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Concise Cu (I) Catalyzed Synthesis of Substituted Benzofurans via a Tandem SNAr/C-O Coupling Process

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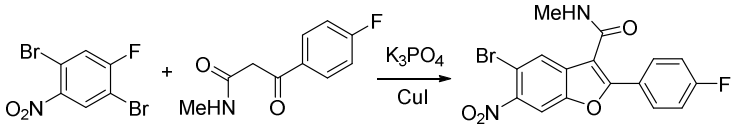
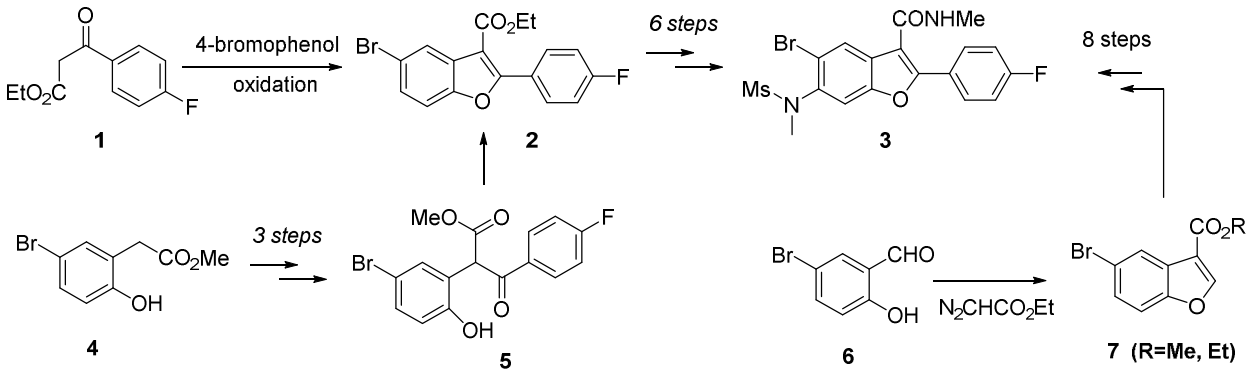


ABSTRACT A novel and convergent approach to tetrasubstituted benzofurans was developed from *ortho*-bromo aryl fluorides and keto-amides via one-pot SNAr displacement and subsequent Cu(I) catalyzed C-O coupling on the *ortho*-bromide. The scope of this methodology was demonstrated on several similar substrates.

KEYWORDS Benzofuran, C-O Coupling, Nitro Reduction, Aryl fluoride displacement by enolate.

Benzofurans are important building blocks for the synthesis of biologically active compounds in the pharmaceutical industry and compound **3** has been an important intermediate in Merck's hepatitis C program.[1,2] The introduction of four substituents around the benzofuran ring poses a significant challenge and the original routes are shown in Scheme 1[1b,2]

