A Convergent Route to 5-(Arylsulfanyl)-6-sulfonamido-3-benzofuranones

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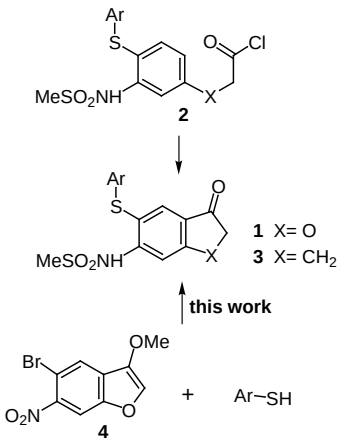
Abstract: A procedure for the synthesis of 5-(arylsulfanyl)-2,3-dihydro-6-sulfonamido-3-benzofuranones (**1**) via 5-bromo-3-methoxy-6-nitrobenzofuran (**4**) as a common advanced synthetic intermediate has been developed. The key step consists of a regioselective nucleophilic aromatic substitution of the bromine atom of **4** by an aryl or heteroarylthiol.

Key words: nucleophilic aromatic substitutions, heterocycles, benzofuranones, sulfonamides, drugs

5-(Arylsulfanyl)-6-sulfonamidobenzofuran-3-ones **1**[1] have been shown to be selective cyclooxygenase-2 (COX-2) inhibitors,[2] with a high antiinflammatory activity but lacking the undesirable side effects of most traditional nonsteroidal antiinflammatory drugs. There are relatively few methods for the preparation of 3-benzofuranones.[3] Among them, the intramolecular Friedel-Crafts acylation of aryloxyacetic acid derivatives,[4] a useful method for the cyclization of arylpropionic acids (**2**, X = CH_2) to the corresponding 1-indanones **3**,[5,6] seemed *a priori* to be a suitable method for the preparation of the target 3-benzofuranones **1**. However, negligible or poor yields (0−10%) were obtained in this cyclization for several substrates **2** (X = O), probably due to the easy decarbonylation[7] of the starting aryloxyacetic acid derivatives. Furthermore, this route suffers from an additional synthetic drawback since the arylsulfanyl substituent at position 5 is introduced in the initial steps of the synthesis therefore, for each specific compound **1**, a complete synthetic sequence has to be developed.

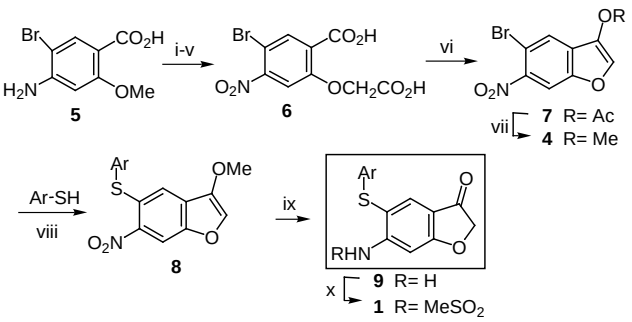


Scheme 1

With these difficulties in mind, we have developed a flexible and efficient route to substituted 3-benzofuranones **1** from a common advanced synthetic intermediate, namely 5-bromo-6-nitrobenzofuran **(4)**, formed in high yield by a Perkin-type cyclization.[8] The synthesis starts from 4-amino-5-bromo-2-methoxybenzoic acid (**5**)[9] and is outlined in Scheme 2. The crucial step is the nucleophilic aromatic substitution of the bromine atom of **4** by an arylthiol. Subsequent manipulation of the nitro substituent and the enol ether functionality provides a variety of 5-(arylsulfanyl)-6-sulfonamido-3-benzofuranones **1**.

Acid **5** was converted in 61% overall yield to diacid **6** in a five step sequence consisting of diazotization with in situ treatment of the diazonium salt with sodium nitrite in the presence of copper powder, cleavage of the methoxy group, esterification, alkylation of the phenolic hydroxy group with ethyl bromoacetate, and finally alkaline hydrolysis of the resulting diester. The closure of the benzofuran ring was accomplished by treatment of diacid **6** with a mixture of acetic acid, acetic anhydride and sodium acetate to afford 3-acetoxybenzofuran **7** in 71% yield. Acid-catalyzed methanolysis of **7** afforded the key intermediate **4** in 85% yield.

Reaction of **4** with a variety of arylthiols[10] under basic conditions gave the corresponding benzofurans **8** in acceptable to good yields (Scheme 2, Table 1).



