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From domino to multicomponent: synthesis of dihydroisobenzofurans

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ABSTRACT

A variety of substituted dihydroisobenzofurans can be easily synthesized in high yields by a one-pot three-component approach starting from *o*-bromoarylaldehydes, methanol, and terminal alkynes. The reaction occurs through an unprecedented cooperative palladium/base promoted coupling/addition/cyclization sequence.

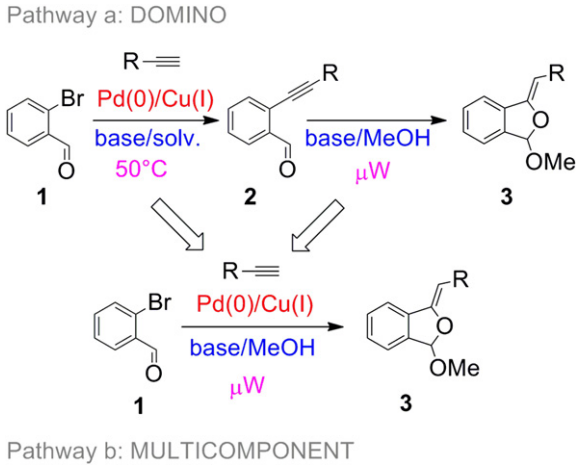
1. Introduction

Multicomponent reactions (MCRs) are a powerful tool for the synthesis of complex molecules starting from readily available building blocks in a 'well-contrived' one-pot sequential procedure.[1] These approaches allow an overall reduction of the time required to obtain the desired product with an advantageous economy of solvents and energy and an overall reduction of waste production. MCRs have been widely used for the preparation of heterocyclic structures,[2] as well as key steps in the total synthesis of natural products.[3] Moreover, the enhancing power of microwaves in MCRs has been recently highlighted.[4]

The dihydroisobenzofuran nucleus is the core of some important biologically active molecules, such as BcF,[5] a compound under investigation as a more lipophilic analogue of the anti-HIV drug d4T (Stavudine),[6] and two diterpenes from the Antarctic sponge *Dendrilla membranosa* called membranolides C and D,[7] that showed antimycotic and antibiotic activity against *Candida albicans* and Gram-negative bacteria.

In the literature there are some examples of the base-promoted domino synthesis of dihydroisobenzofurans and related systems in the presence of different nucleophiles.[8]

We also recently reported a selective synthesis of the dihydroisobenzofuran skeleton by a microwave-promoted domino addition/annulation reaction of 2-alkynylbenzaldehydes and methanol in the presence of a suitable base.[9] The overall process involves two steps (Scheme 1, pathway a): (1) the palladium catalyzed functionalization of the 2-bromobenzaldehyde **1** with a proper monosubstituted acetylene derivative and (2) the base promoted microwave-assisted domino addition/annulation reaction of the 2-alkynylbenzaldehyde derivative **2** in the presence of methanol, to give the desired dihydroisobenzofuran **3**.



Scheme 1.

We wanted to simplify and improve this procedure. The two steps of the domino approach have two common requirements: base and energy. In the first step, it is assumed that the role of the base is to promote the Sonogashira coupling by abstracting the

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acetylenic proton from the terminal alkyne,[10] whereas in the second step, the role of the base is to activate the nucleophile.[8] Furthermore, microwave radiation—that so effectively can promote the cyclization step[9]—could also assist the Sonogashira reaction.[11] Thus a proper choice of base and reaction temperature could be key factors for the success of the planned strategy. Moreover the reagents featured in each step do not seemed to hamper the multicomponent approach; on contrary, the use of methanol as solvent for the Sonogashira coupling is well known[12] and palladium could also assist the cyclization step enhancing the reactivity of triple bond, in particular in the presence of less reactive alkyne derivatives.[13]

On the basis of these preliminary remarks, we planned a novel microwave-enhanced three-component synthesis of the dihydroisobenzofuran nucleus involving a one-pot coupling/addition/annulation reaction (Scheme 1, pathway b) promoted by palladium and base.

In the literature there are some example of MCR's involving a Sonogashira coupling as key step for the synthesis of different heterocycles, such as pyrazoles,[14] isoxazoles,[14,15] halofurans,[16] substituted and annulated pyridines,[17] pyrimidines,[18] dihydroisoquinolines,[19] indoles,[20] indolizines,[21] furo[2,3-*b*]pyridones,[22] thiochromen-4-ones,[23] thiopyran-4-ones,[24] tetrahydro-β-carbolines,[25] and pyrano[4,3-*b*]quinolines[26] but to the best of our knowledge, this is the first example of a multicomponent synthesis of dihydroisobenzofurans.