Scheme 1. Previous Synthetic Routes for 3

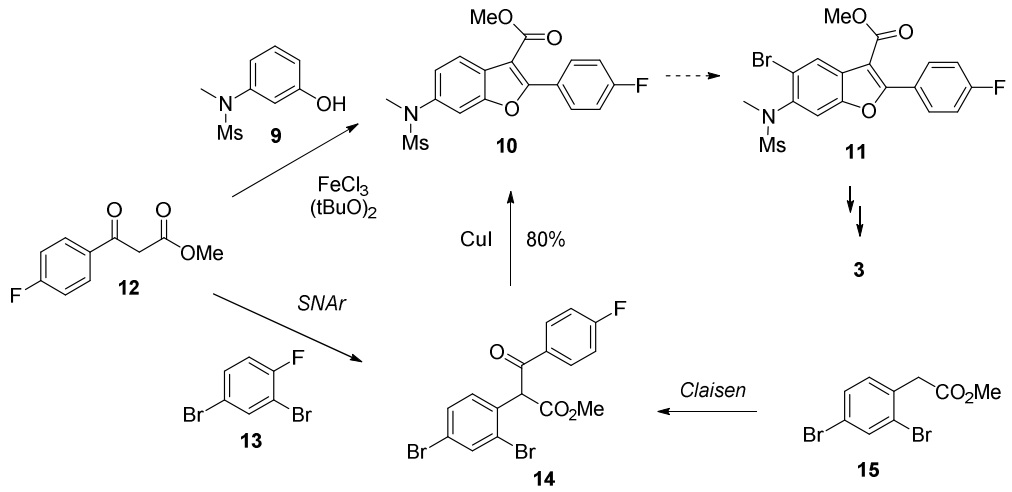


Two related synthetic strategies have been reported that proceed via the key benzofuran intermediate **2** which can be prepared by either oxidative coupling of 4-bromophenol with the keto ester **1**[2,3] or by condensation of bromophenol **4** with 4-fluorobenzoyl chloride.[4] While relatively short, the former route suffers from low yield of the key oxidative coupling step (15%). A third approach involves the preparation of benzofuran **7** with late-stage introduction of the 4-fluorophenyl moiety.[2] All of these synthetic routes are rather lengthy and impractical, ranging from 9 to 12 steps. To make compound **3** on large scale, a more efficient synthesis is desired.

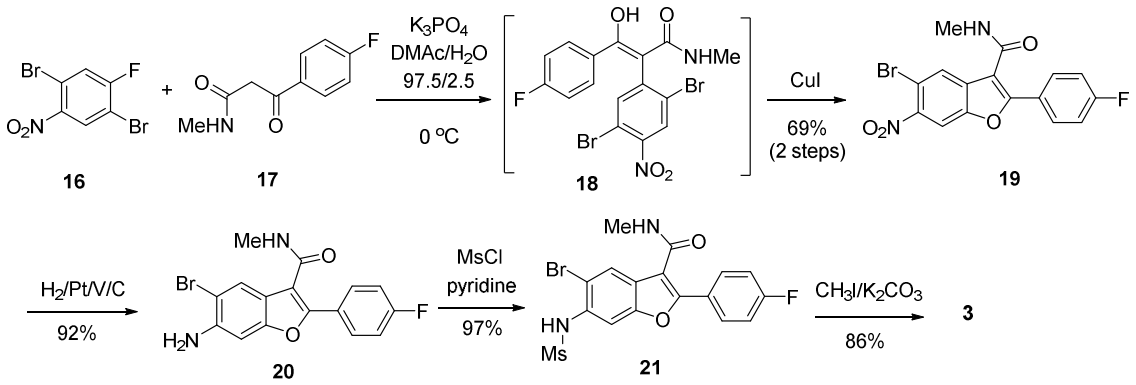
Toward that end we evaluated several potential routes, as illustrated in Scheme 2. One of the shortest routes envisaged was to pre-install the methyl methanesulfonamide on 3-bromophenol to make **9** and then form the benzofuran ring via the oxidative coupling of the β–keto-ester **12**. While the palladium catalyzed C-N coupling between 3-bromophenol and N-methyl

methanesulfonamide to make **9** worked well, the oxidative coupling gave low yield of **10** with a under the reported conditions in dichloroethane.[3] The substrate **9** suffered from poor reactivity and low regio selectivity toward the formation of the desired regio isomer of the substituted benzofuran **10**. We then tested the approach to form the benzofuran via the intramolecular C-O coupling of the β-keto-ester onto the ortho bromide in compound **14**.[5] This intermediate can be prepared from **13** by SNAr displacement of aryl fluoride or by Claisen condensation from **15.** We were encouraged by the fact that the Cu (I) catalyzed intramolecular C-O coupling worked well,[6] but the two substrates **13** and **15** are not as readily available as we would desire. In addition, due to difficulties with the bromination of **10** to make **11**, a pre-installed bromide at the 5-position of the benzofuran would be required. We found that the tetrasubstituted benzene **16** is readily available at very low cost (~$100/kg on scale), providing a raw material with both the desired bromide and nitrogen functionalities as per the requirement. To make the synthesis yet more convergent, we would aim to pre-install the N-methyl carboxamide before the benzofuran formation by using keto-amide **17**, which leads to the overall strategy shown in in Scheme 3. Gratifyingly, these strategic changes ultimately led to a highly efficient route to compound **3** and in the next sections, the key process development results for this route will be described.

