and efficient methods for chemical selective construction of the five-membered ring structures.[4] Among known catalytic systems, Rh-complex was proved to be the most successful and reliable catalyst for this reaction.[5]

As one continued research project to study the reaction of fluorine-containing diazocompounds, we herein reported a building block strategy for the synthesis of fluorine-containing 1,2,4-trisubstituted furan: $Rh_2(OAc)_4$ can catalyze [3+2] cycloaddition reaction of fluoroacetyl-containing diazocompound and aromatic alkyne to form 1,2,4-trisubstituted fluoro-containing furan.

2. Results and discussions

Considering the special diazocompound structure of ethyl 2-diazo-4,4,4-trifluoro-3-oxobutanoate **2a**, the reaction of phenylacetylene **1a** with equimolar of **2a** was firstly investigated in anhydrous DCM at refluxing temperature. After stirring for 4 h, to our delight, the reaction was found to occur very smoothly, and the followed ^{19}F NMR spectra of crude product revealed that there were two main products in a ratio of ~1:1.5. Finally, the two products were obtained after general work-up and purification. The major product **4aa**, obtained in 38% yield, was readily identified as 1-trifluoromethyl substituted furan and a typical singlet at δ −60.9 ppm for trifluorometyl group in ^{19}F NMR spectrum also confirmed the existence of CF_3 functional group. Another product **3aa** with a strong fluorescence property was also isolated successfully in 25% yield. During the identification process, except for the similar ^1H NMR spectrum, the same molecular ion peaks (*m*/*z* 284) were observed evidently in the corresponding mass spectra, which indicated that **3aa** and **4aa** are isomeric compounds, even though the intensities of the other fragmental ion peaks were different. This point was further substantiated by the high-resolution mass spectra (HRMS) of **3aa** and **4aa**. Comparing the ^{19}F NMR spectra of **3aa** and **4aa**, the product **3aa** showed a single strong peak at δ −75.5 ppm, corresponding to the trifluoroacetyl group, which is similar to the chemical shift of $CF_3C(O)$ in substrate **2a**.

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However, despite the above spectral data, it was still difficult to determine the concrete structure of **3aa**. Finally, the similar structure of **3ca** was further elucidated by a single crystal X-ray diffraction analysis. The molecular structure of **3ca** is shown in Figure 1. It is an unexpected 2-trifluoroacethyl substituted furan product. Several interesting features could be seen from Figure 1: the distance of C1–O2 (1.309(2)Å) and C1–O1 (1.326(2)Å) is considerably shorter than the standard single bond of C–O (1.43 Å), but longer than the standard double bond of C=O (1.22 Å). Meanwhile, the distance of C1–C2 (1.373(3) Å) and C2–C5 (1.429(3) Å) is considerably longer than the standard double bond of C=C (1.34 Å), but shorter than the standard single bond of C–C (1.53 Å). These data indicated that the double-bond character for the C1–C2 bond was weakened and the electron density between C1, O2, O1, C2 and C5 was shared. From analyzing the structural data of **3ca**, we were delighted to find that product **3** was a good 1,3-electrophilic reagent. From Figure 1, it can be seen that product **3** has a push–pull alkene group in its right side. Compared to its hydrocarbon analogues, the reaction activity of **3** was greatly increased by the strong electron-withdrawing property of tri- or difluoroacetyl, which could react with various nucleophiles, such as carbonous, phosphorous, sulfide and nitrous nucleophiles. In addition, 1,3-dipolar cycloaddition reactions and other unsaturated ketones with electron-rich alkene, nitrile oxides and azides were also extensively researched.[6] Therefore, it is quite worthy of a well-study to use product **3** as a good 1,3-electrophilic reagent.

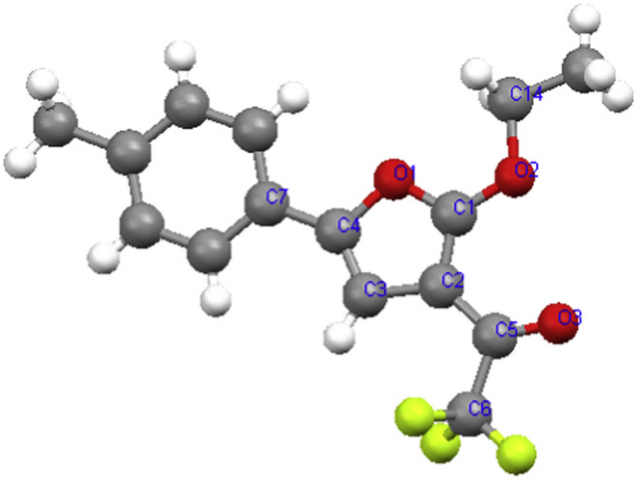
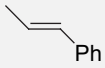


Figure 1. The molecular structure of **3ca**.

