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# Direct Access to Fully Substituted 3-Formyl-4-iodofurans through Iodocyclization of α-Alkynyl β-Alkoxy Enones

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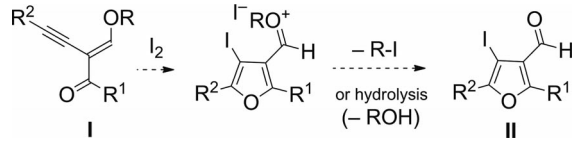
A facile access to 3-formyl-4-iodofurans is presented. This protocol consists of a Sonogashira cross-coupling of an α-iodo β-alkoxy enone with a terminal alkyne and the subsequent iodonium-promoted heteroannulation–dealkoxylation of the resulting α-alkynyl β-alkoxy enone by treatment with *N*-iodosuccinimide in aqueous medium.

## Introduction

The furan structure is a ubiquitous subunit in a variety of bioactive natural products and synthetic materials, including important agrochemicals and pharmaceuticals. Additionally, furan derivatives can serve as versatile building blocks in the construction of highly complex target structures.[1] Thus, the value and utility of this heterocycle continue to stimulate research directed toward its construction.[2] In this area, the development of synthetic strategies that allow the flexible and rapid assembly of furan derivatives with specific substitution patterns, prepared from readily available starting materials and under mild reaction conditions, remains an important goal. Today, electrophilic heteroannulation processes that involve acetylenic compounds bearing a tethered nucleophilic substituent are among the most versatile and efficient synthetic methods to rapidly elaborate highly substituted heterocyclic systems.[3] In particular, furan derivatives have been accessed recently though halonium-promoted heteroannulations of α-alkynyl carbonyl compounds.[4,5] The ready accessibility of the latter compounds combined with the synthetic utility of the halide functional group, thereby installed on the newly formed heterocyclic ring, makes this approach particularly attractive.

We recently demonstrated the high versatility of alkyl β-keto enol ethers for use as masked β-dicarbonyl nucleophiles in the direct construction of the 3-ketofuran unit through an alkynyl cyclization reaction.[6] Along the same line, we envisioned that the iodonium-promoted heteroannulation of α-alkynyl β-alkoxy enones **I** would give direct access to 3-formyl-4-iodofurans **II** after in situ dealkylation – or hydrolysis – of the putative oxonium intermediate (see Scheme 1). Surprisingly, despite their considerable potential synthetic value, no practical and flexible method is currently available to access such compounds, and only rare examples of them have been reported so far in the literature.[7] Indeed, they are expected to be versatile synthetic intermediates, given the great variety of chemical transformations available for each of the halogen and formyl functional groups.[8] Herein, we report the successful development of a two-step, semi-one-pot protocol for such compounds from readily available α-iodo β-alkoxy enones and terminal alkynes.




Scheme 1. Planned strategy toward 3-formyl-4-iodofurans.

## Results and Discussion

To test the feasibility of the proposed concept, we first needed a reliable procedure for the preparation of a series of α-alkynyl ketones **3**. We expected these to be accessible by a Sonogashira cross-coupling of α-iodo β-alkoxy enones **2**, which in turn may be easily prepared by iodination[9] of the corresponding and readily available β-alkoxy enones **1**. Preliminary studies were conducted using iodo enone **2a** and phenylacetylene as model substrates. Initially, the cross-coupling reaction was probed using reaction conditions previously developed in our laboratory for the alkynylation of structurally related compounds [cat. $PdCl_2(PPh_3)_2$, cat. CuI, $K_2CO_3$, THF (tetrahydrofuran), 40 °C].[6c] Interestingly, the desired alkynyl enone **3aa′** proved relatively unstable under these conditions and exhibited a marked propensity to undergo gradual cyclization to 3-formylfuran **4**