Reagents and conditions: i) $HBF_4/NaNO_2$, 0°C, then $Cu/NaNO_2$, 0°C, 75%; ii) 48% HBr/AcOH/Ac_2O, Δ, 97%; iii) MeOH/concd H_2SO_4, Δ, 85%; iv) $BrCH_2CO_2Et/K_2CO_3$/acetone, Δ, 98%; v) 1:1:1 2 N KOH/MeOH/dioxane, r.t., 99%; vi) AcOH/Ac_2O/AcONa, Δ, 71%; vii) 10:1 MeOH/35% HCl, Δ, 85%; viii) *t*-BuOK/*t*-BuOH, reflux, see Table 1; ix) Fe/NH_4Cl, 2:1 EtOH/H_2O, Δ, 82−96%; x) MsCl/Et_3N/CH_2Cl_2, r.t., then 1:10 1 N KOH/THF, r.t., then 1:10 1 N KOH/EtOH, 45°C, 46−68%

Scheme 2

Table 1 5-(Arylsulfanyl)benzofurans **8** Prepared from the Common Intermediate **4**

Product	Aryl	Yield (%)
8a	2-thiazolyl	70
8b	4-methyl-2-thiazolyl	50
8c	4-ethyl-2-thiazolyl	60
8d	4-isopropyl-2-thiazolyl	35
8e	1-methyl-2-imidazolyl	52
8f	2-benzothiazolyl	54
8g	3,5-dichloro-2-pyridyl	21
8h	3-(trifluoromethyl)-2-pyridyl	28
8i	5-(trifluoromethyl)-2-pyridyl	30
8j	phenyl	67
8k	3-fluorophenyl	56
8l	4-fluorophenyl	71
8m	2-fluorophenyl	28
8n	3-chlorophenyl	30
8o	4-chlorophenyl	59
8p	3,4-dichlorophenyl	40
8q	2,5-dichlorophenyl	38
8r	2,3-dichlorophenyl	37
8s	2-bromophenyl	18
8t	2-chloro-4-fluorophenyl	56
8u	2-(trifluoromethyl)phenyl	61
8v	4-(trifluoromethyl)phenyl	50
8w	4-(trifluoromethoxy)phenyl	56
8x	2-ethylphenyl	61
8y	2-isopropylphenyl	62

The reaction was general and worked well with diversely substituted phenyl and heteroarylthiols. The enol ether function present in **4** ensures that the S_NAr process occurs on the carbon atom linked to bromine. In contrast, attempts to displace the bromine atom from the 3-benzofuranone formed by hydrolysis of **4** resulted in the substitution of the nitro group due to the activation exerted by the carbonyl group at the *para* position. Finally, treatment of **8** with iron powder in aqueous ethanol under slightly acidic conditions brought about both reduction of the nitro group and hydrolysis of the enol ether function to give the aminobenzofuranones **9** in 82-96% yield (Scheme 2, Table 2). Sulfonylation with excess methanesulfonyl chloride, followed by two successive controlled alkaline hydrolytic steps from the resulting *N*,*N*,*O*-tris(methylsulfonyl) derivative provided the target 2,3-dihydro-3-benzofuranones **1** in 46−68% yield (Table 3).

In conclusion, an efficient and convergent procedure for the preparation of pharmacologically valuable 5-(arylsulfanyl)-2,3-dihydro-6-sulfonamido-3-benzofuranones **1** via a common advanced intermediate **4** has been developed. Taking advantage of both the activation at C-5 towards the nucleophilic attack and the functionalization of C-6, this intermediate may also provide a synthetic entry to a variety of diversely 5-substituted and 5,6-disubstituted 3-benzofuranones.

Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded on a Varian Gemini spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C). Coupling constants are expressed in Hertz and signals are quoted as follows: s, singlet; d, doublet; dd, doublet of a doublet; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br s, broad singlet. Analytical TLC was carried out on Merck silica gel 60 F_{254} plates, and the spots were located with UV light. Flash chromatography was carried out on silica gel (silica gel 60, SDS, 0.04−0.06 mm). Drying of organic extracts during the work-up of reactions was performed over anhyd Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Microanalyses were performed on a Carlo Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona.