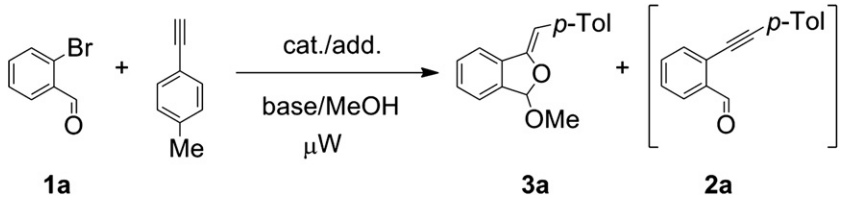
2. Results and discussion

First, we looked for the optimum reaction conditions. The screening was performed with 2-bromobenzadehyde **1a**, methanol, and 1-ethynyl-4-methylbenzene as a model system, and the results are reported in Table 1. The first experiment was performed under the standard Sonogashira conditions ($Pd(PPh_3)_4$, CuI, and K_2CO_3) but with methanol as solvent and at a higher temperature by microwave irradiation. After 1 h at 110 °C the reaction gave the desired product **3a** in a promising 75% yield, with traces of the simple coupling product **2a** (Table 1, entry 1). The reduction of reaction temperature resulted in a worse yield in a twofold time (Table 1, entry 2). In the presence of 3 equiv of a stronger base, such as *t*-BuOK (i.e., using a base analogous to that employed in Cassar reaction condition)[27] the outcome was satisfactory at 80 °C in 2 h (Table 1, entry 3), whereas rising the temperature to 110 °C gave poorer results (Table 1, entry 4). These results suggested that the use of a stronger base allowed the reaction to work at lower temperature. Next we tried to fine-tune-up the reaction conditions. The reduction of the amount of base to 1 equiv made the reaction sluggish, and the alkyne **2a** was the main product detected in the crude reaction mixture (Table 1, entry 5). We were pleasured to find that dichloro bis(triphenyl-phosphine)palladium(II)—cheaper than tetrakis triphenyl-phosphine palladium—gave slightly better results (Table 1, entry 6). A further lowering of the temperature to 60 °C gave a worse result in a twofold reaction time (Table 1, entry 7). The studies on copper-free Sonogashira coupling (more correctly named Cassar–Heck coupling) are widely reported in the literature,[28] and we were delighted to observe that our multicomponent approach also worked well under these favorable conditions, in spite of a modest reduction of yield (Table 1, entry 8). Also, half loading of the catalyst/cocatalyst gave consistent results in the same reaction time (Table 1, entry 9). Finally, on the basis of recent studies on palladium-free coupling between terminal alkynes and aryl halides, we tested some alternative metal promoted routes by means of copper iodide,[29] silver triflate[30] or gold iodide[31] in the presence of an appropriate phosphine ligand, but unfortunately all these conditions did not give noteworthy results (Table 1, entries 10–12).

With the best conditions in hand, we tested the scope and limitation of the approach by changing the substitution pattern on the triple bond, on the benzaldehyde framework and modifying the nature of the aromatic aldehyde. The reactions proceeded with complete regiospecificity, leading to the formation of the corresponding 5-*exo*-*dig* heterocycles in high yields. The (*Z*)-configuration of the exocyclic double bond was established by comparison with literature data[8] and our previous findings.[9] The results are depicted in the Table 2.

Electron-poor phenylacetylenes gave excellent yields under standard conditions (Table 2, entries 1 and 2), whereas in the presence of an electron-donating group on the aryl moiety (Table 2, entry 3) the best result was obtained at 130 °C. When the electron donating substituent on the aryl framework was in a sterically