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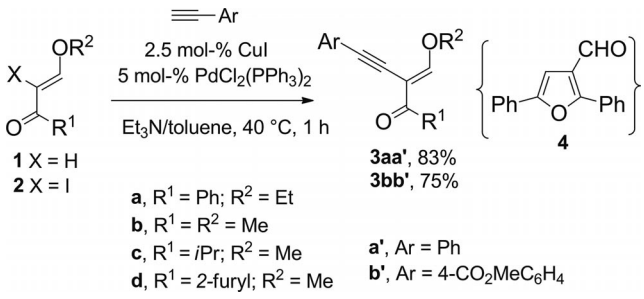
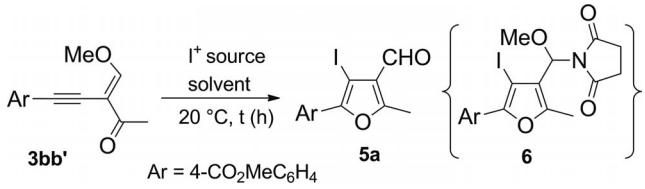
as the main reaction product. For instance, the latter was isolated in 50% yield after 16 h of reaction time, aside from other unidentified side products.[10] Gratifyingly, after further experiments, we found that the use of $Et_3N$/toluene as a base/solvent pair enabled rapid and clean formation of the cross-coupled product and retarded formation of the side products. Under the optimized reaction conditions [alkyne (1.25 equiv.), $PdCl_2(PPh_3)_2$ (5 mol-%), CuI (2.5 mol-%), $Et_3N$/toluene (1:1), 40 °C], **3aa′** was isolated in 83% yield, after only 1 h of reaction time. Accordingly, α-alkynyl β-alkoxy enone **3bb′** was obtained in 75% isolated yield, following the same procedure (see Scheme 2).




Scheme 2. Synthesis of α-alkynyl enones **3**.

Next, the reactivity of alkynyl enone **3bb′**, selected as the model substrate, was investigated with regard to various iodonium-donating systems. The cyclization process was first probed at 20 °C with iodine as the $I^+$ source and $CH_2Cl_2$ (DCM) as the solvent. Pleasingly, a fast reaction took place under these conditions to give the expected iodofuran **5a**, albeit in a disappointing 28% yield (see Table 1, Entry 1). Employing a large excess amount of $I_2$ did not improve the yield (see Table 1, Entry 2). When iodine was replaced with *N*-iodosuccinimide (NIS),[11] the outcome of the reaction proved interesting, despite the longer reaction time and the still poor yield (24%) obtained for **5a**. Indeed, under these conditions, **5a** was accompanied, aside from other minor unidentified side products, by another iodofuran. The structure of this product, having incorporated a succinimide fragment, was assigned as hemiaminal ether **6** (35% yield) and confirmed by X-ray crystal structure analysis[12] (see Table 1, Entry 3). Unfortunately, this latter compound, which can be rationalized as the consequence of the liberation of the succinimide anion in the reaction medium (vide infra), showed remarkable stability and withstood the usual acidic work-up procedures (i.e., 1 N HCl). With the aim of minimizing the interference of the succinimide anion, the same experiment was then repeated in the presence of water as a cosolvent. Gratifyingly, the aqueous solvent system enabled a noticeable improvement in the efficiency of the reaction, not only by giving rise to the desired formylfuran **5a** as the sole reaction product in a satisfying 75% overall isolated yield, but also by accelerating the rate of reaction (see Table 1, Entry 4).[13] Other aqueous solvent systems were screened, but they did not lead to any further improvements (see Table 1, Entries 5–7).

Table 1. Optimization of the iodocyclization process.[a]




| Entry | $I^+$ Source [equiv.] | Solvent | Time [h] | % Yield **5a** |
|---|---|---|---|---|
| 1 | $I_2$ (1.1) | DCM | 0.25 | 28 |
| 2 | $I_2$ (2.0) | DCM | 0.25 | 25 |
| 3 | NIS (1.1) | DCM | 22 | 24 (+ 35% **6**) |
| 4 | NIS (1.1) | DCM/$H_2O$ | 6 | 75 |
| 5 | NIS (1.1) | $Et_2O$/$H_2O$ | 6 | 48 |
| 6 | NIS (1.1) | MeCN/$H_2O$ | 6 | –[b] |
| 7 | NIS (1.1) | PhMe/$H_2O$ | 6 | 45 |

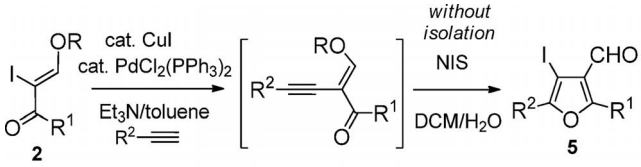
[a] All reactions were carried out on a 0.2 mmol scale. [b] Complex mixture.

