A Concise Route to 2-Amino-3-aryl-3*H*-benzofurans and their Use as Precursors to 3-Aryl-3*H*-benzofuran-2-one and 1*H*-Benzofuro[2,3-*b*]pyridin-2-one Derivatives

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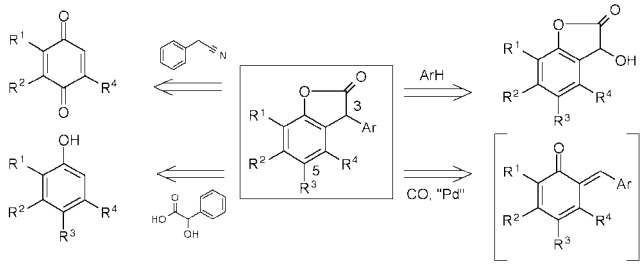
To the memory of Solange Gerster

Abstract: A concise approach to 2-amino-3-aryl-3*H*-benzofurans based on the Michael addition of NaCN onto in situ generated substituted *o*-quinone methides has been developed. Straightforward access to 3-aryl-3*H*-benzofuran-2-ones was achieved upon acidic hydrolysis whereas *N*-Boc-protected 2-amino-3-aryl-3*H*-benzofurans underwent smooth intramolecular cyclisation to give 1*H*-benzofuro[2,3-*b*]pyridin-2-one derivatives.

Key words: furans, Michael additions, quinones, cyclisations, heterocycles

3-Aryl-3*H*-benzofuran-2-ones are an important class of excellent heat stabilisers for polymers.[1] Therefore considerable effort has been devoted to their preparation (Scheme 1). One of the earliest synthetic approaches involved the acid[2]- and thermally[3]-promoted condensation of mandelic acid or mandelonitrile with phenols, which restricted the choice of the 3-aryl-substituent to phenyl, or phenyl substituted with electron donating groups. The addition of benzylcyanides to *p*-benzoquinones afforded in moderate yields benzofuranones bearing a hydroxy substituent at position 5 of the phenyl ring.[4] Additional versatility in the synthesis of this type of compound was recently introduced with a two-step synthesis involving an acid-catalysed cyclocondensation of phenols with glyoxylic acid, followed by the alkylation of the intermediate 3-hydroxy-3*H*-benzofuran-2-ones with aromatic or heteroaromatic hydrocarbons under Friedel–Crafts or acid catalysis.[5] Pd-catalysed CO insertion with *o*-quinone methides has also been used successfully for the synthesis of 3-aryl-3*H*-benzofuran-2-ones.[6]



Scheme 1 Selected synthetic routes to 3-aryl-3*H*-benzofuran-2-ones

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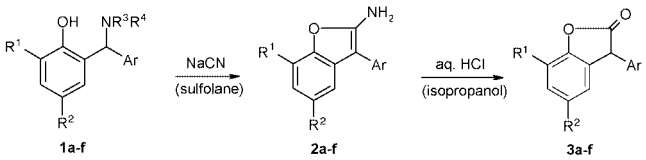
Herein we report a new and simple approach to 3-aryl-3*H*-benzofuran-2-ones **3** (Scheme 2) as well as the further transformation of the key-intermediate 2-amino-3-aryl-3*H*-benzofurans **2** into the new tetracyclic compounds **6** (Scheme 3).

The key-step in the new synthetic route takes advantage of the well-established reactivity of quinone methides with nucleophiles[7]and emphasizes once more their importance as intermediates in organic transformations. The aminoalkylated phenols[6,8]**1** obtained via Mannich reaction of phenols with an aromatic aldehyde and a secondary amine were used as precursors to the *o*-quinone methides. The reactions were performed in sulfolane, at sufficiently high temperature (120 °C) to ensure the thermal decomposition of the Mannich bases to the *o*-quinone methides, which then functioned as efficient Michael acceptors towards sodium cyanide present in a small excess. The addition products were not isolated, as spontaneous intramolecular cyclisation occurred to afford in good yields the 2-amino-3-aryl-3*H*-benzofurans **2**. The latter were readily hydrolysed under acidic catalysis to afford the 3-aryl-3*H*-benzofuran-2-ones **3** in good yields (Scheme 2). Some typical results obtained are summarised in Table 1.



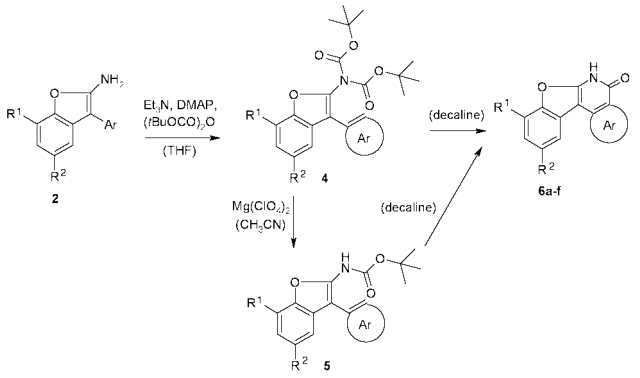
Scheme 2 Synthesis of 3-aryl-3*H*-benzofuran-2-one derivatives **3**