Scheme 2. Route Scouting for 3



Scheme 3. Preferred Route for 3



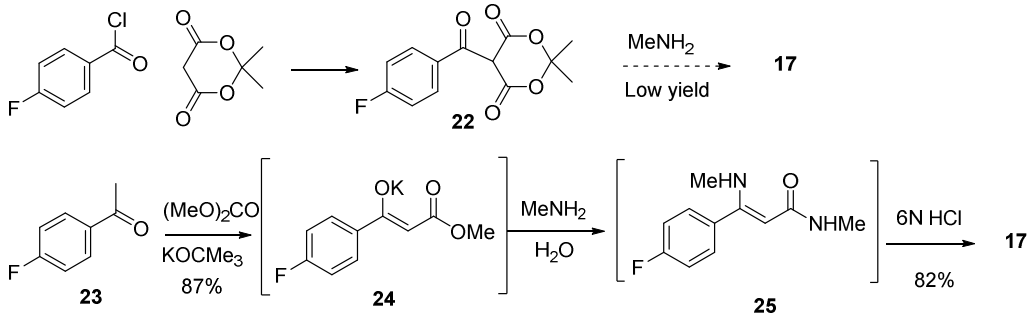
Benzofuran Formation The substitution of the fluoride on compound **16** by the enolate of **17** proved to be very facile, in fact the reaction occurs readily at 0 ^{o}C in a DMAc-water mixture (97.5/2.5) in the presence of K_3PO_4 to generate intermediate **18**. This intermediate was proposed based on consistent LCMS data of a set of two closely eluting peaks on HPLC, presumably the two enol stereo isomers. A range of commonly used solvents for copper-catalyzed C-O couplings were screened for the cyclization (DMF, DMSO, NMP, MeCN, THF, DMAc and toluene) and it was found that the C-O coupling reaction was compatible with the same DMAc-

water mixture used for the formation of **18.** Addition of common ligands, such as 1,10-phenathroline, TMEDA, 2,2'-bypyridyl or N,N-dimethylglycine resulted in much higher levels of the des-bromo side product which significantly reduced the yield.[6] Gratifyingly, we found that a one-pot through process was possible and after formation of intermediate **18,** the cyclization could be effected by simply adding CuI to the reaction mixture and heating to 55 ^{o}C to form the key benzofuran intermediate **19**. The crystalline product can be isolated directly from the reaction mixture in high purity and 69% yield over the 2 steps by addition of water and IPA. Interestingly, during the preparation of this manuscript, the reaction of **16** and **1** under very similar conditions to give the ethyl ester analog of compound **19** was reported by the group of Copley, Xie and co-workers at GlaxoSmithKline.[6e] The authors also attempted the same transformation reported here under different conditions and observed unsatifactory results. The advantage of the sequence reported here is that it is more convergent and higher yielding.