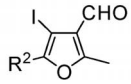
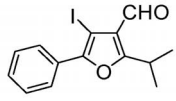
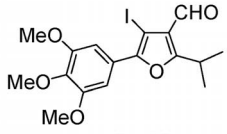
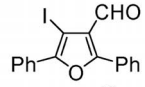
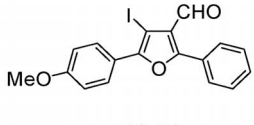
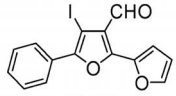
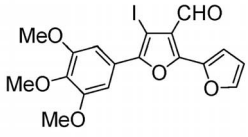
Given the effectiveness and cleanliness of the Sonogashira cross-coupling step and owing to the somewhat fragile nature of the α-alkynyl β-alkoxy enones (see Exp. Section), we next focused on establishing a rapid and effective protocol for formyl iodofuran formation that would avoid isolating and purifying the acetylenic precursors. A convenient experimental procedure for the conversion of α-iodo enone **2b** into iodofuran **5a** was thus conducted. Compound **2b** (1.0 equiv.) and phenylacetylene (1.25 equiv.) underwent a Sonogashira coupling reaction under the previously established conditions [cat. $PdCl_2(PPh_3)_2$, cat. CuI, toluene/$Et_3N$, 40 °C]. After the disappearance of the starting material, as monitored by thin layer chromatography (approximately 1 h), the reaction mixture was diluted with EtOAc, and the resulting solution was washed with brine to remove ammonium salts and then concentrated in vacuo. The crude alkynyl enone was then subjected to iodocyclization with NIS (1.1 equiv.) under our optimized conditions (DCM/$H_2O$, room temp.), and the reaction was complete within 6 h. This resulted in an improved 62% overall yield for the production of **5a**, after the usual workup and silica gel chromatography as the only and final purification step. With this mild, practical protocol in hand, we set out to screen the scope and limitation of this reaction with various α-iodo β-alkoxy enones and terminal alkynes (see Table 2).

The best results were achieved with aryl-substituted alkynes, which provided the corresponding iodofurans in good overall yields. As illustrated by the reactions with alkyl ketones **2b** and **2c** (see Table 2, Entries 1–7), the electronic nature of the arene attached to the triple bond had a noticeable impact on the yield of the reaction, and the presence of electron-donating groups gave better yields. Alkyl-substituted alkynes participated less efficiently in the cyclization process (see Table 2, Entry 5). Phenyl and 2-furyl ketones **2a** and **2d** also participated in the process to give the corresponding 2,5-(hetero)arylfurans in acceptable isolated yields (see Table 2, Entries 8–11). It is noteworthy that 2,5-diphenylfuran **5h** (see Table 2, Entry 8) was accompanied by another furan derivative that was tentatively

Table 2. Two-step synthesis of 3-formyl-4-iodofurans **5**.[a]




| Entry | α-Iodo-enone | Alkyne $R^2$ = | Iodofuran **5** (overall yield %)[b] |
|---|---|---|---|
| 1 | **2b** | 4-$CO_2MeC_6H_4$ |  **5a**, 62 |
| 2 | **2b** | $C_6H_5$ | **5b**, 87[c] |
| 3 | **2b** | 4-$MeOC_6H_4$ | **5c**, 88 |
| 4 | **2b** | 4-$FC_6H_4$ | **5d**, 70 |
| 5 | **2b** | *n*-Bu | **5e**, 47 |
| 6 | **2c** | $C_6H_5$ |  **5f**, 75 |
| 7 | **2c** | 3,4,5-$(MeO)_3C_6H_2$ |  **5g**, 75 |
| 8 | **2a** | $C_6H_5$ |  **5h**, 45 [d] |
| 9 | **2a** | 4-$MeOC_6H_4$ |  **5i**, 74 |
| 10 | **2d** | $C_6H_5$ |  **5j**, 38 |
| 11 | **2d** | 3,4,5-$(MeO)_3C_6H_2$ |  **5k**, 55 |

[a] All reactions were single runs conducted on a 0.4 mmol scale. Reagents and conditions: alkyne (1.25 equiv.), $PdCl_2(PPh_3)_2$ (5 mol-%), CuI (2.5 mol-%), $Et_3N$/toluene (1:1), 40 °C, 1 h (Step 1); NIS (1.1 equiv.), DCM/$H_2O$ (1:1), room temp., 6 h (Step 2). [b] Isolated yields (two steps). [c] This experiment was also performed on a 2 mmol semipreparative scale (74% yield), see Exp. Section. [d] The reaction produced a 4:1 mixture of **5h** and its structural isomer 3-benzoyl-4-iodo-5-phenylfuran (70% combined yield).

assigned as the structural isomer 3-benzoyl-4-iodo-5-phenylfuran (not shown). The mechanism involving the formation of this regioisomeric compound remains unclear. Importantly, this process was successfully applied to the preparative scale (2 mmol) synthesis of furan **5b** (74% isolated yield). The structure of the iodofuraldehydes was confimed by the X-ray crystal structure analysis of **5k** (see Figure 1).[12]