4-Bromo-2-carboxy-5-nitrophenoxyacetic Acid (6)

Aq 4 M $NaNO_2$ solution (140 mL) was added dropwise to an ice-cooled solution of **5**[9] (68.7 g, 279 mmol) in 20% HBF_4 (350 mL). The resulting mixture was stirred at 0 ºC for 30 min, and then was added dropwise to a suspension of Cu powder (84.3 g, 1.32 mol) and $NaNO_2$ (253 g, 3.6 mol) in H_2O (380 mL). After stirring for 3 h at r.t. the mixture was filtered through Celite and the cake was washed with EtOAc (200 mL) and 2 N HCl (50 mL). The organic phase was successively washed with 2 N HCl (2 × 50 mL) and brine (2 × 75 mL), dried, filtered, and concentrated to give 5-bromo-2-methoxy-4-nitrobenzoic acid as a brown solid; yield: 58.4 g (75%).

A solution of the above acid (36 g, 130 mmol) in AcOH (45 mL), Ac_2O (40 mL) and 48% HBr (100 mL) was refluxed for 6 h. After addition of cold H_2O (350 mL), the mixture was extracted with EtOAc (3 × 150 mL). The organic extracts were dried, filtered, and concentrated to give 5-bromo-2-hydroxy-4-nitrobenzoic acid as a brown solid; yield: 33.2 g (97%).

A solution of this acid (33.2 g, 127 mmol) in MeOH (200 mL) and concd H_2SO_4 (15 mL) was refluxed for 24 h. After cooling to 5 ºC, H_2O (200 mL) was added, and the resulting orange solid was crystallized from MeOH; yield: 29.8 g (85%).

A suspension of the above methyl ester (24.9 g, 90.2 mmol), K_2CO_3 (18.7 g, 135.3 mmol) and ethyl bromoacetate (12.6 mL, 108.2 mmol) in acetone (400 mL) was refluxed for 12 h. The inorganic salts were filtered off, and the filtrate was concentrated in vacuo. Then, a solution of the crude product in EtOAc (300 mL) was successively washed with saturated Na_2CO_3 (3 × 100 mL) and brine (200 mL), dried, filtered, and concentrated to give ethyl-4-bromo-2-(methoxycarbonyl)-5-nitrophenoxyacetate as an orange solid; yield: 32 g (98%).

A solution of the above diester (32 g, 88.7 mmol) in a 1:1:1 mixture of 2 N KOH/MeOH/dioxane (500 mL) was stirred at r.t. for 18 h. The mixture was acidified with 2 N HCl and extracted with CH_2Cl_2 (3 × 250 mL). The organic extracts were dried, filtered, and concentrated to give diacid **6** as a brown solid; mp 200-202 °C; yield: 28.1 g (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.76 (s, 2 H), 7.39 (s, 1 H), 8.23 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.9, 106.2, 111.5, 125.5, 138.5, 151.9, 156.4, 164.7, 169.6.

Anal. calcd for $C_9H_6BrNO_7$ (320.9): C, 33.96; H, 1.88; N, 4.36. Found: C, 33.65; H, 1.53; N, 4.63.

3- Acetoxy-5-bromo-6-nitrobenzofuran (7)

A solution of **6** (28.1 g, 87.6 mmol) and AcONa (11.4 g, 130.7 mmol) in AcOH (20 mL) and Ac_2O (110 mL) was refluxed for 4 h. After cooling to 5 °C, H_2O (100 mL) was added, and the brown solid was filtered; mp 109−111 °C; yield: 18.9 g (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.92 (s, 1 H), 8.03 (s, 1 H), 8.26 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 108.1, 110.2, 124.3, 125.8, 133.1, 138.7, 146.4, 149.4, 166.8.

Anal. calcd for $C_{10}H_6BrNO_5$ (300.1): C, 40.02; H, 2.01; N, 4.67. Found: C, 39.75; H, 2.39; N, 4.30.

5-Bromo-3-methoxy-6-nitrobenzofuran (4)

A solution of **7** (38 g, 126.6 mmol) in MeOH (250 mL) and 35% HCl (25 mL) was refluxed for 6 h. The MeOH was evaporated, H_2O (100 mL) was added, and the orange precipitate was collected by filtration. Yield: 29.3 g (85%). An analytical sample was crystallized from hexane/CH_2Cl_2 (3:1), mp 160−161 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 7.46 (s, 1 H), 7.93 (s, 1 H), 7.97 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 58.5, 107.3, 110.1, 124.6, 126.2, 129.6, 144.1, 150.8, 175.4.