Nitro Reduction and Sulfinamide Formation After successful construction of the benzofuran ring in **19**, we then investigated nitro reduction to form the amine. This reaction is complicated by the presence of bromide, which is readily reduced under a variety of typical conditions, such as Pd catalyzed hydrogenation or metal reductions. We screened a number of more bromide-compatible Pt sources and identified a vanadium-doped platinum catalyst that gave clean reduction with <1% bromide reduction.[7] The best conditions were identified after screening solvents and acid additives and we found that THF-water in the presence of 2 eq acetic acid worked well. It was also observed that while residual Cu from the previous step needs to be controlled, but 1200 ppm residue Cu was well. The product **20** was crystallized directly after removal of the catalyst by filtration. Mesylate formation was accomplished using mesyl chloride and pyridine in DCM to produce **21** in 97% isolated yield. Attempts to replace DCM with other

solvents such as DMF, THF or MeCN led to much less clean reaction profiles. To complete the synthesis, the final *N*-methyl group was introduced with methyl iodide and K_2CO_3 in DMF to make the target compound **3** in 86% yield.

Scheme 4. Synthesis of Aryl Keto-amide 17



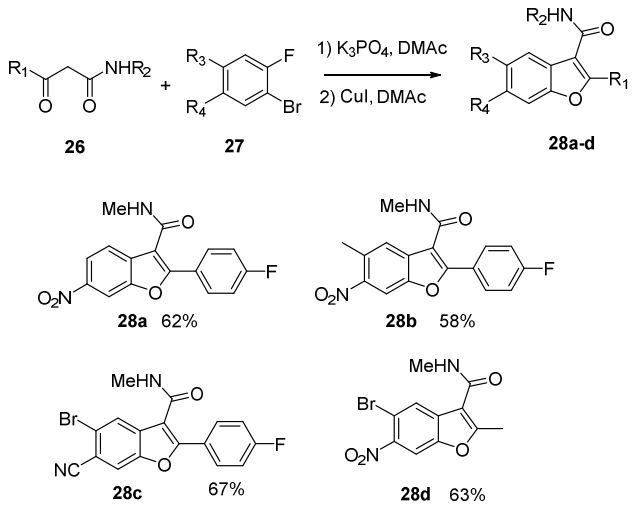
Preparation of keto-amide Although compound **17** is known in the literature, no practical synthesis has been reported.[8a,b,c] As this compound was pivotal to our synthetic strategy, we immediately set out to develop a scalable method for its preparation. As shown in Scheme 4, we explored two potential routes; one via the Meldrum's acid, the other from keto-ester **24** by reaction with methylamine. Even though the reaction between Meldrum's acid and 4-fluorobenzoyl chloride gave the desired intermediate **22**, the subsequent reaction with methylamine resulted in very low yield of desired product under well-established conditions.[8d] An alternative route via the keto-ester was more promising based on preliminary data. The keto-ester **24** could be readily prepared as the potassium enolate by reaction of the acetophenone **23** with dimethyl carbonate in the presence potassium tert-butoxide.[9a,b] This potassium enolate **24** was precipitated out from the reaction mixture in MTBE as an amorphous solid in 87% isolated yield, after correcting for inorganic side-product impurities. When this mixture was used directly in the reaction with excess methylamine,[9c] it was observed that the excess base carried over in the crude solid prevented complete conversion to the keto-amide. When the excess base

was neutralized with 1-2 equiv HCl, the conversion of the keto-ester enolate to the keto-amide **17** proceeded well and the reaction could be conveniently carried out using 30% aqueous methylamine. Solid formation was observed during the reaction and NMR analysis revealed the precipitate to be the enamide **25** formed from methylamine and the keto-amide.[10] This enamide was easily hydrolyzed to the keto-amide **17** by adjusting to pH 2 with HCl. The desired keto-amide **17** then crystallizes out from the aqueous reaction mixture in 82% isolated yield and 99.3% HPLC purity. This one-pot preparation starts from a commodity building block and is easily amenable to large scale operation.

Other Substituted Benzofurans Having established a useful method for preparing our target benzofuran, we then investigated the scope of this methodology with a range of keto-amides and bromo fluorobenzenes. The results are listed in Scheme 5. We observed that very strong electron withdrawing groups *para* to the fluoride (R_4 = NO_2, CN) facilitate the SNAr reaction and subsequent cyclization, so compounds **28a, b and c** were prepared under the same conditions. Less electron withdrawing systems (e.g. R_4 = halide or R_3 = CN) did not lead to any reaction for the SNAr step even at elevated temperature. For the keto-amides, only *N*-methyl acetyl acetamide gave moderate yield product **28d**. Replacing the *N*-methyl group with phenyl resulted in loss of reactivity.