The new 2-amino-3-aryl-3*H*-benzofurans **2** are convenient starting materials for new heterocycles otherwise difficult to obtain. Thus, the *N*-Boc-protected 2-amino-3-aryl-3*H*-benzofuran derivatives **4** and **5** underwent thermal cyclisation to afford the 1*H*-benzofuro[2,3-*b*]pyridin-2-one derivatives **6** as depicted in Scheme 3. The reaction of **2** with di-*tert*-butyl dicarbonate gave high yields of the bis-*N*-Boc-protected amines **4** which were then selectively deprotected upon treatment with a catalytic amount of magnesium perchlorate[9] in acetonitrile to afford **5**. This two-step approach to the carbamates **5** was chosen, as the mono-protection of **2** gave unsatisfactory yields. With the same efficiency, both **4** and **5** underwent thermal ring closure when heated in decaline. Remarkably, no Friedel–

Table 1 Synthesis of 2-Amino-3-aryl-3*H*-benzofurans **2** and of 3-Aryl-3*H*-benzofuran-2-ones **3** ($R^1 = R^2 = t$-Bu)

Ar	**2**	Yield (%), Mp (°C)	**3**	Yield (%), Mp (°C)
Phenyl	**a**[a]	99, 176–178	**a**	85, 116–119
3,4-Dimethylphenyl	**b**[a]	86, 128–130	**b**	96, 130–132
3,4-Dimethoxyphenyl	**c**[a]	95, 172–174	**c**	82 –
p-Bromophenyl	**d**[b]	77, 154–158	**d**	87, 135–136
p-Thiomethylphenyl	**e**[b]	82, 140–141	**e**	85, 133–135
o-Methoxyphenyl	**f**[b]	83 –	**f**	66, 157–159

[a] Obtained from **1** where $NR^3R^4 = NMe_2$
[b] Obtained from **1** where NR^3R^4 = piperidine



Scheme 3 Synthesis of 1*H*-benzofuro[2,3-*b*]pyridin-2-one derivatives **6**

Crafts or Lewis acid catalysis was required for this transformation. The results are summarised in Table 2.

In conclusion, a simple synthetic route to 3-aryl-3*H*-benzofuran-2-ones has been developed. Its success relied on the transformation of Mannich bases to 2-amino-3-aryl-3*H*-benzofurans upon treatment with sodium cyanide, which then underwent rapid acidic hydrolysis to afford good yields of 3-aryl-3*H*-benzofuran-2-ones. Further utility of the intermediate 2-amino-3-aryl-3*H*-benzofurans was demonstrated in the synthesis of novel 1*H*-benzofuro[2,3-*b*]pyridin-2-one derivatives obtained upon intramolecular thermally-induced cyclisation of *N*-Boc-protected 2-amino-3-aryl-3*H*-benzofurans.

The mps were determined on a Büchi 540 capillary apparatus and are not corrected. IR spectra were registered on a Nicolet–Magna-IR™ spectrometer 750. The ^{1}H NMR spectra were recorded in $CDCl_3$, for ^{1}H in ppm relative to $CDCl_3$ ($\delta = 7.26$), for ^{13}C in ppm relative to $CDCl_3$ ($\delta = 77$), on a Bruker ACS 120 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or on a Bruker ACS 60 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The EI mass spectra were measured by GC-MS (HP-5890 gas chromatograph with a Finnigan MAT SSQ 710 mass spectrometer) or by direct introduction (DEP). The APCI mass spectra were measured by LC-MS (Waters-Micromass ZQ). The ESI-HRMS were measured on a QSTAR XL spectrometer operated in positive ion mode. Microanalyses were obtained using a LECO-CHNS-932 element analyser and a LECO-RO-478 element analyser.

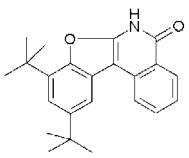
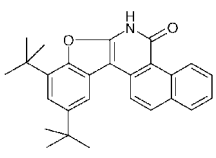
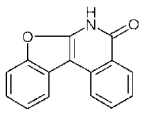
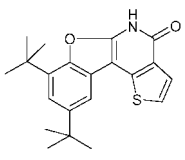
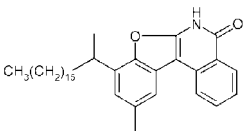
2,4-Di-*tert*-butyl-6-(dimethylaminophenylmethyl)phenol (1a); Typical Procedure

A mixture of 2,4-di-*tert*-butylphenol (51.5 g, 0.25 mol), benzaldehyde (26.5 g, 0.25 mol) and an aq solution of dimethylamine (40%; 42.3 g, 0.38 mol) was heated to 140 °C in a closed vessel for 10 h. The reaction mixture was cooled down to r.t. The residue was crystallised in *i*-PrOH to give **1a**. Compounds **1b** and **1c** were also prepared according to this procedure.

Yield: 65.2 g (77%); white solid; mp 120–123 °C.

IR (neat): 3738, 2954, 2865, 1438, 1360, 1247, 884, 759, 668 cm^{-1}.

Table 2 Synthesis of **6** from Bis-*N*-Boc-protected Amines **4**

6	Structure	Yield (%), Mp (°C)	**6**	Structure	Yield (%), Mp (°C)
a[a]		80, >300	**d**		72, >300
b		81, 275–279	**e**		62, >300
c		39, 126–131			

[a] **6a** was also obtained in 73% from **5**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.38 (s, 1 H, OH), 7.50–7.40 (m, 2 H, ArH), 7.35–7.20 (m, 3 H, ArH), 7.14 (d, *J* = 2.4 Hz, 1 H, ArH), 6.74 (d, *J* = 2.4 Hz, 1 H, ArH), 4.34 (s, 1 H, C*H*Ar), 2.27 (s, 6 H, NCH_3), 1.45 (s, 9 H, *t*-Bu), 1.19 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ =152.2 (C), 139.1 (C), 138.9 (C), 134.7 (C), 127.5 (CH), 127.3 (CH), 126.4 (CH), 123.4 (C), 122.4 (CH), 121.3 (CH), 76.6 (CH), 42.0 (CH_3), 33.8 (C), 32.9 (C), 30.4 (CH_3), 28.4 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 340 (97) [M + 1$^+$], 295 (100).