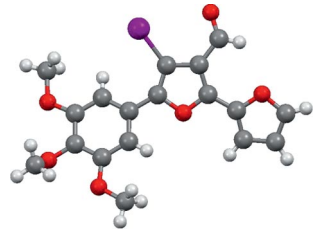
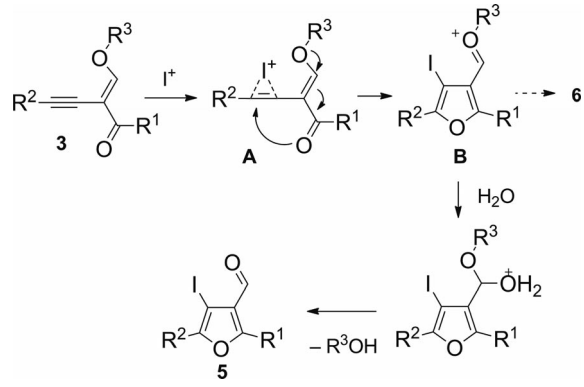


Figure 1. X-ray representation of crystal structure **5k**.

A plausible mechanism for the formation of the formyl iodofurans is shown in Scheme 3. The cyclization reactions are believed to proceed through activation of the carbon–carbon triple bond by coordination to $I^+$, and then subsequent intramolecular attack of the carbonyl oxygen (**A**) gives the corresponding oxonium cation **B**. Subsequent hydrolysis furnishes the desired formylfuran. In the absence of water, nucleophilic attack by the succinimide anion on **B** may occur to form hemiaminal ether **6**. Importantly, the present reaction conditions should avoid the formation of carcinogenic and volatile monohaloalkanes that are generally produced in iodocyclization–dealkylation processes.[4a,14]




Scheme 3. Mechanistic proposal.

## Conclusions

In summary, we have developed a flexible and practical protocol to produce fully substituted 3-formyl-4-iodofurans starting from terminal alkynes and readily accessible α-iodo β-alkoxy enones, which are used as β-ketoaldehyde equivalents. These compounds, which are not easily accessible by other means, are poised for subsequent functionalization

and should offer great opportunities as unique building blocks in synthesis, and particularly in the elaboration of chemical libraries.

## Experimental Section

**General Methods:** All reactions were performed under an open atmosphere, using commercial grade solvents, with the exception that reactions catalyzed by palladium were carried out under argon. Analytical thin layer chromatography was carried out on Merck silica 60/F-240 aluminium-backed plates. The developed chromatograms were visualized by UV absorbance. Flash chromatography was performed with Merck silica gel 60 (40–63 μm). The NMR spectroscopic data were recorded in the indicated solvent with either a 300 or 400 MHz spectrometer. Chemical shifts ($\delta$) are given relative to TMS ($\delta$ = 0.00 ppm) in parts per million (ppm) with the residual signals of the deuterated solvent used as the standards [$^1$H NMR ($CDCl_3$): $\delta$ = 7.26 ppm (s) and $^{13}$C NMR ($CDCl_3$): $\delta$ = 77.16 ppm (t)]. Coupling constants ($J$) are expressed in Hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet) and br. (broad). Commercially available reagents, including alkoxy enone **1b**, were used as purchased. Alkoxy enones **1a**, **1c**, and **1d** were prepared from the corresponding methyl ketones according to published procedures.[15]

**3-Iodo-4-methoxybut-3-en-2-one (2b):** Compound **2b** was prepared following a procedure reported in the literature.[9a]

**Representative Procedure for the Syntheses of α-Iodo β-Alkoxy Enones**

**2-Iodo-3-ethoxy-1-phenylprop-2-en-1-one (2a):** To a suspension of *N*-iodosuccinimide (7.02 g, 31.2 mmol) in dichloromethane (50 mL) were added acetic acid (2.68 mL, 46.8 mmol) and 3-ethoxy-1-phenylprop-2-en-1-one (4.58 g, 26 mmol). The reaction mixture was stirred at room temperature for 1 h and then cooled to 0 °C (ice bath). Triethylamine (14.5 mL, 104.0 mmol) was then added, and the reaction mixture was allowed to reach room temperature (1 h). After this time, it was successively washed with an aqueous $Na_2S_2O_3$ solution (3 × 20 mL) and then an aqueous $Na_2CO_3$ solution (3 × 20 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate) to give **2a** (5.34 g, 68% yield) as a white solid; m.p. 55–57 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.40 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 4.21 (q, $J$ = 7.1 Hz, 2 H, $CH_2$), 7.31 (s, 1 H, =CHO), 7.41–7.45 (m, 2 H, Ar), 7.49–7.51 (m, 1 H, Ar), 7.54–7.58 (m, 2 H, Ar) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 15.2 ($CH_3$), 71.7 ($CH_2$), 83.6 (C–I), 128.5, 128.9, 131.5 (CH Ar), 137.8 (C Ar), 167.3 (=CHO), 191.0 (C=O) ppm. GC–MS: $m/z$ = 302.