In conclusion, a practical, concise and scalable synthesis of an important tetrasubstituted benzofuran core **3** was developed. The key benzofuran formation was achieved through a good-yielding one-pot SNAr / intramolecular C-O coupling and this methodology was shown to be amenable to the preparation of several other similarly substituted benzofurans.

Scheme 5. Preparation of Other Benzofurans



Notes: Yields were determined by HPLC before isolation.

Experimental Section

^{1}H NMR and ^{13}C NMR were recorded on 400 MHz spectrometer. Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturers. All reactions were conducted under an inert N_2 atmosphere. Melting points are uncorrected.

Potassium (Z)-1-(4-fluorophenyl)-3-methoxy-3-oxoprop-1-en-1-olate (24). Potassium tert-butoxide (608 g, 5.44 mol) and dimethyl carbonate (2.5 kg) were sequentially charged to a reactor and temperature adjusted to 20-30 °C. A solution of 1-(4-fluorophenyl)ethanone **23** (300 g, 2.17 mol) in dimethyl carbonate (600 g) was charged over 2 h at 20-30 °C. The reaction mixture was stirred for 3-4 h at 20-25 °C until complete consumption of **23** as indicated by HPLC, following by the addition of MTBE (450 g) and a slurry was formed. The reaction mixture was filtered and the product cake was further dried under vacuum at 30-40 °C to afford **24** as a white solid**,** 370 g, 63.0 wt% as the K enolate, 87% yield, 98.7% LACP, the rest is likely KOMe and $KOCO_2Me$ based on 1H NMR peaks at 4.17 ppm (s) and 3.20 ppm (s). The wt% purity was obtained by HPLC against a pure commercial sample. The crude product was used

directly in the next step without further purification. ^{1}H NMR (400 MHz DMSO-d6) δ 7.72 (t, *J* = 14.4 Hz, 2H), 7.06 (d, *J* = 17.6 Hz, 2H), 4.90 (s, 1H), 3.38 (s, *3*H), extra peaks 4.17 (br, s, 0.5-1 H), 3.20 (s, 1.5-2H); ^{13}C NMR (100 MHz DMSO-d6) δ 48.5, 77.6, 114.3 (d, *J*=10 Hz), 128.6 (d, *J*=8 Hz), 141.6, 162.6 (d, *J*=242.1 Hz), 169.4, 178.5. ^{19}F NMR (376 MHz DMSO-d6) δ 114.9.

3-(4-Fluorophenyl)-N-methyl-3-oxopropanamide (17). To a reactor was added 30% CH_3NH_2 aqueous solution (550 g x 30%, 5.3 mol) and conc. HCl (42 ml, 12M, 0.54 mol), and the mixture was agitated for 30 min at 20-25°C. Intermediate **24** (189 g x63% wt, 0.52 mol) was charged in portions over 1 h at 20-25 °C. The resulting slurry was stirred for 4-6 h until complete consumption of **24** at 20-25 °C (sample was quenched with HCl to ensure pH = 1-2, a sample of the solid was obtained by filtration and NMR is consistent with **25**). The reaction mixture was cooled to 0-5 °C, then 6 M HCl (900 g) was charged over 2 h to adjust the pH to 1 while maintaining the temperature below 0 °C. The resulting slurry was filtered. The cake was washed with water (100 g) and dried under vacuum at 40-45 °C to provide **17** as white solid,[8b] 81.5 g, 99.3% LCAP, 96 wt%, 82% yield. ^{1}H NMR (400 MHz DMSO-d_6), major ketone form and minor enol form ratio about 3/1, only the ketone form is listed) δ 8.1-8.0 (m, 3H), 7.31-7.40 (m, 2H), 3.89 (s, 2H), 2.61 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6) major only δ 25.6, 47.2, 116.3 (d, *J*=22Hz), 128.1 (d, *J*=8Hz), 131.8, 133.6, 165.5 (d, *J*=247.1Hz), 166.6, 193.8. ^{19}F NMR (376 MHz DMSO-d_6) major only δ 112.1.