Under the same reaction conditions, we further examined the scope of the reaction with a variety of differently substituted **1** or **2**. As can be seen from the data in Table 1, the isolated yields were not quite high, probably due to the lost during purification and the generally high purities of the library compounds. It is important to be aware of that the reaction between diazocompound **2b** and EDG substituted ethynylbenzene could only afford the furan structure **3**. The reason was under study in our laboratory. The structures of all compounds could be figured out from the spectral data. Consider **3aa**, for example, the ^{13}C signal of trifluoroacetyl carbons at 173.4 ppm and 116.5 ppm together with the ^{19}F signal at −75.5 ppm for trifluoroacethyl group excluded furan structure **4**. The ^{13}C signal at 145.0, 104.4, 96.8 and 164.2 ppm for the C-1, C-2, C-3 and C-4 furan carbon atoms, respectively, establish the structure of **3**. For **4aa**, the ^{13}C signal of ester carbonyl group at 160.9 ppm and absence of ^{13}C signal of fluoroacetyl carbons at 170–175 ppm as well as ^{19}F signal at −60.9 ppm for trifluoromethyl group proved the furan structure **4**. The ^{13}C signal at 154.9, 106.9, 121.4 and 142.2 ppm for the C-5, C-6, C-7 and C-8 furan carbon atoms, respectively, establish the structure of **4** (Scheme 1).

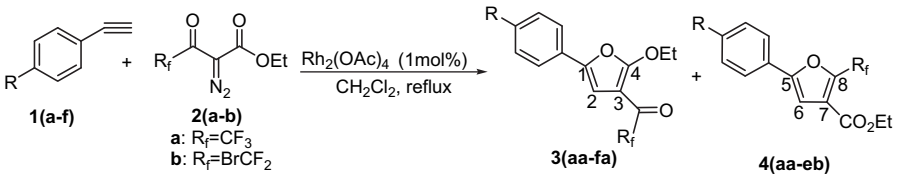
Table 1
The reaction results of **1** with **2**

Entry	1(*R*)	2(R_f)	**3** (yield, %)[a]	**4** (yield, %)[a]
1	H	CF_3	**3aa** (25)	**4aa** (38)
2	H	$BrCF_2$	**3ab** (27)	—[b]
3	C_4H_9	CF_3	**3ba** (26)	**4ba** (26)
4	C_4H_9	$BrCF_2$	**3bb** (14)	—[b]
5	Me	CF_3	**3ca** (21)	**4ca** (36)
6	Me	$BrCF_2$	**3cb** (14)	—[b]
7	OMe	CF_3	**3da** (26)	**4da** (38)
8	OMe	$BrCF_2$	**3db** (15)	—[b]
9	F	CF_3	**3ea** (20)	**4ea** (35)
10	F	$BrCF_2$	**3eb** (13)	—[b]
11		CF_3	—[b]	**4fa** (12)

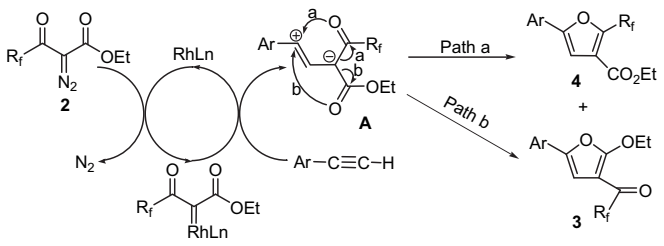
[a] Isolated yield based on diazocompound.
[b] No corresponding product was isolated.

Based on the experimental results and product structures, the proposed reaction mechanism is depicted in Scheme 2. Due to the electron-withdrawing properties of the flanking carbonyl groups, the intermediate **A** was stable. Moreover, the carbon anion was stable by the electron-withdrawing effect of the neighbouring acetyl groups. So the intermediate **A** readily reacted with alkynes in two paths to form two furan isomers.

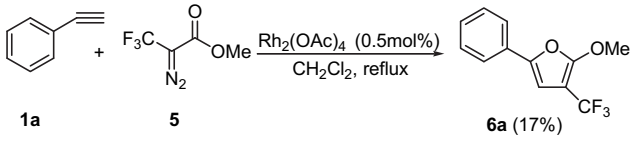
Inspired by the above results, we speculated that the diazocompound with only one carbonyl group could give one furan product exclusively. Fortunately, the reaction result was consistent with what we thought. When methyl 2-diazo-3,3,3-trifluoropropanoate **5** reacted with phenylacetylene, only one product was isolated. From the spectral data, the structure of **6a** is depicted as shown in Scheme 3. But the isolated yield was not so good, the next studies of the reaction was under taken in our laboratory.