Anal. Calcd for $C_{23}H_{33}NO$: C, 81.37; H, 9.80; N, 4.13; O, 4.71. Found: C, 81.31; H, 9.64; N, 4.08; O, 4.58.

2,4-Di-*tert*-butyl-6-[dimethylamino-(3,4-dimethylphenyl)methyl]phenol (1b)

IR (neat): 2952, 2864, 2779, 1467, 1437, 1360, 1248, 1229, 1183, 883, 819, 720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.48 (s, 1 H, OH), 7.22–7.10 (m, 3 H, ArH), 7.08–7.00 (m, 1 H, ArH), 6.75 (d, *J* = 2.1 MHz, 1 H, ArH), 4.28 (s, 1 H, C*H*Ar), 2.25 (s, 6 H, CH_3), 2.22 (s, 6 H, CH_3), 1.44 (s, 9 H, *t*-Bu), 1.19 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9 (C), 140.3 (C), 138.0 (C), 136.9 (C), 136.2 (C), 130.4 (CH), 130.1 (CH), 126.5 (C), 125.3 (CH), 124.1 (CH), 122.7 (CH), 77.9 (CH), 43.6 (CH_3), 35.4 (C), 34.5 (C), 32.1 (CH_3), 30.0 (CH_3), 20.3 (CH_3), 19.8 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 368 (92) [M + 1$^+$], 323 (100).

Anal. Calcd for $C_{25}H_{37}NO$: C, 81.69; H, 10.15; N, 3.81. Found: C, 81.78; H, 9.95; N, 3.80.

2,4-Di-*tert*-butyl-6-[(3,4-dimethoxyphenyl)dimethylaminomethyl]phenol (1c)

IR (neat): 2948, 2866, 2656, 1596, 1516, 1456, 1228, 1140, 1034, 883, 823, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.51 (s, 1 H, OH), 7.20–7.10 (m, 2 H, ArH), 6.92–6.88 (m, 1 H, ArH), 6.80–6.72 (m, 2 H, ArH), 4.24 (s, 1 H, C*H*Ar), 3.85 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.27 (s, 6 H, NCH_3), 1.44 (s, 9 H, *t*-Bu), 1.20 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9 (C), 147.8 (C), 147.2 (C), 139.0 (C), 134.7 (C), 132.3 (C), 123.8 (C), 122.3 (CH), 121.1 (CH), 119.9 (CH), 109.7 (CH), 109.4 (CH), 76.4 (CH), 54.5 (CH_3), 54.4 (CH_3), 42.0 (CH_3), 33.7 (C), 32.8 (C), 30.4 (CH_3), 28.3 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 400 (26) [M + 1$^+$], 355 (100).

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51; O, 12.01. Found: C, 75.23; H, 9.33; N, 3.38; O, 11.97.

2-[(4-Bromophenyl)piperidin-1-ylmethyl]-4,6-di-*tert*-butylphenol (1d); Typical Procedure

Piperidine (17 mL, 173 mmol) was added dropwise at r.t. to a solution of *p*-bromobenzaldehyde (14.5 g, 78.6 mmol) in toluene (50 mL). The reaction mixture was heated under reflux for 4 h with concomitant removal of H_2O. It was then cooled to 90 °C and a solution of 2,4-di-*tert*-butylphenol (15.4 g, 74.7 mmol) in toluene (25 mL) was added slowly. The reaction mixture was heated under reflux for 15 h. After cooling to r.t., the solvent was evaporated. MeOH (70 mL) was added to the oily residue and the solution was stirred at 60 °C for 30 min. A precipitate formed which was filtered off, washed with cold MeOH (2 × 25 mL) to give **1d**. Compounds **1e** and **1f** were also prepared according to this procedure.

Yield: 30.8 g (90%); white solid; mp 166–168 °C.

IR (neat): 2963, 2935, 2863, 1487, 1436, 1248, 1232, 1010, 875, 827, 722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.30 (s, 1 H, OH), 7.38–7.15 (m, 4 H, ArH), 7.07 (d, *J* = 2.4 Hz, 1 H, ArH), 6.63 (d, *J* = 2.4 Hz, 1 H, ArH), 4.30 (s, 1 H, C*H*Ar), 2.45–2.15 (br s, 4 H, NCH_2), 1.60–1.50 (br s, 6 H, $NCH_2CH_2CH_2$), 1.36 (s, 9 H, *t*-Bu), 1.12 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7 (C), 140.7 (C), 139.6 (C), 136.5 (C), 132.1 (CH), 130.8 (CH), 124.5 (C), 124.1 (CH), 123.0 (CH), 121.8 (C), 77.0 (CH), 52.7 (CH_2), 35.4 (C), 34.5 (C), 32.0 (CH_3), 30.0 (CH_3), 26.3 (CH_2), 24.5 (CH_2).

MS (EI): *m*/*z* (%) = 459, 457 (14) [M$^+$], 374 (14), 371 (15), 359 (23), 357 (25), 294 (20), 293 (100), 171 (15), 84 (43), 57 (22), 41 (11).

Anal. Calcd for $C_{26}H_{36}BrNO$: C, 68.11; H, 7.91; Br, 17.43; N, 3.05; O, 3.49. Found: C, 68.14; H, 7.98; Br, 17.5; N, 3.02; O, 3.47.