5-Bromo-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide (19). 3-(4-Fluorophenyl)-N-methyl-3-oxopropanamide (**17**) (46.6 g, 0.24 mol), potassium phosphate (K_3PO_4, 109 g, 0.51 mol), DMAc (270 g), water (10.9 g) were sequentially charged in the reactor, and the mixture was stirred for 30 min. The mixture was purged three times with

nitrogen, and cooled to 10-15 °C. A solution of 1,4-dibromo-2-fluoro-5-nitrobenzene (**16**) (70 g, 0.23 mol) in DMAc (130 g) was charged over 2 h while maintaining the temperature at 10-15 °C. The resulting mixture was stirred for 2 h at 10-15 °C to complete consumption of **16**. CuI (0.45 g, 0.023 mol) was charged, and the mixture was purged three times with nitrogen again. The reaction mixture was warmed to 50-55 °C, and stirred for 14 h until complete consumption of intermediate **18**. The reaction mixture was cooled to 20-25 °C, and a solution IPA (350 g) in water (350 g) was charged drop-wise over 2 h. The resulting slurry was filtered and the cake washed with a solution of IPA (100 g) in water (100 g), and further dried under vacuum at 40-45 °C to provide **19** as off white solid (63.7 g, 69 % yield, 98.4% LCAP, 95.7 wt%). Mp: 243.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73-8.55 (m, 2H), 8.12 (s, 1H), 8.07-7.98 (m, 2H), 7.45 (t, J = 8.9 Hz, 2H), 2.87 (d, J = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.7, 108.2, 110.2, 113.4, 116.6 (d, J=22 Hz), 125.0, 126.2, 130.5 (d, J=8.7 Hz), 132.4, 146.8, 150.8, 157.5, 162.3, 163.8 (d, J=247.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ 108.8. AHR-FAB-MS calcd for $C_{16}H_{10}BrFN_2O_4$: MH^+, 392.9808. Found: 392.9849 (MH^+).

6-Amino-5-bromo-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide (20). 5-bromo-2-(4-fluorophenyl)-N-methyl-6-nitrobenzofuran-3-carboxamide **(19)** (15 g, 0.038 mol), THF (210 g) and water (60 g) was charged in the reactor. The mixture was stirred for 30 min, and then purged three times with nitrogen. Pt/V/C catalyst (1.5 g, 3 wt% Pt, 0.6 wt %V on carbon on dry basis) was charged. The slurry was again purged three times with nitrogen followed by hydrogen at 50-60 psi. The reaction mixture was warmed to 40-45 °C, and stirred for 2 h until complete consumption of **19**. The mixture was cooled to 20-25 °C and filtered through a Celite bed (15 g) to remove the insoluble solid. The reactor and Celite cake was rinsed with THF (30 g), and the combined filtrates was concentrated under reduced pressure below 45 °C to provide crude solid.

The solid was filtered, washed with *n*-heptane (120 g) and further dried under vacuum at 40-45 °C to provide **20** as off-white solid, 13.1 g, 92.1% yield, 97.9% LACP, 95.7 wt%. Mp: 228.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (t, *J* = 4.4 Hz, 1H), 7.89 (dt, *J* = 24.8, 14.1 Hz, 2H), 7.61 (s, 1H), 7.41-7.26 (m, 2H), 7.02 (s, 1H), 5.57 (s, 2H), 2.82 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 96.0, 105.0, 113.0, 115.6 (d, *J*=22Hz), 118.4, 123.4, 126.0, 128.7 (d, *J*=8 Hz), 144.3, 149.9, 153.7, 162.2 (d, *J*=245.6 Hz), 163.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ 111.8. AHR-FAB-MS calcd for $C_{16}H_{12}BrFN_2O_2$: MH^+, 363.0811. Found: 363.0131 (MH^+).