**4-Iodo-5-methoxy-2-methylpent-4-en-3-one (2c):** The reaction was performed on 4.7 mmol scale to give **2c** (766 mg, 64%) as an orange solid; m.p. 68–69 °C (dec.). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.07 [d, $J$ = 6.8 Hz, 6 H, $(CH_3)_2CH$], 3.23 [quint, $J$ = 6.8 Hz, 1 H, $(CH_3)_2CH$], 3.98 (s, 3 H, $OCH_3$), 7.50 (s, 1 H, =CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 19.8 [$(CH_3)_2CH$], 36.0 [$(CH_3)_2CH$], 62.4 ($OCH_3$), 82.1 (C–I), 163.4 (=CHO), 198.5 (CO) ppm. GC–MS: $m/z$ = 254.

**1-(2-Furyl)-2-iodo-3-methoxyprop-2-en-1-one (2d):** The reaction performed on 2.4 mmol scale to give **2d** (441 mg, 65%) as a yellow solid; m.p. 70–72 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.10 (s, 3 H, $CH_3$), 6.55 (dd, $J$ = 3.6 and 1.7 Hz, 1 H, Ar), 7.23 (dd, $J$ = 3.6 and 0.7 Hz, 1 H, Ar), 7.58 (dd, $J$ = 1.7 and 0.7 Hz, 1 H, Ar), 7.95 (s, 1 H, =CHO) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 62.5 ($CH_3$), 82.2 (C–I), 112.3, 118.8, 145.8 (CH Ar), 150.3 (C Ar), 166.6 (=CHO), 176.0 (CO) ppm. GC–MS: $m/z$ = 278.

**Representative Procedure for the Syntheses of α-Alkynyl β-Alkoxy Enones 3:** ***Caution!*** Because of the somewhat acid-sensitive nature of the title compounds, special care should be taken during the isolation and characterization processes. Although the compounds normally withstand classic workup and purification by flash chromatography on silica gel, leaving them in contact with silica gel (or $CDCl_3$) for prolonged periods of time resulted in gradual degradation. In a glass tube fitted with a Teflon® screw seal, the α-iodo enone (0.2 mmol) and the selected alkyne (0.25 mmol) were successively added to a solution of $PdCl_2(PPh_3)_2$ (7.5 mg, 0.01 mmol) and CuI (1 mg, 0.005 mmol) in a mixture of degassed $Et_3N$/toluene (1:1; 1 mL). The reactor was flushed with argon, and the reaction mixture was stirred at 40 °C for 1 h and then diluted with ethyl acetate (10 mL). The resulting solution was washed with brine (2 × 10 mL), and the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, appropriate mixture of cyclohexane/ethyl acetate) to afford the corresponding α-alkynyl enone. The (*E*) configuration was assigned on the basis of NOE spectroscopy.

**(*E*)-3-Ethoxy-1-phenyl-2-(phenylethynyl)prop-2-en-1-one (3aa′):** Tan oil (46 mg, 83%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.46 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 4.28 (q, $J$ = 7.1 Hz, 2 H, $CH_2$), 7.26–7.30 (m, 3 H, Ar), 7.36–7.41 (m, 2 H, Ar), 7.45 (d, $J$ = 7.6 Hz, 2 H, Ar), 7.50–7.56 (m, 1 H, Ar), 7.94 (dd, $J$ = 8.4 and 1.7 Hz, 2 H, Ar) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 15.5 ($CH_3$), 72.1 ($CH_2$), 82.9, 98.5, 103.8 (=C–C≡C), 123.7 (C Ar), 128.0, 128.1, 128.3, 129.2, 131.3, 132.0 (CH Ar), 138.5 (C Ar), 167.3 (=CHO), 192.3 (CO) ppm. HRMS (CI): calcd. for $C_{19}H_{17}O_2$ $[MH]^+$ 277.1223; found 277.1221.

**(*E*)-4-Methoxy-3-[(4-methoxycarbonyl)phenylethynyl]but-3-en-2-one (3bb′):** Yellow solid (39 mg, 75%); m.p. 124–126 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.44 (s, 3 H), 3.92 (s, 3 H), 4.03 (s, 3 H), 7.53 (d, $J$ = 8.5 Hz, 2 H), 7.71 (s, 1 H), 8.00 (d, $J$ = 8.5 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.4, 52.3, 63.1, 85.2, 96.6, 103.5, 128.0, 129.5, 129.6, 131.2, 166.5, 196.0 ppm. HRMS (CI): calcd. for $C_{15}H_{15}O_4$ $[MH]^+$ 259.0965; found 259.0965. The same reaction was performed on a 2 mmol scale to give **3bb′** (408 mg, 79%).