2,4-Di-*tert*-butyl-6-[(4-methylsulfanylphenyl)piperidin-1-ylmethyl]phenol (1e)

IR (neat): 2942, 2866, 2599, 1840, 1478, 1436, 1231, 860, 826, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.50 (br s, 1 H, OH), 7.40–7.25 (m, 2 H, ArH), 7.20–7.15 (m, 2 H, ArH), 7.14 (d, *J* = 2.4 MHz, 1 H, ArH), 6.72 (d, *J* = 2.4 MHz, 1 H, ArH), 4.39 (s, 1 H, C*H*Ar), 2.70–2.20 (m, 4 H, NCH_2), 2.46 (s, 3 H, SCH_3), 1.70–1.50 (m, 6 H, $NCH_2CH_2CH_2$), 1.44 (s, 9 H, *t*-Bu), 1.19 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2 (C), 140.8 (C), 138.2 (C), 137.5 (C), 136.6 (C), 130.0 (CH), 127.2 (CH), 125.2 (C), 124.5 (CH), 123.1 (CH), 77.3 (CH), 53.0 (CH_2), 35.7 (C), 34.8 (C), 32.3 (CH_3), 30.3 (CH_3), 26.7 (CH_2), 24.9 (CH_2), 16.3 (CH_3).

MS (EI): *m*/*z* (%) = 425 (14) [M$^+$], 340 (23), 339 (18), 325 (24), 293 (100), 137 (12), 84 (10), 57 (9).

Anal. Calcd for $C_{27}H_{39}NOS$: C, 76.18; H, 9.23; N, 3.29; O, 3.76; S, 7.53. Found: C, 75.87; H, 8.90; N, 3.13; O, 3.76; S, 7.56.

2,4-Di-*tert*-butyl-6-[(2-methoxyphenyl)piperidin-1-ylmethyl]phenol (1f)

IR (neat): 2936, 2867, 2811, 1602, 1588, 1475, 1434, 1247, 1089, 1033, 877, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.68 (s, 1 H, OH), 7.55–7.45 (m, 1 H, ArH), 7.26–7.15 (m, 1 H, ArH), 7.13 (d, *J* = 2.0 MHz, 1 H, ArH), 6.95–6.82 (m, 2 H, ArH), 6.82–6.65 (m, 1 H, ArH), 5.25 (s, 1 H, C*H*Ar), 3.86 (s, 3 H, OCH_3), 3.00–2.00 (m, 4 H, NCH_2), 1.70–1.50 (br s, 6 H, $NCH_2CH_2CH_2$), 1.44 (s, 9 H, *t*-Bu), 1.19 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1 (C), 153.2 (C), 138.6 (C), 134.4 (C), 128.6 (CH), 127.1 (CH), 126.7 (C), 123.8 (C), 122.9 (CH), 121.0 (CH), 119.7 (CH), 109.6 (CH), 64.9 (CH), 54.4 (CH_3), 32.9 (C), 33.0 (C), 30.6 (CH_3), 28.5 (CH_3), 25.0 (CH_2), 23.2 (CH_2).

MS (EI): *m*/*z* (%) = 409 (16) [M$^+$], 309 (8), 293 (100), 161 (4), 121 (4), 84 (11), 57 (7).

Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.19; H, 9.60; N, 3.42; O, 7.81. Found: C, 79.15; H, 9.65; N, 3.35; O, 7.72.

2-Amino-3-phenyl-5,7-di-*tert*-butylbenzofuran (2a); Typical Procedure

Sodium cyanide (0.98 g, 20.0 mmol) dissolved in the minimum amount of H_2O (2.0 mL) was added to 2,4-di-*tert*-butyl-6-(dimethylaminophenylmethyl)phenol (**1a**) (3.39 g, 10.0 mmol) in sulfolane (10 mL). The mixture was stirred for 1 h at 120 °C under nitrogen. After cooling to r.t., the yellow–orange mixture was poured into *tert*-butyl methyl ether (80 mL) and washed with H_2O (80 mL). The layers were separated and the organic phase repeatedly washed with H_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give **2a**.

Yield: 2.80 g (87%); yellow solid; mp 176–178 °C.

IR (KBr): 3344, 2958, 1781, 1640, 1600, 1422, 979, 760, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.50 (m, 4 H, ArH), 7.43 (d, *J* = 1.8 Hz, 1 H, ArH), 7.38–7.28 (m, 1 H, ArH), 7.15 (d, *J* = 1.8 Hz, 1 H, ArH), 4.31 (br s, 2 H, NH_2), 1.57 (s, 9 H, *t*-Bu), 1.42 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6 (C), 146.6 (C), 146.4 (C), 134.4 (C), 133.1 (C), 130.4 (C), 129.8 (CH), 128.3 (CH), 126.4 (CH), 116.6 (CH), 112.4 (CH), 95.0 (C), 35.5 (C), 35.0 (C), 32.6 (CH_3), 30.6 (CH_3).

GCMS (EI): *m*/*z* (%) = 322 (17) [M + 1$^+$], 321 (100) [M$^+$], 306 (28), 279 (8), 250 (5), 222 (5), 153 (10), 139 (12), 57 (6).

Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36; O, 4.98. Found: C, 82.05; H, 8.39; N, 4.31; O, 4.92.