Anal. calcd for $C_9H_6BrNO_4$ (272.0): C, 39.73; H, 2.22; N, 5.15. Found: C, 40.01; H, 2.40; N, 5.21.

5-(Arylsulfanyl)-3-methoxy-6-nitrobenzofurans 8; General Procedure

t-BuOK (20 mmol) and an appropriate arylthiol[10] (25 mmol) were added to a solution of **4** (10 mmol) in *t*-BuOH (110 mL). After stirring at reflux temperature for 72 h, the solution was concentrated to dryness. The solid residue was dissolved in sat. aq Na_2CO_3 solution, and the aqueous solution was extracted with EtOAc. The organic extracts were dried, filtered, and concentrated to give the corresponding 5-(arylsulfanyl)benzofurans **8a−y** (Tables 1 and 2), which were purified by flash chromatography (hexane/CH_2Cl_2).

6-Amino-5-(arylsulfanyl)-2,3-dihydro-3-benzofuranones 9; General Procedure

NH_4Cl (3.80 mmol) and Fe powder (17 mmol) were added to a solution of **8a−y** (3.50 mmol) in a 2:1 mixture of EtOH/H_2O (30 mL). After stirring at reflux temperature for 4 h, the mixture was filtered and the filtrate was concentrated to dryness. The residue was dissolved in EtOAc, and the organic phase washed with saturated aqueous Na_2CO_3, dried, filtered, and concentrated to give the corresponding benzofuranones **9a−y** in 82−96% yield (Table 2).

5-(Arylsulfanyl)-2,3-dihydro-6-(methylsulfonamido)-3-benzofuranones 1; General Procedure

A solution of $MeSO_2Cl$ (1.0 mL, 13.2 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a solution of **9a−y** (4.0 mmol) and Et_3N (4.5 mL, 32 mmol) in CH_2Cl_2 (75 mL). The mixture was stirred at r.t. for 3 h, and then was concentrated to dryness. The residue was dissolved in EtOAc (75 mL), and the organic phase was successively washed with 1 N HCl (3 × 50 mL) and brine (200 mL), dried, filtered, and concentrated to give the corresponding crude *N*,*N*,*O*-tris(methylsulfonyl) derivative, which was dissolved in a 1:10 mixture of 1 N KOH/THF (90 mL). The resulting solution was stirred at r.t. for 5 h. Then, H_2O (30 mL) was added, and the mixture was acidified with 2 N HCl and extracted with EtOAc. The organic extract was dried, filtered, and concentrated. A solution of the resulting crude *N*,*O*-bis(methylsulfonyl) derivative in a 1:10 mixture of 1N KOH/MeOH (50 mL) was stirred at 45 °C for 1.5 h. Then, cold H_2O (30 mL) was added, and the mixture was acidified with 2N HCl and extracted with EtOAc. The organic extract was successively washed with 5% aq $NaHCO_3$ solution and brine, dried, filtered, and concentrated to give the target benzofuranones **1** in a 46-68% yield (Table 3).

Table 2 Spectroscopic Data of Selected Benzofurans **8** and Benzofuranones **9**