Scheme 1.



Scheme 2.



Scheme 3.

3. Conclusions

In summary, [3+2] cycloaddition reaction of aromatic alkyne **1** with fluoroacetyl-containing diazocompound **2** in the presence of rhodium(II) acetate was investigated. When the diazocompounds have two strong electron-withdrawing groups (such as acetyl group) besides the C=N_2 bond, the reaction tends to proceed through a polar transition state towards the formation of furan products and the cycloaddition products of fluorine-containing 1,2,4-trisubstituted furans **3** and **4** are important structural units in natural products with remarkable biological activities and useful building blocks in organic synthesis. The further synthetic application of these compounds is carrying on in our laboratory.

4. Experimental section

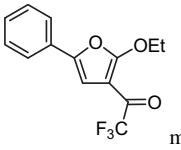
4.1. General

Uncorrected melting points were measured by an SGWX-4 micro-melting point apparatus. ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ (unless mentioned in text), Bruker AM-300 spectrometer with Me_4Si and $CFCl_3$ (with up field negative) as the internal and external standards, respectively. IR spectra were carried on a Nicolet AV-360 spectrophotometer. Lower resolution mass or high-resolution mass spectra (HRMS) were obtained from a Finnigan GC–MS 4021 or a Finnigan MAR-8430 instrument using the electron impact ionization technique (70 eV), respectively. The X-ray structural analysis was performed on a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by Shanghai Institute of Organic Chemistry.

4.2. Typical procedure of the cycloaddition reaction of fluoroacetyl-containing diazocompounds and aromatic alkynes

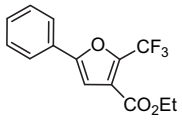
Under nitrogen atmosphere, to a dry schlenk tube containing $Rh_2(OAc)_4$ (4 mg, 1 mol%), phenylacetylenes **1** (1.2 equiv) and CH_2Cl_2 (2 mL), a solution of diazocompound **2** (210 mg, 1 mmol) in 2 mL CH_2Cl_2 was added over 4 h by a syringe pump. After addition, the reaction mixture was stirred at reflux temperature for about 8 h, until the starting material of diazocompound disappeared while monitoring by TLC. The solvent was removed in vacuum and the residue was purified on silica gel using ethyl acetate–hexane as eluent to afford the corresponding products.

4.2.1. 1-(2-Ethoxy-5-phenylfuran-3-yl)-2,2,2-trifluoroethanone (***3aa***).



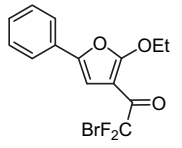
Mp: 45–47 °C. IR (KBr): ν=2988, 1737, 1702, 1617, 1564, 1462, 1442, 1390, 1361, 1308, 1285, 1257, 1141, 1009, 877, 759, 723, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.56–7.42 (m, 2H, Ph–H), 7.40–7.37 (m, 2H, Ph–H), 7.32–7.30 (m, 1H, Ph–H), 6.91 (s, 1H, CH), 4.67 (q, 2H, J=7.2 Hz, CH_2), 1.57 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7, 68.6, 96.8, 104.4, 116.5 (q, J=288.4 Hz), 123.2, 128.0, 128.8, 144.9, 164.2, 173.2 (q, J=36.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−75.5 (s, 3F). MS: m/z (%)=284 (M^+, 41), 256 (98), 227 (12), 186 (82), 177 (12), 159 (30), 131 (34), 105 (100), 77 (99), 51 (33). HRMS (EI) Calcd for $C_{14}H_{11}O_3F_3$: 284.0660; found: 284.0655.

4.2.2. Ethyl 5-phenyl-2-(trifluoromethyl)furan-3-carboxylate (***4aa***).



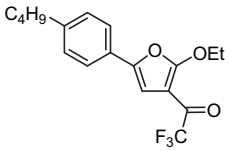
Mp: 37–39 °C. IR (KBr): ν=2986, 1738, 1619, 1603, 1585, 1556, 1488, 1452, 1400, 1387, 1324, 1250, 1174, 1134, 1052, 1034, 930, 835, 778, 762, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.61–7.60 (m, 2H, Ph–H), 7.35–7.28 (m, 3H, Ph–H), 6.94 (s, 1H, CH), 4.28 (q, 2H, J=7.2 Hz, CH_2), 1.29 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 61.5, 106.9, 118.7 (q, J=267.5 Hz), 121.4, 128.4, 128.9, 129.3, 142.2 (q, J=42.3 Hz), 154.9, 160.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.9(s, 3F). MS: m/z (%)=284 (M^+, 100), 256 (42), 239 (46), 211 (28), 183 (17), 159 (6), 133 (15), 114 (16), 105 (48), 77 (29). HRMS (EI) calcd for $C_{14}H_{11}O_3F_3$: 284.0660; found: 284.0662.