5,7-Di-*tert*-butyl-3-(3,4-dimethylphenyl)benzofuran-2-ylamine (2b)

IR (neat): 3321, 2960, 2872, 1650, 1598, 1455, 1362, 1081, 984 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.05 (m, 4 H, ArH), 6.88 (d, *J* = 1.8 Hz, 1 H, ArH), 4.03 (br s, 2 H, NH_2), 2.15 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 1.32 (s, 9 H, *t*-Bu), 1.17 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5 (C), 144.8 (C), 144.4 (C), 136.1 (C), 133.0 (C), 131.2 (C), 129.9 (C), 129.2 (CH), 128.8 (C), 127.8 (CH), 124.1 (CH), 114.6 (CH), 110.7 (CH), 93.2 (C), 33.7 (C), 33.1 (C), 30.8 (CH_3), 28.9 (CH_3), 18.7 (CH_3), 18.3 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 350 (100) [M + 1$^+$].

HRMS (ESI): *m*/*z* (%) calcd for $C_{24}H_{32}NO$ [M + H$^+$]: 350.2483; found: 350.2424.

5,7-Di-*tert*-butyl-3-(3,4-dimethoxyphenyl)benzofuran-2-ylamine (2c)

IR (neat): 3476, 3350, 2958, 2906, 1656, 1516, 1247, 1026, 996, 856, 815 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 2.1 Hz, 1 H, ArH), 7.12–6.95 (m, 4 H, ArH), 4.21 (br s, 2 H, NH_2), 3.94 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 1.50 (s, 9 H, *t*-Bu), 1.35 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0 (C), 149.9 (C), 147.7 (C), 146.3 (C), 146.1 (C), 132.9 (C), 130.4 (C), 126.7 (C), 120.4 (CH), 116.3 (CH), 112.5 (CH), 112.0 (CH), 111.7 (CH), 94.7 (C), 56.4 (CH_3), 56.3 (CH_3), 35.3 (C), 34.8 (C), 32.4 (CH_3), 30.5 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 382 (100) [M + 1$^+$].

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67; O, 12.58. Found: C, 75.51; H, 8.09; N, 3.57; O, 12.63.

3-(4-Bromophenyl)-5,7-di-*tert*-butylbenzofuran-2-ylamine (2d)

IR (KBr): 3415, 3330, 2962, 2904, 2868, 2383, 1649, 1489, 1427, 988 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 2 H, ArH), 7.55–7.50 (m, 2 H, ArH), 7.42 (d, *J* = 2.1 Hz, 1 H, ArH), 7.21 (d, *J* = 2.1 Hz, 1 H, ArH), 4.37 (br s, 2 H, NH_2), 1.65 (s, 9 H, *t*-Bu), 1.47 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4 (C), 146.4 (C), 133.2 (C), 133.0 (C), 132.7 (CH), 129.8 (C), 129.7 (CH), 119.7 (C), 116.6 (CH), 111.9 (CH), 93.8 (C), 35.3 (C), 34.8 (C), 32.4 (CH_3), 30.5 (CH_3).

MS (EI): *m*/*z* (%) = 401, 399 (100) [M$^+$], 386 (26), 384 (26), 193 (24), 192 (24), 179 (34), 178 (36), 131 (21), 57 (71), 41 (19).

Anal. Calcd for $C_{22}H_{26}BrNO$: C, 66.00; H, 6.55; Br, 19.96; N, 3.50; O, 4.00. Found: C, 65.81; H, 6.52; Br, 19.7; N, 3.39; O, 4.16.

5,7-Di-*tert*-butyl-3-(4-methylsulfanylphenyl)benzofuran-2-ylamine (2e)

IR (neat): 3430, 3348, 2956, 2904, 2867, 1650, 1595, 1500, 1425, 1360, 984, 859, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.50 (m, 2 H, ArH), 7.48–7.38 (m, 3 H, ArH), 7.14 (d, *J* = 2.1 Hz, 1 H, ArH), 4.30 (br s, 2 H, NH_2), 2.58 (s, 3 H, SCH_3), 1.56 (s, 9 H, *t*-Bu), 1.42 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3 (C), 146.4 (C), 146.2 (C), 135.9 (C), 132.9 (C), 131.1 (C), 130.1 (C), 128.6 (CH), 128.1 (CH), 116.4 (CH), 112.1 (CH), 94.3 (C), 35.3 (C), 34.7 (C), 32.4 (CH_3), 30.5 (CH_3), 16.6 (CH_3).

GCMS (EI): *m*/*z* (%) = 368 (23) [M + 1$^+$], 367 (100) [M$^+$], 352 (16), 176 (17), 162 (15), 57 (7).

Anal. Calcd for $C_{23}H_{29}NOS$: C, 75.16; H, 7.95; N, 3.81; O, 4.35; S, 8.72. Found: C, 75.10; H, 7.77; N, 3.60; O, 4.37; S, 8.69.

5,7-Di-*tert*-butyl-3-(2-methoxyphenyl)benzofuran-2-ylamine (2f)

IR (KBr): 3345, 2962, 2293, 1424, 1376, 1039 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 1 H, ArH), 7.40–7.30 (m, 2 H, ArH), 7.20–7.05 (m, 3 H, ArH), 4.46 (br s, 2 H, NH_2), 3.95 (s, 3 H, OCH_3), 1.57 (s, 9 H, *t*-Bu), 1.41 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4 (C), 153.9 (C), 146.8 (C), 145.7 (C), 132.6 (C), 131.0 (C), 130.7 (CH), 127.8 (CH), 122.7 (C), 121.9 (CH), 116.0 (CH), 112.6 (CH), 91.1 (C), 56.5 (CH_3), 35.3 (C), 34.8 (C), 32.4 (CH_3), 30.5 (CH_3).