Product[a]	^{1}H NMR (300 MHz, $CDCl_3$), δ, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$), δ
8a	3.84 (s, 3 H), 7.41 (s, 1 H), 7.44 (s, 1 H), 7.55 (d, 1 H, *J* = 3.4), 7.99 (d, 1 H, *J* = 3.2), 8.28 (s, 1 H)	58.4, 109.9, 110.1, 120.2, 124.5, 126.8, 127.4, 130.1, 144.5, 144.9, 150.9, 159.8
8b	2.54 (s, 3 H), 3.84 (s, 3 H), 7.11 (s, 1 H), 7.39 (s, 1 H), 7.44 (s, 1 H), 8.25 (s, 1 H)	17.3, 58.4, 109.7, 111.4, 119.3, 119.8, 126.8, 128.1, 130.1, 144.4, 150.7, 155.3, 158.2
8c	1.34 (t, 3 H, *J* = 7.6), 2.89 (q, 2 H, *J* = 7.6), 3.84 (s, 3 H), 7.11 (s, 1 H), 7.40 (s, 1 H), 7.44 (s, 1 H), 8.26 (s, 1 H)	13.3, 24.9, 58.3, 109.7, 117.9, 119.6, 126.8, 128.2, 130.1, 144.3, 150.6, 158.1, 161.5
8d	1.36 (d, 6 H, *J* = 6.9), 3.19 (m, 1 H), 3.84 (s, 3 H), 7.09 (s, 1 H), 7.43 (s, 1 H), 7.44 (s, 1 H), 8.27 (s, 1 H)	22.1, 31.0, 58.3, 109.6, 116.7, 119.4, 126.7, 128.2, 130.0, 144.3, 150.5, 158.1, 166.0
8e	3.67 (s, 3 H), 3.81 (s, 3 H), 6.67 (s, 1 H), 7.21 (s, 1 H), 7.34 (s, 1 H), 7.42 (s, 1 H), 8.33 (s, 1 H)	33.9, 58.3, 110.0, 117.2, 124.5, 127.2, 129.7, 130.3, 131.0, 137.1, 142.8, 144.2, 150.2
9a	4.62 (s, 2 H), 5.40 (br s, 2 H), 6.38 (s, 1 H), 7.20 (d, 1 H, *J* = 3.2), 7.65 (d, 1 H, *J* = 3.2), 7.94 (s, 1 H)	75.6, 96.0, 109.2, 112.8, 120.3, 134.8, 143.4, 156.5, 176.5, 195.7
9b	2.39 (s, 3 H), 4.63 (s, 2 H), 5.26 (br s, 2 H), 6.37 (s, 1 H), 6.74 (s, 1 H), 7.95 (s, 1 H)	17.2, 75.6, 96.0, 109.3, 112.9, 114.8, 135.0, 153.9, 156.5, 176.5, 195.7
9c	1.25 (t, 3 H, *J* = 7.5), 2.73 (q, 2 H, *J* = 7.5), 4.62 (s, 2 H), 5.43 (br s, 2 H), 6.39 (s, 1 H), 6.74 (s, 1 H), 7.92 (s, 1 H)	13.0, 24.8, 75.5, 95.9, 109.2, 112.6, 113.4, 134.8, 156.6, 160.0, 164.8, 176.3, 195.7
9d	1.27 (d, 6 H, *J* = 6.8), 3.01 (m, 1 H), 4.62 (s, 2 H), 5.43 (br s, 2 H), 6.38 (s, 1 H), 6.72 (s, 1 H), 7.93 (s, 1 H)	22.0, 30.9, 75.5, 95.9, 109.4, 112.4, 112.7, 134.8, 156.5, 164.5 164.7, 176.4, 195.7
9e	3.74 (s, 3 H), 4.56 (s, 2 H), 5.80 (br s, 2 H), 6.23 (s, 1 H), 6.97 (s, 1 H), 7.04 (s, 1 H), 7.84 (s, 1 H)	34.1, 75.5, 95.8, 109.9, 111.7, 123.8, 129.1, 132.2, 137.6, 157.5, 175.9, 196.0

[a] All new compounds gave satisfactory elemental analyses: C± 0.12, H± 0.15, N± 0.11.