Table 1
Optimization of the reaction conditions

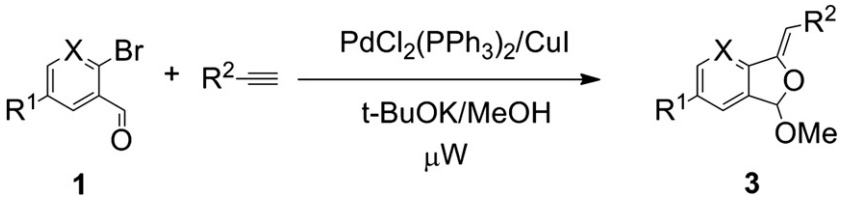


1a **3a** **2a**

Entry	Base	Catalyst	Co-catalyst/ligand	Time (h)	Temp (°C)	**3a** (Yield %)[a]	**2a** (Yield %)[a]
1	K_2CO_3 (5 equiv)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	1	110	75	3
2	K_2CO_3 (5 equiv)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	63	17
3	*t*-BuOK (3 equiv)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	80	2
4	*t*-BuOK (3 equiv)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	1	110	63	1
5	*t*-BuOK (1 equiv)	$Pd(PPh_3)_4$ (2 mol %)	CuI (2 mol %)	2	80	30[b]	60[b]
6	***t*-BuOK (3 equiv)**	**$PdCl_2(PPh_3)_2$ (2 mol %)**	**CuI (2 mol %)**	**2**	**80**	**82**[c]	—
7	*t*-BuOK (3 equiv)	$PdCl_2(PPh_3)_2$ (2 mol %)	CuI (2 mol %)	4	60	70	3
8	*t*-BuOK (3 equiv)	$PdCl_2(PPh_3)_2$ (2 mol %)	—	2	80	67	2
9	*t*-BuOK (3 equiv)	$PdCl_2(PPh_3)_2$ (1 mol %)	CuI (1 mol %)	2	80	72	1
10	*t*-BuOK (3 equiv)	CuI (10 mol %)	PPh_3 (2 mol %)	4	60	—	—
11	*t*-BuOK (3 equiv)	AgOTf (10 mol %)	PPh_3 (3 mol %)	2	80	—	—
12	*t*-BuOK (3 equiv)	AuI (1 mol %)	dppf (1 mol %)	4	80	Trace	—

[a] Yields refer to pure isolated product.
[b] Yields calculated from ^{1}H NMR spectroscopy of the reaction crude.
[c] Under conventional heating the reaction was complete in 2 h and gave **3a** in 71% yield.

Table 2
Scope and limitation of the three-component approach to dihydroisobenzofuran derivatives

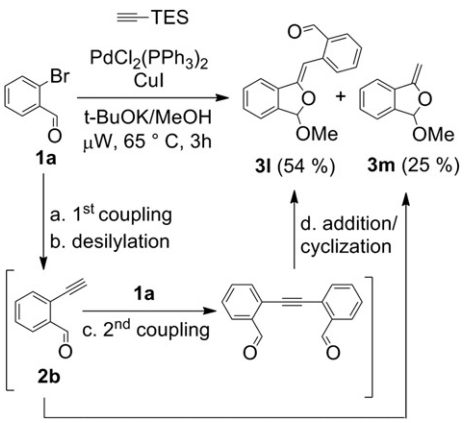


Entry	X	R^1	Aldehyde	R^2	Time (h)	Temp (°C)	Product	Yield[a] (%)
1	CH	–H	**1a**	*m*-CF_3–Ph–	2	80	**3b**	88
2	CH	–H	**1a**	*m*-F–Ph–	2	80	**3c**	92
3	CH	–H	**1a**	*p*-MeO–Ph–	2	130	**3d**	99
4	CH	–H	**1a**	*p*-MeO–(*o*-Me)–Ph–	4	130	**3e**	79
5	CH	–H	**1a**	$(EtO)_2$–CH–	2	80	**3f**	89
6	N	–H	**1b**	*p*-CH_3–Ph–	2	80	**3g**	66
7	N	–H	**1b**	*p*-CH_3–Ph–	2	60	**3g**	78
8	N	–H	**1b**	*m*-F–Ph–	2	60	**3h**	85
9	N	–H	**1b**	$(EtO)_2CH$–	1	60	**3i**	77
10	CH	–F	**1c**	Ph–	2	80	**3j**	98
11	CH	–OMe	**1d**	Ph–	2.5	80	**3k**	88

[a] Yields refer to pure isolated product.