GCMS (EI): *m*/*z* (%) = 352 (21) [M + 1$^+$], 351 (100) [M$^+$], 336 (13), 280 (6), 168 (15), 154 (7), 57 (12).

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98; O, 9.10. Found: C, 78.32; H, 8.33; N, 3.85; O, 9.14.

5,7-Di-*tert*-butyl-3-phenyl-3*H*-benzofuran-2-one (3a); Typical Procedure

HCl (2 N; 4.8 mL, 9.58 mmol) was added at r.t. to 2-amino-3-phenyl-5,7-di-*tert*-butylbenzofuran (**2a**) (3.08 g, 9.58 mmol) in *i*-PrOH (10 mL). The mixture was stirred for 1.5 h. The precipitate was then filtered off and washed with *i*-PrOH. The yellow residue was dried under high vacuum (10^{-2} mbar) to give **3a**.

Yield: 2.75 g (85%); pale yellow solid; mp 116–119 °C.

IR (neat): 2960, 2871, 1800, 1076, 893, 881, 747, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 4 H, ArH), 7.25–7.10 (m, 2 H, ArH), 7.10–7.00 (m, 1 H, ArH), 4.83 (s, 1 H, C*H*Ar), 1.44 (s, 9 H, *t*-Bu), 1.29 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (C), 147.7 (C), 145.3 (C), 133.5 (C), 131.4 (C), 127.0 (CH), 126.3 (CH), 126.0 (CH), 124.7 (C), 121.2 (CH), 117.6 (CH), 47.6 (CH), 32.8 (C), 32.4 (C), 29.5 (CH_3), 27.6 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 323 (100) [M + 1$^+$].

Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.93; H, 8.13.

5,7-Di-*tert*-butyl-3-(3,4-dimethylphenyl)-3*H*-benzofuran-2-one (3b)

IR (neat): 2958, 2871, 1800, 1483, 1224, 1117, 1070, 902, 878, 813, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 1 H, ArH), 7.15–7.08 (m, 1 H, ArH), 7.08–6.98 (m, 2 H, ArH), 6.95–6.88 (m, 1 H, ArH), 4.76 (s, 1 H, C*H*Ar), 2.25 (s, 6 H, CH_3), 1.44 (s, 9 H, *t*-Bu), 1.29 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4 (C), 150.2 (C), 147.6 (C), 137.8 (C), 136.9 (C), 133.7 (C), 133.4 (C), 130.7 (CH), 130.1 (CH),

127.5 (C), 126.1 (CH), 123.6 (CH), 120.1 (CH), 49.8 (CH), 35.3 (C), 34.8 (C), 32.0 (CH_3), 30.1 (CH_3), 20.2 (CH_3), 19.8 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 351 (100) [M + 1$^+$].

Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 81.91; H, 8.90.

5,7-Di-*tert*-butyl-3-(3,4-dimethoxyphenyl)-3*H*-benzofuran-2-one (3c)

IR (neat): 2958, 2871, 1794, 1518, 1234, 1075, 1026, 901, 756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 1 H, ArH), 7.02–6.95 (m, 1 H, ArH), 6.80–6.65 (m, 3 H, ArH), 4.71 (s, 1 H, C*H*Ar), 3.80 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.37 (s, 9 H, *t*-Bu), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (C), 150.1 (C), 149.8 (C), 149.3 (C), 147.7 (C), 133.8 (C), 128.2 (C), 127.2 (C), 123.6 (CH), 121.0 (CH), 120.2 (CH), 112.0 (CH), 111.9 (CH), 56.3 (CH_3), 56.2 (CH_3), 49.5 (CH), 35.2 (C), 34.8 (C), 32.0 (CH_3), 30.0 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 383 (100) [M + 1$^+$].

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.35; H, 7.93.

3-(4-Bromophenyl)-5,7-di-*tert*-butyl-3*H*-benzofuran-2-one (3d)

IR (neat): 2961, 2867, 1810, 1480, 1360, 1071, 1013, 912, 811, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.60 (m, 2 H, ArH), 7.52–7.48 (m, 1 H, ArH), 7.30–7.22 (m, 2 H, ArH), 7.18–7.15 (m, 1 H, ArH), 4.94 (s, 1 H, C*H*Ar), 1.58 (s, 9 H, *t*-Bu), 1.44 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C), 147.7 (C), 145.5 (C), 132.5 (C), 131.6 (C), 130.2 (CH), 128.0 (CH), 124.4 (C), 121.6 (CH), 120.2 (C), 117.5 (CH), 47.1 (CH), 32.8 (C), 32.4 (C), 29.6 (CH_3), 27.6 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 403, 401 (100) [M + 1$^+$].

Anal. Calcd for $C_{22}H_{25}BrO_2$: C, 65.84; H, 6.28; Br, 19.91; O, 7.97. Found: C, 65.83; H, 6.32; Br, 19.7; O, 7.94.

5,7-Di-*tert*-butyl-3-(4-methylsulfanylphenyl)-3*H*-benzofuran-2-one (3e)

IR (neat): 2965, 2871, 1796, 1613, 1477, 1077, 910, 812 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.42 (m, 1 H, ArH), 7.30–7.23 (m, 2 H, ArH), 7.22–7.15 (m, 2 H, ArH), 7.10–7.05 (m, 1 H, ArH), 4.82 (s, 1 H, C*H*Ar), 2.50 (s, 3 H, SCH_3), 1.53 (s, 9 H, *t*-Bu), 1.32 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0 (C), 149.2 (C), 146.8 (C), 138.0 (C), 132.9 (C), 131.7 (C), 128.2 (CH), 126.5 (CH), 126.1 (C), 122.8 (CH), 119.0 (CH), 48.6 (CH), 34.3 (C), 33.8 (C), 31.0 (CH_3), 29.1 (CH_3), 15.2 (CH_3).