**General Procedure for Syntheses of 3-Formyl-4-iodofurans 5:** In a glass tube fitted with a Teflon® screw seal, α-iodo enone **2** (0.4 mmol) and the selected terminal alkyne (0.5 mmol) were successively added to a solution of $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and CuI (2 mg, 0.01 mmol) in a mixture of degassed $Et_3N$/toluene (1:1; 1 mL). The reactor was flushed with argon, and the reaction mixture was stirred at 40 °C for 1 h and then diluted with ethyl acetate (10 mL). The resulting solution was washed with brine (2 × 10 mL). The organic layer was concentrated in vacuo, and the resulting residue was dissolved in a mixture of $CH_2Cl_2$/water (1:1; 4 mL). *N*-iodosuccinimide (100 mg, 0.44 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (10 mL). The resulting solution was washed successively with an aqueous $Na_2S_2O_3$ solution (2 × 10 mL) and then HCl (1 N solution, 3 × 10 mL). The organic layer was dried with $MgSO_4$ and then concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, appropriate mixture of cyclohexane/ethyl acetate) to afford the corresponding furan **5**.

**4-Iodo-2-methyl-5-(4-methoxycarbonyl)phenylfuran-3-carbaldehyde (5a):** White solid (92 mg, 62%); m.p. 170–172 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.68 (s, 3 H, $CH_3$), 3.94 (s, 3 H, $OCH_3$), 8.04–8.12 (m, 4 H, Ar), 9.90 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.7 ($CH_3$), 52.4 ($OCH_3$), 63.6 (C–I), 122.2 (C Ar), 126.2 (CH Ar), 129.9 (CH Ar), 130.0 (C Ar), 133.3 (C Ar), 150.0 (=CO), 161.7 (=CO), 166.6 (O=CO), 187.7 (CHO) ppm. HRMS (CI): calcd. for $C_{14}H_{12}IO_4$ $[MH]^+$ 370.9775; found 370.9772.

**4-Iodo-2-methyl-5-phenylfuran-3-carbaldehyde (5b):** Yellow solid (109 mg, 87%); m.p. 74–75 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.67 (s, 3 H, $CH_3$), 7.39 (m, $J$ = 7.3 and 1.3 Hz, 1 H, Ar), 7.43–7.47 (m, 2 H, Ar), 7.95 (dd, $J$ = 7.3 and 1.3 Hz, 2 H, Ar), 9.91 (s, 1 H, CHO) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.6 ($CH_3$), 61.4 (C–I), 121.9 (C Ar), 126.8 (CH Ar), 128.6 (CH Ar), 129.0 (CH Ar), 129.3 (C Ar), 151.2 (=CO), 161.1 (=CO), 187.9 (CHO) ppm. HRMS (ESI): calcd for $C_{12}H_9INaO_2$ $[M + Na]^+$ 334.9539; found 334.9532. The same reaction was performed on 2 mmol scale to give **5b** (462 mg, 74%).

**4-Iodo-2-methyl-5-(4-methoxy)phenylfuran-3-carbaldehyde (5c):** Yellow solid (120 mg, 88%); m.p. 70–72 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.64 (s, 3 H, $CH_3$), 3.85 (s, 3 H, $OCH_3$), 6.97 (d, $J$ = 8.7 Hz, 2 H, Ar), 7.87 (d, $J$ = 8.7 Hz, 2 H, Ar), 9.88 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.5 ($CH_3$), 55.5 ($OCH_3$), 59.7 (C–I), 114.0 (CH Ar), 121.7 (C Ar), 121.9 (C Ar), 128.4 (CH Ar), 151.4 (=CO), 160.1 (=CO), 160.7 (=CO), 187.8 (CHO) ppm. HRMS (ESI): calcd. for $C_{13}H_{11}INaO_3$ $[M + Na]^+$ 364.9645; found 364.9649.

**4-Iodo-2-methyl-5-(4-fluoro)phenylfuran-3-carbaldehyde (5d):** Yellow solid (93 mg, 70%); m.p. 99–100 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.66 (s, 3 H, $CH_3$), 7.14 (t, $J$ = 8.8 Hz, 2 H, Ar), 7.92 (dd, $J$ = 8.8 and 5.1 Hz, 2 H, Ar), 9.89 (s, 1 H, CHO) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 12.4 ($CH_3$), 60.0 (C–I), 114.6 (d, $^2J_{C,F}$ = 21.8 Hz), 120.7 (C Ar), 124.4 (d, $^4J_{C,F}$ = 2.9 Hz), 127.7 (d, $^3J_{C,F}$ = 8.0 Hz), 149.4 (=CO), 160.0 (=CO), 161.8 (d, $^1J_{C,F}$ = 248.6 Hz), 186.5 (CHO) ppm. HRMS (CI): calcd. for $C_{12}H_9FIO_2$ $[MH]^+$ 330.9626; found 330.9623.