demanding *ortho*-position, a twofold reaction time was required (Table 2, entry 4). When the triple bond was substituted with an acetal moiety the reaction gave the corresponding dihydroisobenzofuran **3f** in very good yield (Table 2, entry 5).[32] The approach was also effective starting from the electron-poor 2-bromonicotinaldehyde **1b** (Table 2, entry 6), but for this more reactive substrate best results were obtained lowering the temperature to 60 °C (Table 2, entries 7–9). Finally, the effect of electron-withdrawing and electron-donating groups on the 2-bromobenzaldehyde was briefly investigated (Table 2, entries 10 and 11). In the first case the yields are excellent under standard conditions (Table 2, entry 10), whereas in the presence of EDG the best result was obtained in a quite longer reaction time (Table 2, entry 11). Unfortunately, several attempts to react aliphatic alkynes under the standard MCR conditions completely failed, also in the presence of catalytic amounts of gold salts.[33]

A different result was observed in the reaction of **1a** with triethylsilylacetylene (TES). The main product obtained was **3l** along with a minor amount of the expected desilylated compound **3m**. This is probably due to an early desilylation path occurring after the Sonogashira coupling, followed by a second coupling of terminal acetylene **2b** with **1a**, and a final addition/cyclization step to give **3l** (Scheme 2).



Scheme 2.

According to literature, the reaction mechanism probably involves an earlier Sonogashira coupling (testified by the isolation of the coupling product if the reaction partners were reacted for an insufficient reaction time), followed by a sequential base triggered addition/annulation cascade. The involvement of metal in the activation of the triple bond during the cyclization step was not investigated but at the moment, it cannot be ruled out. This contribution has been proven on the related cyclization of carbonyl groups on alkynes, activated with palladium/copper,[13,34] gold/silver[35] and also ruthenium or tungsten.[36] Moreover it is worth noting that the 5-*exo*-*dig* cyclization observed here with palladium is quite different to the cyclization observed in similar reactions with different benzylic *O*-nucleophiles catalyzed by gold, which proceeds by a 6-*endo*-*dig* ring closure.[37]

3. Conclusions

In summary, we have successfully transformed the previously reported two-step domino approach[9] to dihydroisobenzofurans into an unprecedented high yielding MCR. The strategy demonstrated tolerance to a variety of substituents on both alkynyl and aldehyde partners. Moreover the approach was successfully applied to the preparation of related dihydrofuro[3,4-*b*]pyridines. With respect to the domino approach, this MCR allows a slight improvement on reaction yields together with a considerable reduction in operative steps, reaction times, and consumption of energy, solvent and reagents.

4. Experimental section

4.1. General

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Catalysts were purchased from Sigma–Aldrich. Silica gel F_{254} thin-layer plates were employed for thin-layer chromatography (TLC). Silica gel 40–63 μ/60Å was employed for flash column chromatography. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer using KBr tablets for solids and NaCl disks for oils. Proton NMR spectra were recorded at room temperature, at 200 or 500 MHz, with the resonance of solvent as the

internal reference. ^{13}C NMR spectra were recorded at room temperature at 50.3 or 125.75 MHz, with the resonance of solvent as the internal reference. The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. 2D-NOESY spectra were acquired at 500 MHz in the phase-sensitive TPPI mode with 2 K×256 complex FIDs, spectral width of 5682 Hz, recycling delay of 3 s, 8 scans and a mixing time of 1.3 s. All spectra were transformed and weighted with a 90° shifted sine-bell squared function to 1 ×1 K real data points. Microwave assisted reactions were performed in multimode oven, using 12 mL sealed glass vessels. The reaction times specified in Tables 1 and 2 include 'ramp times'. The internal temperature was detected with a fiber optic sensor.

4.2. Representative procedure for the synthesis of compounds 3

In a 12 mL MW glass vessel, a mixture of the appropriate 2-bromoarylaldehyde **1** (1 mmol), alkyne (1.2 mmol), *t*-BuOK (337 mg, 3 mmol), and $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol) in dry methanol (4 mL) was stirred at room temperature under a nitrogen atmosphere for 10 min, then CuI (3.81 mg, 0.02 mmol) was added. The reactor vessel was sealed and the stirred mixture was heated at the suitable temperature for the proper time in a multimode microwave oven (for times and temperatures see Table 2). After cooling, the reaction mixture was poured into $NaHCO_3$ satd soln (20 mL) and extracted with ethyl acetate (3×10 mL). The organic layer, dried over Na_2SO_4, was evaporated under reduced pressure. The reaction crude was purified by flash column chromatography on SiO_2 (40–63 μm). Compounds **3a**–**c**, **e** are known.[9]

