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Synthesis of 5-substituted 2,3-dihydrobenzofurans in a one-pot oxidation/cyclization reaction

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ABSTRACT

Variously substituted 2,3-dihydrobenzofurans have been synthesized according to a sequential one-pot oxidation/cyclization procedure between *para*-aminophenol derivatives and an azadiene.

1. Introduction

The 2,3-dihydrobenzofuran core is present in many compounds having various interesting biological properties (Fig. 1). For example, we can mention 2-carboxamide **1** (κ-opioid antagonist),[1] 5-amino-2,3-dihydrobenzofuran TAK-218 (stroke and CNS trauma treatments),[2] efaroxan **2a** (either α_2-adrenergic antagonist compound for the dextrorotatory enantiomer[3] and insulin secretion inducer for the laevorotatory enantiomer[4]) or the propafenone-derived dihydrobenzofurans **3**, which have demonstrated anti-Multi Drug Resistance (MDR) properties.[5]

Hence, the development of synthetic methods to this heterocyclic class of compounds has attracted the interest of numerous research groups[6] and, among all these methods, multi-component reactions and one-pot processes appeared to be the most elegant ones.[7]

We were also interested in the discovery of new strategies to this oxygenated heterocycle as we have described the preparation of 2,3-dihydrobenzofuran derivatives **4** according to a [3+2] cycloaddition reaction between heterodienes **5** and quinone sulfonamides **6** (Scheme 1).[8] Besides the absence of a catalyst or a promoter during the reaction,[9] the other interest of our methodology was the introduction of an hydrazone at the C2 position. This group could be of great interest for a subsequent introduction of either aldehyde or cyano functionalities, as mentioned in the literature.[10]

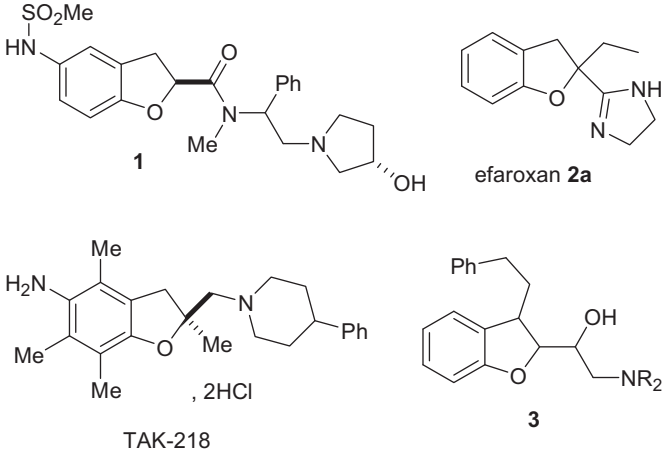

Fig. 1. Some bioactive 2,3-dihydrobenzofuran derivatives.

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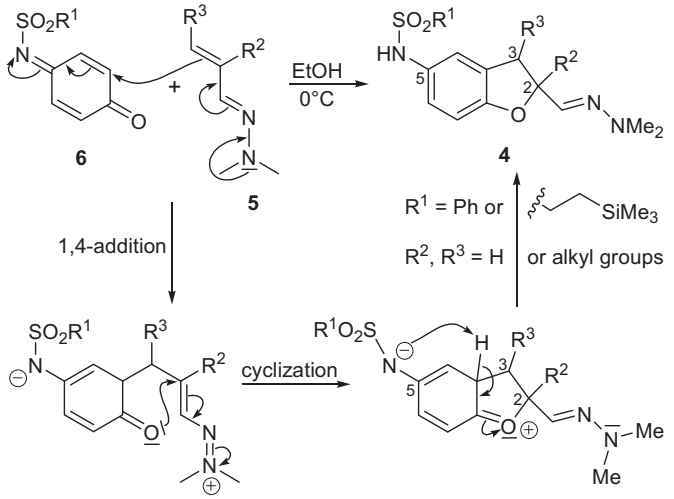
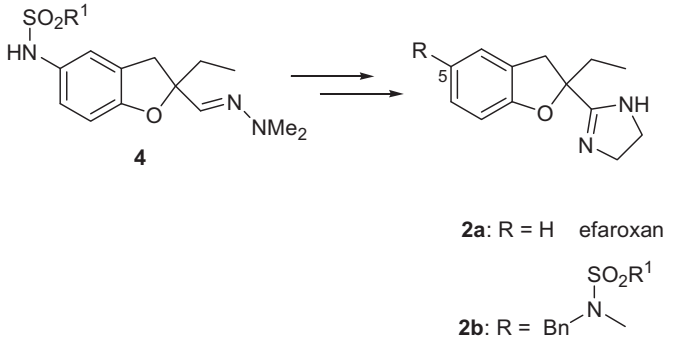