4.2.3. 2-Bromo-1-(2-ethoxy-5-phenylfuran-3-yl)-2,2-difluoroethanone (***3ab***).



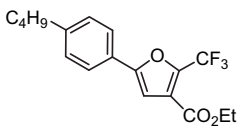
Mp: 64–66 °C. IR (KBr): ν=2985, 1684, 1617, 1560, 1474, 1457, 1434, 1390, 1361, 1307, 1293, 1256, 1169, 1124, 1020, 961, 918, 883, 854, 766, 727, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57–7.54 (m, 2H, Ph–H), 7.42–7.37 (m, 2H, Ph–H), 7.32–7.29 (m, 1H, Ph–H), 6.93 (s, 1H, CH), 4.68 (q, 2H, J=7.2 Hz, CH_2), 1.58 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.8, 68.5, 95.1, 104.9, 113.8 (t, J=317.9 Hz), 123.2, 128.0, 128.9, 144.5, 164.5, 174.9 (t, J=27.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.4 (s, 3F). MS: m/z (%)=344 (M^+, 14), 316 (17), 237 (100), 215 (31), 209 (55), 187 (33), 159 (42), 131 (13), 115 (13), 105 (85), 77 (63), 51 (20). HRMS (EI) calcd for $C_{14}H_{11}O_3F_2Br$: 343.9860; found: 343.9871.

*4.2.4. 1-(5-(4-Butylphenyl)-2-ethoxyfuran-3-yl)-2,2,2-trifluoroethanone (**3ba**).*



IR (KBr): ν=2960, 2932, 2861, 1701, 1585, 1509, 1458, 1414, 1390, 1361, 1308, 1290, 1257, 1200, 1154, 1013, 938, 911, 877, 835, 812, 769, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, 2H, J=8.7 Hz, Ph–H), 7.21 (d, 2H, J=8.4 Hz, Ph–H), 6.85 (s, 1H, CH), 4.57 (q, 2H, J=7.2 Hz, CH_2), 2.63 (t, 2H, J=7.8 Hz, C_2H_4), 1.66–1.58 (m, 2H, C_2H_4), 1.56 (t, 3H, J=7.2 Hz, CH_3), 1.43–1.27 (m, 2H, C_2H_4), 0.94 (t, 3H, J=7.8 Hz, C_2H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8, 14.6, 22.2, 33.4, 35.3, 68.4, 96.7, 103.4, 116.5 (q, J=288.3 Hz), 123.1, 126.2, 128.8, 143.1, 145.3, 164.0, 173.0 (q, J=36.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−75.5 (s, 3F). MS: m/z (%)=340 (M$^+$, 38), 312 (100), 285 (16), 269 (92), 255 (25), 242 (30), 227 (17), 199 (52), 161 (74), 115 (24), 91 (45), 57 (30). HRMS (EI) calcd for $C_{18}H_{19}O_3F_3$: 340.1286; found: 340.1290.

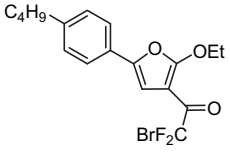
*4.2.5. Ethyl 5-(4-butylphenyl)-2-(trifluoromethyl)furan-3-carboxylate (**4ba**).*



mp: 42-44℃.

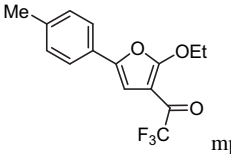
Mp: 42–44 °C. IR (KBr): ν=2960, 2932, 2874, 1736, 1610, 1579, 1557, 1499, 1467, 1423, 1385, 1323, 1247, 1173, 1136, 1117, 1050, 1032, 1018, 931, 829, 776, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, 2H, J=8.1 Hz, Ph–H), 7.12 (d, 2H, J=7.8 Hz, Ph–H), 6.88 (s, 1H, CH), 4.26 (q, 2H, J=7.2 Hz, CH_2), 2.52 (t, 2H, J=7.8 Hz, C_2H_4), 1.55–1.45 (m, 2H, C_2H_4), 1.32–1.22 (m, 2H, C_2H_4), 1.28 (t, 3H, J=7.2 Hz, CH_3), 0.83 (t, 3H, J=7.5 Hz, C_2H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8, 13.9, 22.3, 33.4, 35.5, 61.5, 106.2, 118.8 (q, J=267.7 Hz), 121.4, 124.6, 125.9, 129.0, 141.8 (q, J=42.6 Hz), 144.6, 155.2, 160.9. MS: m/z (%)=340 (M$^+$, 61), 297 (100), 269 (49), 225 (2), 196 (4), 155 (3), 128 (4), 115 (4), 91 (3). HRMS (EI) calcd for $C_{14}H_{11}O_3F_3$: 340.1286; found: 340.1290.