*4.2.1. (Z)-1-Methoxy-3-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (**3d**).* Yield: 201 mg (75%). R_f (5% EtOAc/hexane) 0.15. Eluent for chromatography: hexane/EtOAc/TEA (99:1:0.6). Orange solid; mp 97–99 °C. IR (KBr): ν_{max}=2897, 2838, 1693, 1604, 1508, 1467, 1377, 1115, 1088, 844, 763 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=3.49 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.96 (s, 1H, C_{sp2}–H), 6.56 (s, 1H, C_{sp3}–H), 6.91 (d, *J*=8.4 Hz, 2H, arom.), 7.35–7.60 (m, 4H, arom.), 7.73 (d, *J*=8.4 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ=54.3, 55.5, 98.1, 107.5, 114.2, 119.7, 123.3, 128.8, 128.9, 129.8, 130.1, 136.0, 136.9, 151.8, 158.2 ppm. ESI-MS: *m*/*z* (%)=291 (95) $[M+Na]^+$, 237 (100) $[M-OCH_3]^+$. HRMS (ESI) calcd for $C_{17}H_{16}O_3Na(+1)$, 291.0992. Found: 291.0990.

*4.2.2. (Z)-1-(2,2-Diethoxyethylidene)-3-methoxy-1,3-dihydroisobenzofuran (**3f**).* Yield: 235 mg (89%). R_f (20% EtOAc/hexane) 0.34. Eluent for chromatography: hexane/EtOAc/TEA (90:10:0.6). Pale yellow oil. IR (neat, NaCl): ν_{max}=2975, 2930, 2881, 1689, 1469, 1373, 1116, 1092, 1054, 994, 954, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=1.25 (t, *J*=6.8 Hz, 6H, $2CH_3$), 3.42 (s, 3H, CH_3), 3.53–3.80 (m, 4H, $2CH_2$), 5.21 (d, *J*=7.6 Hz, 1H, CH), 5.61 (d, *J*=7.6 Hz, 1H, CH), 6.40 (s, 1H, CH), 7.39–7.51 (m, 4H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=15.5, 54.3, 61.4, 95.7, 97.7, 106.9, 120.6, 123.2, 129.7, 130.0, 134.3, 138.0, 155.0 ppm. ESI-MS: *m*/*z* (%)=287 (100) $[M+Na]^+$, 219 (25) $[M-OEt]^+$. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.09; H, 7.65.

*4.2.3. (Z)-5-Methoxy-7-(4-methylbenzylidene)-5,7-dihydrofuro[3,4-b]pyridine (**3g**).* Yield: 197 mg (78%). R_f (40% EtOAc/hexane) 0.30. Eluent for chromatography: hexane/EtOAc/TEA (90:10:0.6). Orange solid; mp 122–126 °C. IR (KBr): ν_{max}=2954, 2924, 1667, 1583, 1422, 1378, 1117, 1085, 943, 790 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=2.36 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 6.49 (s, 1H, CH), 6.56 (s, 1H, CH), 7.17–7.29 (m, 3H, arom.), 7.70–7.80 (m, 3H, arom.), 8.66 (dd, *J*=5.1, 1.5 Hz, 1H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=21.5, 54.9, 100.4, 105.8, 122.9, 129.2, 129.4, 130.4, 131.6, 132.6, 136.6, 150.6, 152.2, 154.7 ppm. ESI-MS: *m*/*z* (%)=254 (100) $[M+1]^+$. MS–MS: *m*/*z* (%)=222 (100) $[M-OCH_3]$. HRMS (ESI) calcd for $C_{16}H_{16}NO_2(+1)$, 254.1176. Found: 254.1175.