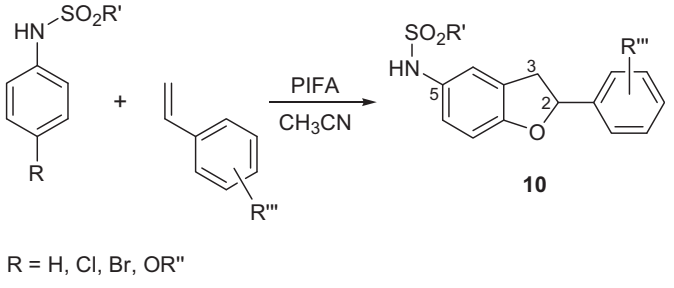
Scheme 1.

This strategy has been recently applied to prepare efaroxan **2a** and its 5-amino analogues **2b**, taking advantage of the presence of the hydrazone group in **4** to introduce the imidazoline ring, via a nitrile (Scheme 2).[11]



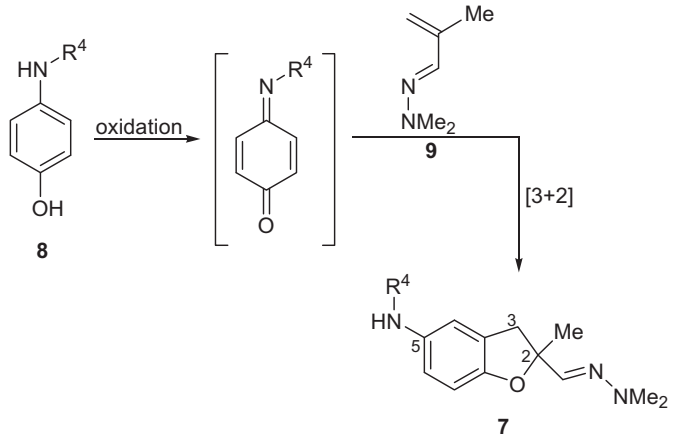
Scheme 2.

Recently, Fan et al. have described an efficient one-pot access to 2,3-dihydrobenzofurans **10** starting from a wide variety of arylsulfonamides (Scheme 3).[7c] This method used PIFA (2.5 equiv or 1.2 equiv when 10 mol % of $Cu(OTf)_2$ was employed as a co-catalyst) for the *para*-hydroxylation/oxidation steps and was limited to styrenic derivatives for the C2–C3 building block.



Scheme 3.

Herein we wish to report a new development concerning the sequential one-pot version of this reaction: an oxidation/cycloaddition process to obtain 2,3-dihydrobenzofurans **7** from *p*-hydroxy-sulfonamides or carboxamides **8**, using an oxidizing agent and 2-methylacrolein dimethylhydrazone **9** as the heterodiene (Scheme 4).



Scheme 4.

2. Results and discussion

2.1. Quinone imides formation

Quinone monoimides[12] could be obtained after oxidation of arylsulfonamides or, preferentially, 4-hydroxy-arylsulfonamides, by using several oxidizing reagents: $Pb(OAc)_4$,[13] $NaIO_4$ in its silica-supported version,[14] or hypervalent organoiodine reagents[15] (iodosylbenzene or [bis(trifluoroacetoxy)iodo]benzene (PIFA))[16,17] as we have previously described.

Our preliminary studies to perform our one-pot reaction in a convenient way were directed towards the choice of the appropriate oxidation reagent for the first step formation of quinone imides **11** bearing different groups on the nitrogen atom.[18] A solid-supported (and so easily removed after the reaction) oxidizing agent has drawn our attention: Ag_2CO_3 adsorbed onto Celite, also known as Fétizon's reagent, as this reagent proved to be efficient for the oxidation of *para*-phenylaminophenol into the corresponding quinone imide[19] in an excellent yield (Table 1, entry 7).

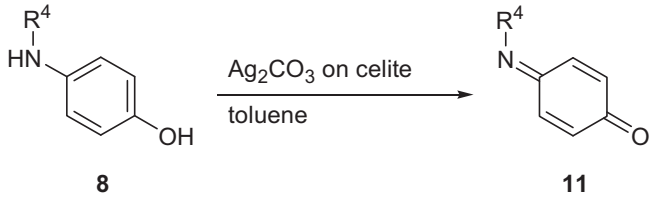
Table 1
Synthesis of quinone imides **11**

Entry	R^4	Reaction conditions[a]	Yield %
1	SO_2Ph (**11a**)	0 °C, 30 min	98 (98[b])
2	SO_2SiMe_3 (**11b**)	110 °C, 30 min	95
3	SO_2CH_3 (**11c**)	rt, 30 min	69
4	$COCF_3$	rt, 4 h	0
5	COPh	rt, 4 h	0
6	COO*t*-Bu	rt, 4 h	0
7	Ph (**11h**)	110 °C, 15 min	100 (98[c])

[a] All reactions were carried using 2.1 equiv of Ag_2CO_3 on Celite, in toluene.
[b] Reaction carried out with 1.2 equiv PIFA, in toluene at 0 °C, 30 min.
[c] Reaction carried out with 1.2 equiv PIFA, in toluene at 110 °C, 15 min.