5-Bromo-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide (21). 6-Amino-5-bromo-2-(4-fluorophenyl)-N-methylbenzofuran-3-carboxamide **(20)** (44.3 kg, 122.4 mol) and DCM (532 kg) was charged into the reactor. The mixture was stirred for 30 min, and pyridine (48 kg, 607.6 mol) was charged and followed by addition of methanesulfonyl chloride (24 kg, 210.5 mol) over 2 h while maintaining the temperature at 27-32 °C. The reaction mixture was stirred for 15 h to complete consumption of **20**. Water (333 kg) was charged, and the mixture was stirred for 2-3 h at 27-32 °C, followed by addition of HCl aqueous solution (1M, 200 kg). The resulting mixture was concentrated under reduced pressure below 40 °C to a volume of ~530 L, and then cooled to 20-30 °C. The slurry was stirred for 1 h and was filtered. The cake was washed with water twice (80 kg x 2). The wet cake and EtOAc (160 kg) was charged in a reactor. The mixture was warmed to 40-45 °C and stirred for 2-3 h to generate a solution. The solution was cooled to 5-10 °C slowly over 5 h and filtered. The product cake was washed with EtOAc (101 kg) and dried by vacuum at 50-60 °C to afford **21** as off-white solid (49.4 kg, 97.5% yield, 98.8% LACP, 97.5 wt%). Mp: >240 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.51 (d, *J* = 4.6 Hz, 1H), 8.04-7.91 (m, 2H), 7.93 (s, 1H), 7.79 (s, 1H), 7.41 (t, *J* = 8.9 Hz, 2H), 3.11 (s, 3H), 2.85 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 41.0,

111.0, 112.7, 115.8 (d, *J*=8 Hz), 124.0, 125.2 (d, *J*=3.7 Hz), 127.1, 129.5 (d, *J*=8.8 Hz), 132.2, 151.8, 153.8, 162.6, 162.9 (d, *J*=247.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ 110.1. AHR-FAB-MS calcd for $C_{17}H_{14}BrFN_2O_4S$： MH^+, 442.2715. Found: 441.9909 (MH^+).

5-Bromo-2-(4-fluorophenyl)-N-methyl-6-(N-methylmethylsulfonamido)benzofuran-3-carboxamide (3). 5-Bromo-2-(4-fluorophenyl)-N-methyl-6-(methylsulfonamido)benzofuran-3-carboxamide **(21)** (3.6 kg, 8.2 mol), potassium carbonate (K_2CO_3, 2.26 kg, 16.4 mol), were sequentially charged in the reactor. The mixture was stirred over 20 min at 20-25 °C. Methyl iodide (2.3 kg, 16.4 mol) was charged drop-wise while maintaining the temperature at 20-25 °C. The reaction mixture was warmed to 55-60 °C and stirred an additional 2 h to complete consumption of **21**. The mixture was cooled to 20-25 °C, and water (28 kg) was charged drop-wise over 1 h. The resulting slurry was stirred for 1 h at 20-25 °C and was filtered. The product cake was dried under vacuum at 60-65 °C to afford **1** as pale yellow solid (3.1 kg, 86% yield, 98.8% LACP). Mp: >240 °C. ^{1}H NMR (400 MHz, DMSO-d_6)δ 8.54 (d, *J* = 4.5 Hz, 1H), 8.07 (s, 1H), 8.07-7.94 (m, 3H), 7.42 (t, *J* = 8.9 Hz, 2H), 3.34 (s, 3H), 3.22 (d, *J* = 4.1 Hz, 3H), 2.85 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 38.2, 112.8, 113.4, 115.9 (d, *J*=22 Hz), 119.7, 124.2, 125.2, 128.7, 129.6 (d, *J*=8.8 Hz), 136.9, 151.8, 154.4, 162.4, 162.9 (d, *J*=247.1 Hz). ^{19}F NMR (376 MHz DMSO-d6) δ 109.9 AHR-FAB-MS calcd for $C_{18}H_{16}BrFN_2O_4S$： MH^+, 455.2980. Found: 455.0055 (MH^+).