*4.2.6. 2-Bromo-1-(5-(4-butylphenyl)-2-ethoxyfuran-3-yl)-2,2-difluoroethanone (**3bb**).*



IR (KBr): ν=2961, 2931, 2859, 1737, 1693, 1604, 1582, 1559, 1443, 1389, 1261, 1159, 1095, 1015, 966, 882, 852, 801 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.47 (d, 2H, J=8.1 Hz, Ph–H), 7.21 (d, 2H, J=8.4 Hz, Ph–H), 6.87 (s, 1H, CH), 4.67 (q, 2H, J=7.2 Hz, CH_2), 2.62 (t, 2H, J=7.5 Hz, C_2H_4), 1.61–1.55 (m, 2H, C_2H_4), 1.57 (t, 3H, J=7.2 Hz, CH_3), 1.40–1.32 (m, 2H, C_2H_4), 0.93 (t, 3H, J=7.5 Hz, C_2H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 14.8, 22.3, 33.4, 35.4, 68.5, 95.0, 109.6, 113.8 (t, J=318.1 Hz), 123.2, 126.4, 128.9, 143.1, 144.9, 164.4, 174.9 (t, J=27.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.5 (s, 3F). MS: m/z (%)=400 (M$^+$, 14), 371 (12), 293 (100), 271 (15), 243 (14), 215 (18), 161 (30), 115 (25), 91 (24), 57 (46). HRMS (EI) calcd for $C_{18}H19O_3F_2Br$: 400.0486; found: 400.0486.

*4.2.7. 1-(2-Ethoxy-5-p-tolylfuran-3-yl)-2,2,2-trifluoroethanone (**3ca**).*



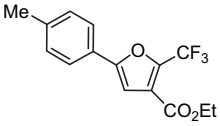
mp: .94-96℃.

Mp: 94–96 °C. IR (KBr): ν=3007, 1683, 1562, 1443, 1389, 1359, 1284, 1193, 1135, 1020, 937, 910, 813, 770, 722, 692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43 (d, 2H, J=7.8 Hz, Ph–H), 7.22 (d, 2H, J=8.7 Hz, Ph–H), 6.83 (s, 1H, CH), 4.65 (q, 2H, J=7.2 Hz, CH_2), 2.36 (s, 3H, Me), 1.55 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 21.2, 68.5, 96.7, 103.4, 116.5 (q, J=288.1 Hz), 123.2, 126.1, 129.5, 138.0, 145.2, 164.1, 173.1 (q, J=36.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−75.5 (s, 3F). MS: m/z (%)=298 (M$^+$, 34), 270 (100), 241 (16), 201 (44), 200 (62), 191 (11), 173 (20), 145 (26), 119 (68), 91 (60). HRMS (EI) calcd for $C_{15}H_{13}O_3F_3$: 298.0817; found: 298.0821.

*X-ray data of **3ca**.* $C_{15}H_{13}F_3O_3$: M_w=298.25, CCDC no. 654747, monoclinic, space group: $P2(1)/n$, a=7.2318(9) Å, b=13.0877(15) Å, c=15.2582(18) Å; α=90.00°, β=103.244(2)°, γ=90.00°; V=1405.7 (3) Å^3, Z=4, D_c=1.409 g/cm^3, F(000)=616. Radiation, Mo Kα (λ=0.71073 Å). Crystal dimension, 0.502×0.450×0.357 mm.

Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). A total of 2755 independent reflection was measured in range 5.486<θ<44.948°. The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of fullmatrix least-square refinement was based on F^2. The final R and wR values were 0.0560 and 0.1469, respectively. All calculations were performed using the SHELX-97 program.

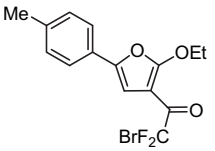
*4.2.8. Ethyl 5-p-tolyl-2-(trifluoromethyl)furan-3-carboxylate (**4ca**).*



mp: 72-74℃.