*4.2.4. (Z)-7-(3-Fluorobenzylidene)-5-methoxy-5,7-dihydrofuro[3,4-b]pyridine (**3h**).* Yield: 220 mg (85%). R_f (40% EtOAc/hexane) 0.26. Eluent for chromatography: hexane/EtOAc/TEA (85:15:0.6). Orange solid; mp 89–93 °C. IR (KBr): ν_{max}=3069, 2939, 1671, 1613, 1579, 1485, 1443, 1423, 1385, 1271, 1146, 1118, 1089, 945, 785, 680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=3.60 (s, 3H, CH_3), 6.48 (s, 1H, CH), 6.56 (s, 1H, CH), 6.87–6.97 (m, 1H, arom.), 7.26–7.37 (m, 2H, arom.), 7.47 (d, *J*=7.7 Hz, 1H, arom.), 7.59–7.67 (m, 1H, arom.), 7.79 (dd, *J*=7.7, 1.1 Hz, 1H, arom), 8.68 (dd, *J*=4.8, 1.5 Hz, 1H, arom.) ppm. ^{13}C NMR (50.3 MHz, CDCl3, APT): δ=55.3, 99.2 (d, $^4J_{C,F}$=2.7 Hz), 106.3, 113.5 (d, $^2J_{C,F}$=21.7 Hz), 115.5 (d, $^2J_{C,F}$=22.5 Hz), 123.4, 124.9 (d, $^4J_{C,F}$=2.7 Hz), 129.9 (d, $^3J_{C,F}$=8.4 Hz), 130.8, 131.7, 137.7 (d, $^3J_{C,F}$=8.4 Hz), 152.1, 152.4, 154.2, 160.8, 165.6 (d, $^1J_{C,F}$=244 Hz) ppm. ESI-MS: *m*/*z* (%)=258 (100) $[M+1]^+$. MS–MS: *m*/*z* (%)=226 (100) $[M-OCH_3]$. HRMS (ESI) calcd for $C_{15}H_{12}NO_2F(+1)$, 258.0925. Found: 258.0925.

*4.2.5. (Z)-7-(2,2-Diethoxyethylidene)-5-methoxy-5,7-dihydrofuro[3,4-b]pyridine (**3i**).* Yield: 204 mg (77%). R_f (40% EtOAc/hexane) 0.20. Eluent for chromatography: hexane/EtOAc/TEA (80:20:0.6). Orange oil. IR (neat, NaCl): ν_{max}=2975, 2931, 2897, 1695, 1588, 1424, 1376, 1119, 1093, 1055, 993, 948, 792 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=1.24 (t, *J*=6.9 Hz, 6H, $2CH_3$), 3.49 (s, 3H, CH_3), 3.57–3.79 (m, 4H, $2CH_2$), 5.62 (d, *J*=7.7 Hz, 1H, CH), 5.72 (d, *J*=7.7 Hz, 1H, CH), 6.39 (s, 1H, CH), 7.25–7.31 (m, 1H, arom.), 7.74 (dd, *J*=7.7, 1.1 Hz, 1H, arom.), 8.65 (dd, *J*=4.8, 1.5 Hz, 1H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=15.5, 55.0, 61.1, 97.2, 97.8, 105.3, 123.7, 131.4, 131.5, 152.3, 153.1, 153.4 ppm. ESI-MS: *m*/*z* (%)=288 (80) $[M+Na]^+$, 220 (100) $[M-OEt]^+$. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H 7.22; N, 5.28. Found: C, 63.44; H, 7.23; N, 5.26.

*4.2.6. (Z)-1-Benzylidene-5-fluoro-3-methoxy-1,3-dihydroisobenzofuran (**3j**).* Yield: 250 mg (98%). R_f (10% EtOAc/hexane) 0.28. Eluent for chromatography: hexane/EtOAc/TEA (99:1:0.6). Red oil. IR (neat, NaCl): ν_{max}=3064, 2935, 1666, 1618, 1595, 1493, 1483, 1449, 1370, 1255, 1142, 1119, 1084, 964, 783, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=3.52 (s, 3H, CH_3), 5.93 (s, 1H, CH), 6.52 (s, 1H, CH), 7.12–7.26 (m, 3H, arom.), 7.32–7.40 (m, 2H, arom.), 7.50–7.57 (m, 1H, arom), 7.74–7.78 (m, 2H, arom.) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=54.6, 98.3 (d, $^6J_{C,F}$=2.3 Hz), 106.9 (d, $^4J_{C,F}$=2.7 Hz), 110.5 (d, $^2J_{C,F}$=24.0 Hz), 117.9 (d, $^2J_{C,F}$=24.0 Hz), 121.6 (d, $^3J_{C,F}$=9.1 Hz), 126.2, 128.5, 128.6, 131.8 (d, $^4J_{C,F}$=2.7 Hz), 135.9, 139.2 (d, $^3J_{C,F}$=8.8 Hz), 152.3, 161.1, 166.1 (d, $^1J_{C,F}$=249 Hz) ppm. ESI-MS: *m*/*z* (%)=257 (100) $[M+1]^+$. MS–MS: *m*/*z* (%)=225 (100) $[M-OCH_3]$. Anal. Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H 5.11. Found: C, 75.08; H, 5.07.