Table 3 Characteristic Physical and Spectroscopic Data of Benzofuranones **1**

Product[a]	mp (ºC)	^{1}H NMR (300 MHz, $CDCl_3$), δ, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$), δ, *J* (Hz)
1a	171−172	3.10 (s, 3 H), 4.70 (s, 2 H), 7.33 (d, 1 H, *J* = 3.4), 7.54 (s, 1 H), 7.71 (d, 1 H, *J* = 3.4), 8.06 (s, 1 H), 8.82 (br s, 1 H)	40.2, 75.8, 102.5, 114.3, 117.3, 121.9, 133.6, 143.7, 147.8, 161.7, 176.1, 196.5
1b	177−178	2.40 (s, 3 H), 3.10 (s, 3 H), 4.70 (s, 2 H), 6.85 (s, 1 H), 7.54 (s, 1 H), 8.05 (s, 1 H), 9.10 (br s, 1 H)	17.1, 40.2, 75.8, 102.5, 114.7, 116.5, 117.2, 133.4, 147.9, 154.3, 160.5, 176.1, 196.6
1c	146−147	1.28 (t, 3 H, *J* = 7.5), 2.75 (q, 2 H, *J* = 7.5), 3.10 (s, 3 H), 4.69 (s, 2 H), 6.86 (s, 1 H), 7.53 (s, 1 H), 8.05 (s, 1 H), 9.29 (br s, 1 H)	13.1, 24.8, 40.3, 75.8, 102.8, 115.0, 115.4, 117.2, 133.3, 147.9, 176.0, 196.6
1d	138−139	1.27 (d, 6 H, *J* = 6.8), 3.03 (m, 1 H), 3.10 (s, 3 H), 4.70 (s, 2 H), 6.86 (s, 1 H), 7.53 (s, 1 H), 8.05 (s, 1 H), 9.49 (br s, 1 H)	22.1, 30.9, 40.4, 75.8, 103.2, 114.5, 115.4, 117.3, 133.1, 148.0, 160.5, 165.1, 176.0, 196.7
1e	–[b]	3.15 (s, 3 H), 3.80 (s, 3 H), 4.66 (s, 2 H), 6.99 (s, 1 H), 7.10 (s, 1 H), 7.51 (s, 1 H), 7.96 (s, 1 H)	34.1, 40.5, 75.7, 104.3, 115.2, 116.9, 123.7, 129.0, 131.5, 138.3, 148.9, 175.7, 197.0
1f	157−158	3.01 (s, 3 H), 4.72 (s, 2 H), 7.32 (td, 1 H, J_1= 1.5, J_2 = 7.3, J_3 = 7.9), 7.42 (td, 1 H, J_1= 1.5, J_2 = 7.2, J_3 = 8.2), 7.57 (s, 1 H), 7.70 (d, 1 H, *J* = 7.8), 7.80 (d, 1 H, *J* = 7.8), 8.07 (s, 1 H), 8.37 (br s, 2H)	40.2, 75.9, 101.9, 112.1, 117.3, 121.1, 122.1, 125.2, 126.6, 134.4, 135.5, 147.8, 153.3, 164.9, 176.6, 196.3
1g	129−131	3.07 (s, 3 H), 4.69 (s, 2 H), 7.51 (s, 1 H), 7.67 (s, 1 H), 7.79 (s, 1 H), 7.90 (s, 1 H), 8.10 (s, 1 H)	40.0, 75.8, 101.2, 111.5, 117.2, 129.4, 129.6, 134.5, 136.5, 146.2, 148.3, 152.9, 176.1, 196.5
1h	181−183	3.10 (s, 3 H), 4.69 (s, 2 H), 7.25 (dd, 1 H, J_1= 4.6, J_2 = 7.9), 7.53 (s, 1 H), 7.95 (d, 1 H, *J* = 8.1), 7.96 (s, 1 H), 8.31 (br s, 1 H), 8.42 (d, 1 H, *J* = 3.6)	40.0, 75.7, 101.9, 112.7, 117.2, 120.8, 122.9 (q, *J* = 271.9), 124.9 (q, *J* = 33.8), 134.5, 135.3 (q, *J* = 5.2), 148.6, 151.9, 155.7, 176.1, 196.5
1i	171−173	3.12 (s, 3 H), 4.72 (s, 2 H), 7.27 (d, 1 H, *J* = 9.3), 7.54 (s, 1 H), 7.79 (dd, 1 H, J_1= 2.1, J_2 = 8.4), 7.91 (s, 1 H), 8.12 (s, 1 H), 8.58 (br s, 1 H)	40.1, 75.8, 101.5, 111.7, 117.3, 121.2, 123.1 (q, *J* = 270.5), 124.3 (q, *J* = 32.8), 134.1 (q, *J* = 3.1), 134.4, 146.7 (q, *J* = 4.2), 148.1, 161.9, 176.1, 196.4