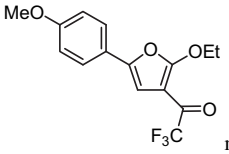
Mp: 72–74 °C. IR (KBr): ν=2995, 1731, 1606, 1579, 1556, 1499, 1446, 1325, 1248, 1147, 1051, 1031, 929, 858, 836, 820, 779, 749 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57 (d, 2H, J=8.4 Hz, Ph–H), 7.22 (d, 2H, J=7.8 Hz, Ph–H), 6.97 (s, 1H, CH), 4.36 (q, 2H, J=7.2 Hz, CH_2), 2.37 (s, 3H, Me), 1.38 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 21.3, 61.5, 106.2, 118.8 (q, J=267.9 Hz), 121.3, 124.5, 125.7, 129.6, 139.5, 141.8 (q, J=42.3 Hz), 155.2, 160.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ=−61.3(s, 3F). MS: m/z (%)=298 (M$^+$, 100), 270 (38), 253 (26), 225 (20), 197 (15), 119 (42), 91 (12). HRMS (EI) calcd for $C_{15}H_{13}O_3F_3$: 298.0817; found: 298.0818.

*4.2.9. 2-Bromo-1-(2-ethoxy-5-p-tolylfuran-3-yl)-2,2-difluoroethanone (**3cb**).*



IR (KBr): ν=2984, 1738, 1693, 1560, 1444, 1390, 1360, 1267, 1160, 1013, 965, 884, 852, 817, 726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.45 (d, 2H, J=8.7 Hz, Ph–H), 7.20 (d, 2H, J=7.8 Hz, Ph–H), 6.87 (s, 1H, CH), 4.66 (q, 2H, J=7.2 Hz, CH_2), 2.37 (s, 3H, Me), 1.57 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.8, 21.3, 68.5, 95.0, 104.0, 109.6 (t, J=316.8 Hz), 123.2, 126.1, 129.6, 138.0, 164.4, 174.9 (t, J=28.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.8 (s, 3F). MS: m/z (%)=358 (M^+, 17), 330 (14), 251 (74), 223 (25), 201 (22), 173 (29), 119 (100), 91 (55), 65 (24). HRMS (EI) calcd for $C_{15}H_{13}O_3F_2Br$: 358.0016; found: 358.0022.

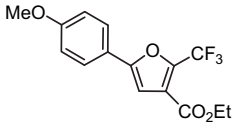
*4.2.10. 1-(2-Ethoxy-5-(4-methoxyphenyl)furan-3-yl)-2,2,2-trifluoroethanone (**3da**).*



mp: 79-81℃.

Mp: 79–81 °C. IR (KBr): ν=2939, 1697, 1586, 1509, 1459, 1389, 1361, 1298, 1251, 1141, 1021, 938, 910, 876, 832, 768, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.47 (d, 2H, J=7.8 Hz, Ph–H), 6.92 (d, 2H, J=7.5 Hz, Ph–H), 6.74 (s, 1H, CH), 4.64 (q, 2H, J=6.6 Hz, CH_2), 3.83 (s, 3H, OMe), 1.55 (t, 3H, J=6.6 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 55.3, 68.5, 96.8, 102.4, 114.4, 116.6 (q, J=288.4 Hz), 121.7, 124.8, 145.1, 159.6, 164.0, 172.7 (q, J=36.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−75.9 (s, 3F). MS: m/z (%)=314 (M^+, 56), 286 (100), 257 (38), 216 (42), 207 (27), 161 (13), 135 (60), 107 (14), 92 (16), 77 (24). HRMS (EI) calcd for $C_{15}H_{13}O_4F_3$: 314.0766; found: 314.0777.

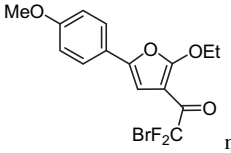
*4.2.11. Ethyl 5-(4-methoxyphenyl)-2-(trifluoromethyl)furan-3-carboxylate (**4da**).*



mp: 73-75℃.

Mp: 73–75 °C. IR (KBr): ν=2991, 1721, 1606, 1582, 1500, 1457, 1327, 1248, 1179, 1134, 1029, 930, 835, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.62 (d, 2H, J=9.0 Hz, Ph–H), 6.94 (d, 2H, J=9.0 Hz, Ph–H), 6.90 (s, 1H, CH), 4.36 (q, 2H, J=6.9 Hz, CH_2), 3.84 (s, 3H, OMe), 1.38 (t, 3H, J=6.9 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 55.3, 61.5, 105.4, 114.4, 118.8 (q, J=267.3 Hz), 121.3, 121.4, 126.2, 141.5 (q, J=42.3 Hz), 155.1, 160.5, 161.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ=−61.7(s, 3F). MS: m/z (%)=314 (M^+, 100), 286 (34), 269 (15), 257 (7), 214 (11), 216 (15), 135 (33). HRMS (EI) calcd for $C_{15}H_{13}O_4F_3$: 314.0766; found: 314.0780.