**4-Iodo-2-methyl-5-butylfuran-3-carbaldehyde (5e):** CuI (10 mol-%) and the alkyne (3 equiv.) were used to give **5e** (61 mg, 47%) as a tan oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.93 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 1.35 (sext, $J$ = 7.3 Hz, 2 H, $CH_2$), 1.60 (quint, $J$ = 7.3 Hz, 2 H, $CH_2$), 2.55 (s, 3 H, $CH_3$), 2.65 (t, $J$ = 7.3 Hz, 2 H, $CH_2$), 9.79 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.4 ($CH_3$), 13.9 ($CH_3$), 22.2 ($CH_2$), 26.8 ($CH_2$), 30.05 ($CH_2$), 62.2 (C–I), 120.5 (C Ar), 156.3 (=CO), 160.8 (=CO), 187.0 (CHO) ppm. HRMS (ESI): calcd. for $C_{10}H_{14}IO_2$ $[M]^+$ 293.0036; found 293.0033.

**4-Iodo-2-isopropyl-5-phenylfuran-3-carbaldehyde (5f):** Solid (101 mg, 75%); m.p. 44–46 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.36 [d, $J$ = 6.9 Hz, 6 H, $(CH_3)_2CH$], 3.73 [quint, $J$ = 6.9 Hz, 1 H, $(CH_3)_2CH$], 7.36–7.48 (m, 3 H, Ar), 7.96 (d, $J$ = 7.5 Hz, 2 H, Ar), 9.94 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.6 [$(CH_3)_2CH$], 27.3 [$(CH_3)_2CH$], 61.5 (C–I), 120.0 (C Ar), 126.8 (CH Ar), 128.6 (CH Ar), 128.9 (CH Ar), 129.4 (C Ar), 150.8 (=CO), 169.1 (=CO), 187.6 (CHO) ppm. HRMS (ESI): calcd. for $C_{14}H_{14}IO_2$ $[MH]^+$ 341.0033; found 341.0039.

**4-Iodo-2-isopropyl-5-(3,4,5-trimethoxy)phenylfuran-3-carbaldehyde (5g):** Solid (132 mg, 76%); m.p. 91–93 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.35 [d, $J$ = 6.9 Hz, 6 H, $(CH_3)_2CH$], 3.69 [quint, $J$ = 6.9 Hz, 1 H, $(CH_3)_2CH$], 3.88 (s, 3 H, $OCH_3$), 3.92 (s, 6 H, 2 $OCH_3$), 7.17 (s, 2 H, Ar), 9.92 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.6 [$(CH_3)_2CH$], 27.3 [$(CH_3)_2CH$], 56.4 ($OCH_3$), 61.0 ($OCH_3$), 61.1 (C–I), 104.4 (CH Ar), 120.0 (C Ar), 124.7 (C Ar), 138.8 (=CO), 150.6 (=CO), 153.3 (=CO), 168.9 (=CO), 187.3 (CHO) ppm. HRMS (ESI): calcd. for $C_{17}H_{20}IO_5$ $[MH]^+$ 431.0350; found 431.0347.

**4-Iodo-2,5-diphenylfuran-3-carbaldehyde (5h):** The reaction produced a 4:1 mixture of the two hardly separable products **5h** and its structural isomer 3-benzoyl-4-iodo-5-phenylfuran (combined yield of 70%). Data for **5h**: Yellow solid (70 mg, 45%); m.p. 85–87 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–7.53 (m, 6 H, Ar), 7.87–7.91 (m, 2 H, Ar), 8.06 (dd, $J$ = 6.9 and 1.6 Hz, 2 H), 10.09 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 61.8 (C–I), 121.9 (C Ar), 127.4 (CH Ar), 128.2 (C Ar), 128.5 (CH Ar), 128.7 (CH Ar), 129.0 (CH Ar), 129.2 (C Ar), 129.4 (CH Ar), 130.9 (CH Ar), 152.5 (=CO), 161.1 (=CO), 186.8 (CHO) ppm. HRMS (ESI): calcd for $C_{17}H_{11}INaO_2$ $[M + Na]^+$ 396.9696; found 396.9697. Data for 3-benzoyl-4-iodo-5-phenylfuran: This compound could not be obtained in pure form. $^1$H NMR (300 MHz, $CDCl_3$, deduced from the crude mixture): $\delta$ = 7.39–7.51 (m, 4 H, Ar), 7.57–7.62 (m, 1 H, Ar), 7.83 (s, 1 H, $H_{furyl}$), 7.88 (dd, $J$ = 8.3 and 1.5 Hz, 2 H, Ar), 7.99 (dd, $J$ = 8.3 and 1.5 Hz, 2 H, Ar) ppm.