1j	163−165	2.79 (s, 3 H), 4.68 (s, 2 H), 7.10 (d, 2 H, *J* = 7.5), 7.23 (m, 3 H), 7.46 (s, 1 H), 8.00 (br s, 2 H)	39.6, 75.7, 101.2, 115.1, 117.1, 127.2, 127.8, 129.5, 133.9, 134.6, 147.1, 175.7, 196.2
1k	140−142	2.94 (s, 3 H), 4.72 (s, 2 H), 6.70 (d, 1 H, *J* = 7.2), 6.89 (m, 2 H), 7.25 (m, 1 H), 7.49 (s, 1 H), 7.97 (br s, 1 H), 8.01 (s, 1 H)	39.9, 75.7, 101.1, 113.3, 113.9 (d, *J* = 24), 114.0 (d, *J* = 20.8), 117.2, 122.6 (d, *J* = 3.8), 130.9 (d, *J* = 8.5), 134.4, 137.2 (d, *J* = 7.4), 147.2, 163.1 (d, *J* = 248.7), 175.9, 196.4
1l	100−102	2.91 (s, 3 H), 4.71 (s, 2 H), 7.02 (t, 2 H, *J* = 8.1), 7.14 (dd, 2 H, J_1= 4.8, J_2 = 8.1), 7.45 (s, 1 H), 8.02 (br s, 2 H)	39.9, 75.7, 101.0, 115.3, 116.7 (d, *J* = 21), 117.0, 129.5, 130.1 (d, *J* = 8.2), 133.6, 146.8, 161.9 (d, *J* = 246.8), 175.6, 196.5
1m	146−148	3.01 (s, 3 H), 4.68 (s, 2 H), 7.09 (m, 3 H), 7.28 (m, 1 H), 7.45 (s, 1 H), 8.00 (s, 1 H), 8.10 (br s, 1 H)	39.8, 75.6, 100.6, 114.1, 116.2 (d, *J* = 21), 117.0, 121.5 (d, *J* = 17.5), 125.0, 129.8 (d, *J* = 7.7), 131.1, 133.9, 147.0, 160.4 (d, *J* = 244.6), 175.5, 196.4
1n	87−89	2.94 (s, 3 H), 4.73 (s, 2 H), 7.00 (d, 1 H, *J* = 2.4), 7.19 (m, 3 H), 7.50 (s, 1 H), 7.94 (br s, 1 H), 8.02 (s, 1 H)	39.9, 75.7, 101.1, 113.3, 117.3, 125.2, 126.5, 127.2, 130.5, 134.4, 135.5, 136.7, 147.1, 176.0, 196.4
1o	150−152	2.96 (s, 3 H), 4.73 (s, 2 H), 7.06 (d, 2 H, *J*= 10.2), 7.27 (d, 2 H, *J* = 9.5), 7.49 (s, 1 H), 8.00 (br s, 1 H), 8.03 (s, 1 H)	39.9, 75.7, 100.9, 114.1, 117.1, 128.7, 129.6, 133.1, 134.1, 146.9, 175.8, 196.5
1p	141−143	3.01 (s, 3 H), 4.71 (s, 2 H), 6.90 (d, 1 H, *J*= 8.1), 7.08 (s, 1 H), 7.32 (d, 1 H, *J* = 8.4), 7.46 (s, 1 H), 7.97 (s, 1 H)	40.1, 75.8, 101.1, 112.8, 117.3, 126.1, 128.2, 131.1, 133.7, 134.4, 134.9, 147.1, 176.0, 196.5
1q	190−192	3.05 (s, 3 H), 4.75 (s, 2 H), 6.52 (d, 1 H, *J* = 2.4), 7.13 (dd, 1 H, J_1= 2.4, J_2 = 8.4), 7.34 (d, 1 H, *J* = 8.4), 7.55 (s, 1 H), 7.87 (br s, 1 H), 8.00 (s, 1 H)	40.1, 75.9, 101.1, 111.6, 117.6, 126.2, 127.7, 130.1, 131.1, 133.6, 134.8, 136.0, 147.3, 176.1, 196.2,
1r	156–158	3.07 (s, 3 H), 4.73 (s, 2 H), 6.48 (dd, 1 H, J_1= 1.2, J_2 = 7.9), 7.04 (t, 1 H, J_1 = 7.9, J_2 = 8.2), 7.30 (dd, 1 H, J_1= 1.2, J_2 = 8.2), 7.51 (s, 1 H), 7.95 (br s, 1 H), 7.98 (s, 1 H)	40.2, 75.8, 100.9, 112.1, 117.4, 124.4, 127.7, 128.1, 129.7, 134.0, 134.8, 136.7, 147.4, 175.9, 196.1