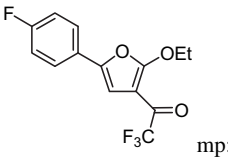
*4.2.12. 2-Bromo-1-(2-ethoxy-5-(4-methoxyphenyl)furan-3-yl)-2,2-difluoroethanone (**3db**).*



mp: 76-77℃.

Mp: 76–77 °C. IR (KBr): ν=3438, 2967, 2842, 1763, 1743, 1678, 1599, 1579, 1513, 1493, 1465, 1259, 1175, 1027, 974, 834, 778, 759, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.47 (d, 2H, J=8.7 Hz, Ph–H), 6.92 (d, 2H, J=9.3 Hz, Ph–H), 6.76 (s, 1H, CH), 4.64 (q, 2H, J=6.6 Hz, CH_2), 3.82 (s, 3H, OMe), 1.56 (t, 3H, J=6.6 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.8, 55.4, 68.5, 96.0, 103.0, 113.9 (t, J=319.0 Hz), 114.4, 121.7, 124.8, 144.7, 159.5, 164.3, 174.9 (t, J=26.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.4 (s, 3F). MS: m/z (%)=374 (M^+, 12), 347 (18), 317 (3), 267 (50), 239 (12), 216 (16), 135 (100), 107 (15), 92 (17), 77 (26). HRMS (EI) calcd for $C_{15}H_{13}O_3F_2Br$: 373.9965; found: 373.9977.

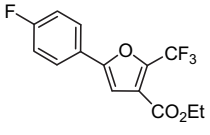
*4.2.13. 1-(2-Ethoxy-5-(4-fluorophenyl)furan-3-yl)-2,2,2-trifluoroethanone (**3ea**).*



mp: 82-84℃.

Mp: 82–84 °C. IR (KBr): ν=3118, 3001, 1663, 1576, 1508, 1467, 1392, 1362, 1318, 1285, 1255, 1233, 1193, 1183, 1168, 1148, 1007, 947, 909, 878, 810, 768, 722, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.53 (dd, 2H, J_{HH}=8.4 Hz, J_{HF}=5.1 Hz, Ph–H), 7.10 (dd, 2H, J_{HH}=J_{HF}=8.4 Hz, Ph–H), 6.84 (s, 1H, CH), 4.67 (q, 2H, J=7.2 Hz, CH_2), 1.56 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7, 68.7, 96.8, 104.0, 116.0 (d, J=22.1 Hz), 116.5 (q, J=290.0 Hz), 125.1 (d, J=8.0 Hz), 125.2, 144.1, 162.4 (d, J=248.1 Hz), 164.2, 173.1 (q, J=36.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−76.0 (s, 3F), −113.2 (s, 1F). MS: m/z (%)=302 (M^+, 27), 274 (86), 245 (13), 204 (77), 195 (17), 177 (31), 149 (33), 123 (100), 95 (60). HRMS (EI) calcd for $C_{14}H_{10}O_3F_4$: 302.0566; found: 302.0555.

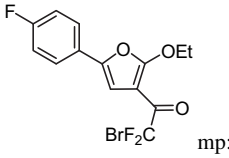
*4.2.14. Ethyl 5-(4-fluorophenyl)-2-(trifluoromethyl)furan-3-carboxylate (**4ea**).*



mp: 84-86℃.

Mp: 84–86 °C. IR (KBr): ν=3127, 2982, 1727, 1606, 1597, 1560, 1497, 1459, 1431, 1325, 1296, 1251, 1194, 1163, 1133, 1054, 1031, 1013, 930, 838, 809, 778, 748, 619 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.68 (dd, 2H, J_{HH}=J_{HF}=6.9 Hz, Ph–H), 7.16 (dd, 2H, J_{HH}=J_{HF}=8.1 Hz, Ph–H), 6.99 (s, 1H, CH), 4.37 (q, 2H, J=6.9 Hz, CH_2), 1.38 (t, 3H, J=6.6 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 61.6, 106.7, 116.1 (d, J=21.9 Hz), 118.6 (q, J=266.8 Hz), 121.4, 124.8 (d, J=2.9 Hz), 126.6 (d, J=8.1 Hz), 142.2 (q, J=42.9 Hz), 154.0, 160.8, 163.3 (d, J=250.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−61.8 (s, 3F), −111.2 (s, 1F). MS: m/z (%)=302 (M^+, 100), 274 (45), 257 (46), 229 (31), 229 (31), 201 (22), 177 (8), 151 (23), 132 (19), 123 (61), 95 (19). HRMS (EI) calcd for $C_{14}H_{10}O_3F_4$: 302.0566; found: 302.0571.