**4-Iodo-2-phenyl-5-(4-methoxy)phenylfuran-3-carbaldehyde (5i):** Yellow solid (123 mg, 74%); m.p. 117–120 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.86 (s, 3 H, $OCH_3$), 7.00 (d, $J$ = 8.8 Hz, Ar), 7.49–7.52 (m, 3 H, Ar), 7.84–7.88 (m, 2 H, Ar), 10.06 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 55.5 ($OCH_3$), 60.2 (C–I), 114.1 (CH Ar), 121.8 (C Ar), 128.4 (CH Ar), 128.8 (CH Ar), 128.9 (CH Ar), 130.7 (CH Ar), 152.7 (=CO), 160.4 (=CO), 160.6 (=CO), 186.7 (CHO) ppm. HRMS (ESI): calcd. for $C_{18}H_{14}IO_3$ $[MH]^+$ 404.9982; found 404.9968.

**2-Furyl-4-iodo-5-phenylfuran-3-carbaldehyde (5j):** Solid (55 mg, 38%); m.p. 118–120 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 6.60 (dd, $J$ = 3.6, 1.7 Hz, 1 H, Ar), 7.39–7.50 (m, 4 H, Ar), 7.61 (d, $J$ = 0.9 Hz, 1 H, Ar), 8.03 (dd, $J$ = 7.0, 1.5 Hz, 2 H, Ar), 10.27 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 61.4 (C–I), 112.4 (CH Ar), 113.7 (CH Ar), 120.7 (C Ar), 127.3 (CH Ar), 128.6 (CH Ar), 129.0 (C Ar), 129.4 (CH Ar), 144.3 (C Ar), 145.2 (CH Ar), 150.9 (=CO), 151.9 (=CO), 186.4 (CHO) ppm. HRMS (ESI): calcd. for $C_{15}H_{10}IO_3$ $[MH]^+$ 364.9669; found 364.9678.

**2-Furyl-4-iodo-5-(3,4,5-trimethoxy)phenylfuran-3-carbaldehyde (5k):** Solid (103 mg, 55%); m.p. 159–160 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.91 (s, 3 H, $OCH_3$), 3.95 (s, 6 H, 2 $OCH_3$), 6.60 (dd, $J$ = 3.6 and 1.7 Hz, 1 H, Ar), 7.27 (s, 2 H, Ar), 7.41 (d, $J$ = 3.5 Hz, 1 H, Ar), 7.62 (d, $J$ = 1.7 Hz, 1 H, Ar), 10.26 (s, 1 H, CHO) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 56.4 ($OCH_3$), 61.0 (C–I), 61.1 ($OCH_3$), 104.9 (CH Ar), 112.4 (CH Ar), 113.7 (CH Ar), 120.8 (C Ar), 124.2 (C Ar), 139.2 (=CO), 144.2 (C Ar), 145.2 (C Ar), 150.7 (=CO), 151.8 (=CO), 153.3 (=CO), 186.4 (CHO) ppm. HRMS (ESI): calcd. for $C_{18}H_{16}IO_6$ $[MH]^+$ 454.9986; found 454.9980.

**Characterization for Compound 6:** Compound **6** was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/ethyl acetate) to give a yellow solid; m.p. 131–133 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.58 (s, 3 H, $CH_3$), 2.72 [s, 4 H, $(CH_2)_2$], 3.46 (s, 3 H, $OCH_3$), 3.92 (s, 3 H, $CO_2CH_3$), 6.03 (s, 1 H, NCHO), 7.99–8.07 (m, 4 H, Ar) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.4 ($CH_3$), 28.2 ($CH_2$), 52.3 ($OCH_3$), 57.2 ($OCH_3$), 65.4 (C–I), 80.7 (NCHO), 118.0 (C Ar), 125.6 (CH Ar), 129.1 (C Ar), 129.8 (CH Ar), 134.3 (C Ar), 148.5 (=CO), 154.3 (=CO), 166.9 (OC=O), 176.1 (NC=O) ppm. HRMS (ESI): calcd. for $C_{19}H_{18}INNaO_6$ $[M + Na]^+$ 506.0071; found 506.0077.

**Supporting Information** (see footnote on the first page of this article): Crystal data for compounds **5k** and **6** and $^1$H and $^{13}$C NMR spectra for compounds **5**.

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