HPLC-MS (APCI): *m*/*z* (%) = 369 (100) [M + 1$^+$].

Anal. Calcd for $C_{23}H_{28}O_2S$: C, 74.96; H, 7.66; S, 8.70. Found: C, 74.80; H, 7.78; S, 8.75.

5,7-Di-*tert*-butyl-3-(2-methoxyphenyl)-3*H*-benzofuran-2-one (3f)

IR (neat): 2955, 2871, 1799, 1458, 1263, 1117, 1078, 931, 912, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 3 H, ArH), 7.05–6.95 (m, 1 H, ArH), 6.95–6.85 (m, 2 H, ArH), 4.94 (s, 1 H, C*H*Ar), 3.71 (s, 3 H, OCH_3), 1.49 (s, 9 H, *t*-Bu), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8 (C), 155.5 (C), 148.2 (C), 145.1 (C), 131.2 (C), 128.9 (CH), 127.9 (CH), 126.2 (C), 123.8 (C), 120.9 (CH), 119.4 (CH), 117.0 (CH), 110.2 (CH), 54.1 (CH_3), 44.8 (CH), 33.1 (C), 32.7 (C), 30.0 (CH_3), 28.0 (CH_3).

GCMS (EI): *m*/*z* (%) = 353 (21) [M + 1$^+$], 352 (95) [M$^+$], 337 (25), 309 (28), 297 (14), 296 (77), 294 (21), 293 (100), 240 (17), 203 (26), 147 (38), 104 (22), 91 (22), 57 (34), 41 (16).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.06; H, 8.20.

Compound 4a; Typical Procedure

Et_3N (3.3 mL, 24.0 mmol) was added to a solution of 2-amino-3-phenyl-5,7-di-*tert*-butylbenzofuran (**2a**) (7.00 g, 21.8 mmol) in anhyd THF (70 mL). The mixture was stirred for 20 min. at r.t. under nitrogen, whereupon DMAP (266 mg, 21.8 mmol) and di-*tert*-butyl dicarbonate (9.52 g, 43.6 mmol) were added. The resulting red mixture was then heated under reflux for 90 min. After cooling to r.t., the mixture was poured into H_2O (150 mL) and extracted with Et_2O (200 mL). The organic phase was repeatedly washed with H_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give **4a**.

Yield: 11.2 g (99%); light yellow resin.

IR (neat): 2964, 1799, 1759, 1730, 1368, 1242, 1143, 1087, 869, 846, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.15 (m, 7 H, ArH), 1.45 (s, 9 H, *t*-Bu), 1.30 (s, 9 H, *t*-Bu), 1.21 (s, 18 H, *t*-BuO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3 (C), 148.9 (C), 145.9 (C), 142.5 (C), 134.2 (C), 132.1 (C), 129.3 (CH), 128.4 (CH), 127.8 (CH), 119.9 (CH), 114.6 (CH), 83.8 (C), 35.4 (C), 34.9 (C), 32.3 (CH_3), 30.3 (CH_3), 28.1 (CH_3).

MS (EI): *m*/*z* (%) = 521 (3) [M$^+$], 421 (3), 365 (100), 321 (34), 306 (17), 57 (71), 41 (11).

8,10-Di-*tert*-butyl-6*H*-7-oxa-6-azabenzo[*c*]fluoren-5-one (6a); Typical Procedure

A solution of **4a** (24.4 g, 46.7 mmol) in decaline (200 mL) was stirred for 20 h at 200 °C. The reaction mixture was cooled down and a precipitate formed which was filtered off. The solid was washed with hexane (2 × 10 mL) and dried under high vacuum (10^{-2} mbar) to give **6a**.

Yield: 13.0 g (80%); white solid; mp > 300 °C.

IR (KBr): 2957, 2907, 2871, 1642, 1603, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.40–11.60 (br s, 1 H, NH), 8.62 (d, *J* = 8.0 MHz, 1 H, ArH), 8.23 (d, *J* = 8.0 MHz, 1 H, ArH), 7.90 (s, 1 H, ArH), 7.88 (t, *J* = 8.0 MHz, 1 H, ArH), 7.53 (t, *J* = 8.0 MHz, 1 H, ArH), 7.35 (s, 1 H, ArH), 1.60 (s, 9 H, *t*-Bu), 1.50 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9 (C), 150.1 (C), 148.9 (C), 147.5 (C), 134.9 (C), 134.6 (C), 133.9 (CH), 129.7 (CH), 125.2 (CH), 125.1 (C), 123.3 (C), 122.9 (CH), 118.9 (CH), 114.4 (CH), 96.2 (C), 35.5 (C), 35.0 (C), 32.4 (CH_3), 30.5 (CH_3).

MS (EI): *m*/*z* (%) = 348 (21) [M + 1$^+$], 347 (100) [M$^+$], 332 (50), 304 (58), 276 (64), 152 (14), 57 (10).

Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03; O, 9.21. Found: C, 79.41; H, 7.35; N, 4.00; O, 9.10.

6*H*-7-Oxa-6-azabenzo[*c*]fluoren-5-one (6b)

IR (neat): 2730, 1653, 1627, 1452, 880, 855, 761, 735 cm^{-1}.