*4.2.15. 2-Bromo-1-(2-ethoxy-5-(4-fluorophenyl)furan-3-yl)-2,2-difluoroethanone (**3eb**).*



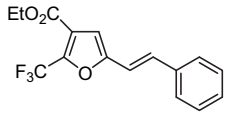
mp: 59-63℃.

Mp: 59–63 °C. IR (KBr): ν=3425, 2986, 1696, 1585, 1561, 1506, 1443, 1359, 1235, 1158, 1134, 1010, 965, 852, 837, 726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.53 (dd, 2H, J_{HH}=8.4 Hz, J_{HF}=6.9 Hz, Ph–H), 7.09 (dd, 2H, J_{HH}=J_{HF}=8.4 Hz, Ph–H), 6.87 (s, 1H, CH), 4.67 (q, 2H, J=7.2 Hz, CH_2), 1.58 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7, 68.6, 95.0, 104.6, 113.7 (t, J=317.2 Hz), 116.0 (q, J=22.0 Hz), 125.1 (d, J=8.7 Hz), 125.2, 143.7, 162.4 (d, J=246.7 Hz), 164.4, 174.9 (t, J=28.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−60.4 (s, 3F), −113.3 (s, 1F). MS: m/z (%)=362 (M^+, 8), 334 (9), 255 (72), 227 (40), 205 (24), 177 (41), 149 (9), 133 (13), 123 (100), 95 (46). HRMS (EI) calcd for $C_{14}H_{10}O_3F_3Br$: 361.9765; found: 361.9779.

X-ray data of ***3eb***. $C_{14}H_{10}BrF_3O_3$: M_w=363.13, CCDC no. 674746, triclinic, space group: P−1, a=9.1062(3) Å, b=10.9613(4) Å, c=15.6322(6) Å; α=73.452(2)°, β=77.710(2)°, γ=84.341(2)°; V=1460.23(9) $Å^3$, Z=4, D_c=1.652 g/cm^3, F(000)=720. Radiation, Mo Kα (λ=0.71073 Å). Crystal dimension, 0.30×0.28×0.20 mm.

Intensity data were collected at 298(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). A total of 6733 independent reflection was measured in range 2.29<θ<20.69°. The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of fullmatrix least-square refinement was based on F^2. The final R and wR values were 0.0936 and 0.2295, respectively. All calculations were performed using the SHELX-97 program.

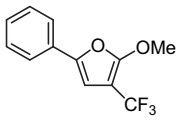
4.2.16. Ethyl 5-phenyl-2-(trifluoromethyl)furan-3-carboxylate (***4fa***).



mp: 56-57℃.

Mp: 56–57 °C. IR (KBr): ν=2984, 2962, 2933, 1739, 1602, 1536, 1448, 1422, 1404, 1389, 1322, 1288, 1254, 1232, 1174, 1108, 1035, 959, 838, 776, 751, 740, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.51–7.48 (m, 2H, Ph–H), 7.41–7.32 (m, 3H, Ph–H), 7.20 (d, J=15.9 Hz, 1H, CH), 6.84 (d, J=16.5 Hz, 1H, CH), 6.76 (s, 1H, CH), 4.32 (q, 2H, J=7.2 Hz, CH_2), 1.38 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.0, 61.6, 109.4, 114.3, 118.7 (q, J=269.8 Hz), 121.2, 123.9, 126.9, 128.8, 128.9, 132.0, 135.7, 141.9 (q, J=36.4 Hz), 154.0, 160.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ=−61.3(s, 3F). MS: m/z (%)=310 (M^+, 90), 282 (5), 265 (13), 241 (10), 195 (100), 167 (18), 159 (7), 139 (55), 131 (17), 115 (15), 103 (13), 77 (12). HRMS (EI) calcd for $C_{16}H_{13}O_3F_3$: 310.0817; found: 310.0825.

4.2.17. 2-Methoxy-5-phenyl-3-(trifluoromethyl)furan (***5a***).



IR (KBr): ν=3155, 2957, 1739, 1490, 1448, 1438, 1317, 1145, 1040, 1019, 934, 908, 814, 790, 767, 721, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.54–7.50 (m, 2H, Ph–H), 7.40–7.38 (m, 3H, Ph–H), 6.74 (s, 1H, CH), 3.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.5, 93.0, 111.1, 123.3, 124.6 (q, J=274.5 Hz), 129.1, 130.3, 131.1, 169.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ=−65.0 (s, 3F). MS: m/z (%)=242 (M^+, 17), 227 (100), 183 (77), 179 (49), 164 (10), 151 (18), 133 (80), 109 (23), 105 (62), 77 (18), 69 (8). HRMS (EI) calcd for $C_{12}H_9O_2F_3$: 242.0555; found: 242.0563.

Acknowledgements

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