Other Benzufurans 28 Compounds **28a, b, c, d** were prepared similar procedure as **19** and the pure samples were obtained through silica gel chromatography eluting with ethyl acetate and heptane. The solution assay yields by HPLC against the pure sample were reported in scheme 5. **28a**: 62% Yield, Mp: 220.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (dd, *J* = 16.0, 2.8 Hz, 2H), 8.23 (dd, *J* = 8.7, 1.7 Hz, 1H), 8.00 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.44

(t, *J* = 8.8 Hz, 2H), 2.86 (d, *J* = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.1, 108.6, 114.6, 116.3 (d, *J*=22.6 Hz), 120.1, 122.1, 125.7, 130.0 (d, *J*=8.8 Hz), 134.2, 145.8, 152.4, 157.6, 162.3, 163.3 (d, *J*=248.6 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ 109.0. AHR-FAB-MS calcd for $C_{16}H_{11}FN_2O_4$: MH^+, 315.0703. Found: 315.0769 (MH^+).

28b: 58% Yield, Mp: 222.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 4.5 Hz, 1H), 8.33 (s, 1H), 7.92 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.65 (s, 1H), 7.35 (t, *J* = 8.8 Hz, 2H), 2.79 (d, *J* = 4.6 Hz, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.0, 26.2, 108.3, 113.2, 116.2 (d, *J*=21.8 Hz), 123.4, 124.9, 128.4, 129.7 (d, *J*=8.7 Hz), 131.6, 146.0, 149.9, 156.3, 162.5, 163.1 (d, *J*=247.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ 109.3. AHR-FAB-MS calcd for $C_{17}H_{13}FN_2O_4$: MH^+, 329.0859. Found: 329.0947 (MH^+).

28c: 67% Yield, Mp: >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, *J* = 4.7 Hz, 1H), 8.47 (s, 1H), 8.10 (s, 1H), 8.00 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.43 (t, *J* = 8.8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 109.7, 113.3, 116.2 (d, *J*=22.6 Hz), 117.6, 118.3 (d, J=12.4 Hz), 124.5, 124.9, 130.0 (d, *J*=8.7 Hz), 133.2, 150.5, 156.4, 161.9, 162.1, 163.3 (d, *J*=248.6 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ 109.3. AHR-FAB-MS calcd for $C_{17}H_{10}BrFN_2O_2$: MH^+, 374.9910. Found: 374.9951 (MH^+).

28d: 63% Yield, Mp: 223.0°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.20-7.98 (m, 2H), 2.83 (d, *J* = 4.5 Hz, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 26.1, 107.5, 109.3, 112.4, 125.4, 130.8, 145.4, 150.3, 161.9, 163.6. AHR-FAB-MS calcd for $C_{11}H_9BrN_2O_4$: MH^+, 312.9746. Found: 312.9811 (MH^+).

Supporting Information. HPLC analysis conditions for preparation of compounds **17, 19, 21, 3** are listed.

AUTHOR INFORMATION

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10. Compound **26**: ^{1}H NMR (400 MHz DMSO-d6) δ 7.6-7.8 (m, 1H), 7.3-7.5 (m, 2H), 7.15-7.30 (m, 3H), 4,49 (s, 1H), 2.50-2.65 (m, 6H).