*4.2.7. (Z)-1-Benzylidene-3,5-dimethoxy-1,3-dihydroisobenzofuran (**3k**).* Yield: 206 mg (77%). R_f (10% EtOAc/hexane) 0.13. Eluent for chromatography: hexane/EtOAc/TEA (98:2:0.6). Red solid; mp 64–67 °C. IR (KBr): ν_{max}=2915, 2838, 1659, 1612, 1492, 1454, 1369, 1262, 1035, 964, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ=3.51 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.86 (s, 1H, C–H), 6.52 (s, 1H, C–H), 6.94–7.03 (m, 2H, arom.), 7.12–7.21 (m, 1H, arom.), 7.31–7.39 (m, 2H, arom.), 7.49 (d, *J*=8.4 Hz, 1H, arom.), 7.75 (dd, *J*=8.4, 1.1 Hz, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz, APT): δ=54.3, 55.9, 96.8, 107.2 (two signals), 117.8, 121.2, 125.7, 128.3, 128.4, 128.6, 136.4, 138.9, 153.3, 161.2 ppm. ESI-MS: *m*/*z* (%)=269 (100) $[M+1]^+$. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H 6.01. Found: C, 76.04; H, 6.08.

*4.2.8. (Z)-2-((3-Methoxyisobenzofuran-1(3H)-ylidene)methyl)benzaldehyde (**3l**).* Yield: 71 mg (54%). R_f (5% EtOAc/hexane) 0.10. Eluent for chromatography: hexane/EtOAc/TEA (95:5:0.6). Dark yellow oil. IR (KBr): ν_{max}=2933, 2836, 1692, 1647, 1612, 1594, 1484, 1467, 1375,

1205, 1117, 1089, 946, 762 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): δ=3.22 (s, 3H, CH_3), 6.29 (s, 1H, C–H), 7.04–7.10 (m, 2H, arom.), 7.12–7.21 (m, 1H, arom.), 7.19 (m, 1H, arom.), 7.38 (dt, J=7.8, 1.5 Hz, 1H, arom.), 7.52 (dd, J=6.6, 1.4 Hz, 1H, arom.), 7.59 (s, 1H, C–H), 7.63 (dd, J=7.7, 1.4 Hz, 1H, arom.), 8.57 (dd, J=8.0, 0.6 Hz, 1H, arom.), 10.2 (s, 1H, CHO) ppm. ^{13}C NMR (C_6D_6, 125.75 MHz, APT): δ=53.0, 92.7, 107.2, 119.9, 122.3, 125.6, 128.6, 129.2, 129.5, 131.8, 132.2, 132.9, 134.8, 136.8, 134.8, 155.1, 191.8 ppm. ESI-MS: m/z (%)=267 (100) $[M+1]^+$. MS–MS: m/z (%)=235 (100) [M–OCH_3]. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H 5.30. Found: C, 76.64; H, 5.31.

*4.2.9. 1-Methoxy-3-methylene-1,3-dihydroisobenzofuran (**3m**).* Yield: 41 mg (25%). R_f (5% EtOAc/hexane) 0.26. Eluent for chromatography: hexane/EtOAc/TEA (98:2:0.6). Yellow oil. IR (NaCl): ν_{max}=3079, 2934, 1668, 1467, 1377, 1210, 1100, 982, 766, 749 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz): δ=3.14 (s, 3H, CH_3), 4.54 (d, 1H, J=2.1 Hz, =CH_2), 4.73 (d, 1H, J=2.1 Hz, =CH_2), 6.09 (s, 1H, C–H), 6.91–6.96 (m, 2H, arom.), 7.05–7.13 (m, 2H, arom.) ppm. ^{13}C NMR (C_6D_6, 50.3 MHz, APT): δ=54.7, 81.2, 107.4, 121.2, 124.0, 129.9, 130.4, 135.7, 139.6, 160.4 ppm. APCI-MS: m/z (%)=163 (100) $[M+1]^+$. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H 6.21. Found: C, 74.12; H, 6.17.

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Supplementary data

Supplementary data associated with this article (^1H, ^{13}C, and HSQC NMR spectra for compounds **3a**–**m**) can be found in online version at doi:10.1016/j.tet.2010.12.056. These data include MOL files and InChIKeys of the most important compounds described in this article.

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