Table 3 (continued)

Product[a]	mp (ºC)	^{1}H NMR (300 MHz, $CDCl_3$), δ, *J* (Hz)	^{13}C NMR (75 MHz, $CDCl_3$), δ, *J* (Hz)
1s	187−189	2.98 (s, 3 H), 4.71 (s, 2 H), 6.54 (dd, 1 H, J_1= 1.5, J_2 = 7.8), 7.07 (td, 1 H, J_1= 1.8, J_2 = 7.3, J_3 = 7.8), 7.15 (td, 1 H, J_1= 1.5, J_2 = 7.5, J_3 = 7.8), 7.50 (s, 1 H), 7.57 (dd, 1 H, J_1= 1.5, J_2 = 7.8), 7.97 (br s, 1 H), 8.01 (s, 1 H)	40.0, 75.7, 101.1, 113.7, 117.4, 122.0, 127.4, 128.0, 128.2, 133.4, 134.5, 136.0, 147.3, 175.9, 196.4
1t	160−162	3.04 (s, 3 H), 4.71 (s, 2 H), 6.84 (m, 2 H), 7.18 (dd, 1 H, J_1= 2.7, J_2 = 8.4), 7.47 (s, 1 H), 7.98 (s, 1 H), 8.02 (br s, 1 H)	40.1, 75.7, 100.9, 113.6, 115.3 (d, *J* = 21.5), 117.3, 117.9 (d, *J* = 25.2), 129.1, 129.9 (d, *J* = 8.5), 133.9 (d, *J* = 10.0), 134.1, 147.1, 161.5 (d, *J* = 250.2), 175.8, 196.3
1u	172−173	2.93 (s, 3 H), 4.74 (s, 2 H), 6.92 (d, 1 H, *J* = 9), 7.36 (m, 2 H), 7.50 (s, 1 H), 7.72 (d, 1 H, *J* = 8.7), 7.96 (br s, 1 H), 8.04 (s, 1 H)	39.9, 75.7, 101.3, 113.4, 117.2, 123.5 (q, *J* = 327), 127.1 (q, *J* = 5.4), 127.2, 128.4 (q, *J* = 36.8), 128.9, 132.5, 134.2, 134.7, 147.2, 176.0, 196.4
1v	130−132	2.93 (s, 3 H), 4.72 (s, 2 H), 7.13 (d, 2 H, *J*= 7.8), 7.49 (s, 1 H), 7.51 (d, 2 H, *J* = 7.8), 7.97 (s, 1 H), 8.01 (s, 1 H)	40.1, 75.8, 101.0, 112.4, 117.3, 123.8 (q, *J* = 270.5), 126.3 (q, *J* = 3.9), 126.5, 138.9 (q, *J* = 32.8), 134.6, 139.9, 147.3, 176.0, 196.3
1w	152−153	2.94 (s, 3 H), 4.72 (s, 2 H), 7.14 (s, 2 H), 7.48 (s, 1 H), 8.00 (br s, 1 H), 8.02 (s, 1 H)	39.9, 75.7, 101.0, 114.0, 117.2, 120.2 (q, *J* = 254.2), 122.1, 128.8, 133.3, 134.2, 147.0, 148.1, 175.8, 196.4
1x	134−136	1.30 (t, 3 H, *J* = 7.5), 2.82 (s, 3 H), 2.84 (q, 2 H, *J* = 7.5), 4.70 (s, 2 H), 6.66 (dd, 1 H, J_1= 0.9, J_2 = 7.9), 7.03 (td, 1 H, J_1= 1.5, J_2 = 7.8, J_3= 7.8), 7.15 (td, 1 H, J_1= 0.9, J_2 = 7.5, J_3= 7.5), 7.23 (dd, 1 H, J_1= 1.5, J_2 = 7.6), 7.49 (s, 1 H), 7.87 (br s, 1 H), 7.96 (s, 1 H)	14.4, 26.7, 39.6, 75.7, 101.2, 114.9, 117.3, 126.8, 126.9, 127.1, 129.1, 133.2, 133.9, 142.3, 147.0, 175.7, 196.6
1y	188−190	1.31 (d, 6 H, *J* = 6.9), 2.79 (s, 3 H), 3.46 (m, 1 H), 4.70 (s, 2 H), 6.66 (dd, 1 H, J_1= 0.9, J_2 = 7.9), 7.01 (td, 1 H, J_1= 1.5, J_2 = 7.8, J_3= 7.8), 7.19 (td, 1 H, J_1= 0.9, J_2 = 7.5, J_3= 7.5), 7.32 (dd, 1 H, J_1= 1.5, J_2 = 7.6), 7.49 (s, 1 H), 7.85 (br s, 1H), 7.97 (s, 1 H)	23.2, 30.5, 39.6, 75.7, 101.2, 115.3, 117.3, 126.2, 126.8, 127.0, 129.3, 132.6, 133.8, 147.0, 175.7, 196.6

[a] All new compounds gave satisfactory elemental analyses: C± 0.37, H± 0.25, N± 0.39.
[b] Decomposes above 120ºC.

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