^{1}H NMR (300 MHz, THF-d_8): δ = 8.50–8.38 (m, 1 H, ArH), 8.38–8.25 (m, 1 H, ArH), 8.20–8.10 (m, 1 H, ArH), 7.90–7.75 (m, 1 H, ArH), 7.65–7.52 (m, 1 H, ArH), 7.52–7.25 (m, 3 H, ArH).

^{13}C NMR (75 MHz, THF-d_8): δ = 159.9 (C), 151.9 (C), 150.7 (C), 132.5 (C), 131.0 (CH), 126.7 (CH), 123.4 (C), 122.9 (CH), 122.2 (CH), 121.6 (CH), 121.0 (CH), 120.6 (C), 118.0 (CH), 109.4 (CH), 94.1 (C).

MS (EI): *m*/*z* (%) = 236 (14) [M + 1$^+$], 235 (100) [M$^+$], 206 (17), 178 (5), 152 (11), 117 (7), 76 (11).

Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95; O, 13.60. Found: C, 76.38; H, 4.01; N, 5.92; O, 13.57.

10-Methyl-8-(1-methylheptadecyl)-6*H*-7-oxa-6-azabenzo[*c*]fluoren-5-one (6c)

IR (neat): 2921, 2851, 1627, 1602, 1434, 1333, 1184, 1134, 838, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.65 (br s, 1 H, NH), 8.54 (d, *J* = 7.5 MHz, 1 H, ArH), 8.10 (d, *J* = 8.1 MHz, 1 H, ArH), 7.77 (t, *J* = 7.2 MHz, 1 H, ArH), 7.57 (s, 1 H, ArH), 7.43 (t, *J* = 7.5 MHz, 1 H, ArH), 6.91 (s, 1 H, ArH), 3.35–3.15 (m, 1 H, C*H*CH_3), 2.46 (s, 3 H, ArC*H*$_3$), 1.80–1.55 (m, 2 H), 1.32 (d, *J* = 6.9 MHz, 3 H, CHC*H*$_3$), 1.30–1.00 (m, 28 H), 0.85–0.70 (m, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (C), 150.5 (C), 149.1 (C), 134.9 (C), 134.3 (C), 133.9 (CH), 131.8 (CH), 129.6 (C), 125.2 (CH), 124.7 (C), 123.2 (C), 122.9 (CH), 117.5 (CH), 96.5 (C), 36.5 (CH_2), 34.1 (CH_3), 32.3 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 22.2 (CH_3), 21.6 (CH_3), 14.5 (CH_3).

MS (EI): *m*/*z* (%) = 502 (31) [M + 1$^+$], 501 (100) [M$^+$], 277 (31), 276 (50), 262 (33), 130 (11), 43 (14).

HRMS (ESI): *m*/*z* (%) calcd for $C_{34}H_{48}NO_2$ [M + H$^+$]: 502.3685; found: 502.3646.

8,10-Di-*tert*-butyl-6*H*-7-oxa-6-azaindeno[1,2-*a*]phenanthren-5-one (6d)

IR (neat): 2962, 2479, 1600,1422, 1246, 1209, 1087, 1060, 855, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.60 (br s, 1 H, NH), 10.28 (d, *J* = 8.4 MHz, 1 H, ArH), 8.37 (d, *J* = 8.8 MHz, 1 H, ArH), 8.25 (d, *J* = 8.8 MHz, 1 H, ArH), 8.05–7.95 (m, 2 H, ArH), 7.85–7.78 (m, 1 H, ArH), 7.68–7.60 (m, 1 H, ArH), 7.39 (d, *J* = 2.0 MHz, 1 H, ArH), 1.65 (s, 9 H, *t*-Bu), 1.51 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.1 (C), 146.5 (C), 144.6 (C), 133.9 (CH), 132.5 (C), 131.4 (C), 129.6 (C), 129.2 (C), 127.0 (CH), 126.4 (CH), 124.5 (CH), 123.8 (CH), 122.3 (C), 119.7 (CH), 116.7 (CH), 113.0 (CH), 33.15 (C), 32.4 (C), 30.0 (CH_3), 27.9 (CH_3).

MS (EI): *m*/*z* (%) = 398 (25) [M + 1$^+$], 397 (100) [M$^+$], 382 (29), 326 (11), 191 (11), 177 (12), 57 (10), 41 (7).

Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52; O, 8.05. Found: C, 81.51; H, 7.08; N, 3.46; O, 8.22.

7,9-Di-*tert*-butyl-5*H*-6-oxa-1-thia-5-azacyclopenta[*c*]fluoren-4-one (6e)

IR (neat): 2957, 1618, 1593, 1485, 1360, 1068, 861, 685 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 5.2 MHz, 1 H, ArH), 7.58 (d, *J* = 2.0 MHz, 1 H, ArH), 7.31 (d, *J* = 2.0 MHz, 1 H, ArH), 7.29 (d, *J* = 5.6 MHz, 1 H, ArH), 1.53 (s, 9 H, *t*-Bu), 1.41 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C), 152.7 (C), 149.4 (C), 147.6 (C), 144.2 (C), 134.8 (C), 125.0 (C), 124.6 (CH), 123.3 (C), 122.7 (CH), 120.0 (CH), 114.2 (CH), 99.4 (C), 35.4 (C), 35.1 (C), 32.3 (CH_3), 30.5 (CH_3).

MS (EI): *m*/*z* (%) = 354 (21) [M + 1$^+$], 353 (100) [M$^+$], 339 (15), 338 (71), 282 (33), 155 (12), 134 (11), 57 (23), 41 (13).

Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.96; O, 9.05; S, 9.07. Found: C, 71.66; H, 6.48; N, 3.67; O, 8.97; S, 8.88.

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