So, the oxidation reactions of different amides were performed with 2.1 equiv of this reagent,[20] at rt or 0 °C, in toluene and the best results were observed with 4-hydroxyphenylsulfonamides, leading to quinone imides **11** in 69–98% yields (Scheme 5 and Table 1, entries 1–3).

On the other hand, when this oxidation was realized onto different carboxamides (Table 1, entries 4–6), the corresponding quinone imides were not stable enough to be isolated. These last results are in agreement with a precedent literature report showing that isolation of the quinone imide derived from paracetamol (R^4=$COCH_3$), after oxidation with freshly prepared silver oxide, was



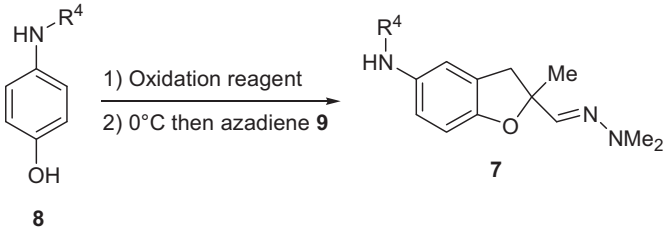
Scheme 5.

only possible through its glutathione or *N*-acetylcysteine 1,4-adducts.[21]

The comparison of this oxidizing reagent with 1.2 equiv of PIFA in toluene, in the presence of K_2CO_3 (2.4 equiv to trap the released trifluoroacetic acid) was also realized in some cases and this latter was also very efficient for the oxidation of *para*-phenylsulfonamido phenol and *para*-(phenylamino)phenol as the corresponding quinone imides were obtained in quantitative yields (Table 1, entries 1 and 7).

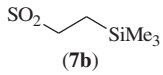
2.2. One-pot synthesis of *N*5-substituted 2,3-dihydrobenzofurans

The sequential one-pot oxidation/cycloaddition reaction was then investigated on the same substrates by using either Fétizon's reagent or PIFA. After complete conversion of the *N*-substituted *para*-aminophenols **8** during the first oxidation step (monitored by TLC), the reaction mixture was then cooled down to 0 °C and 2 equiv of azadiene **9** were added. After an additional stirring time, the solvent was removed and, after purification of the crude product, dihydrobenzofurans **7** were obtained (Scheme 6 and Table 2).



Scheme 6.

Table 2
Sequential one-pot synthesis of 2,3-dihydrobenzofurans **7**

Entry	R^4	Oxidation step	Second step[a]	Yield %
1	SO_2Ph (**7a**)	Ag_2CO_3 on Celite EtOH, 0 °C, 1 h	30 min	96 (57[b])
2	 (**7b**)	Ag_2CO_3 on Celite EtOH, 0 °C, 1 h	1 h	93
3	SO_2CH_3 (**7c**)	Ag_2CO_3 on Celite EtOH, rt, 30 min	15 min	81
4	SO_2CF_3 (**7d**)	Ag_2CO_3 on Celite toluene, rt, 15 min	30 min	60
5	$COCF_3$ (**7e**)	Ag_2CO_3 on Celite toluene, 110 °C, 1 h	15 min	16
6	COPh (**7f**)	PIFA/K_2CO_3, EtOH, rt, 15 min	1 h	17
7	COO*t*-Bu (**7g**)	PIFA/K_2CO_3, EtOH, rt, 30 min	15 min	20
8	Ph (**7h**)	PIFA, toluene, 0 °C, 30 min	30 min	61

[a] Upon oxidation completion, the mixture was cooled to 0 °C, 2 equiv of azadiene **9** were added and the reaction mixture was stirred at 0 °C for the indicated additional time.

[b] Reaction carried out with PIFA/K_2CO_3, in toluene (5 min reflux for the oxidation, then 5 min condensation at 0 °C with **9**).

As previously mentioned (Table 1, entries 4–6), quinone imides derived from carboxamides (paracetamol analogues) were not stable and thus could not be isolated. The only way to obtain the corresponding dihydrobenzofurans **7** would be the in situ preparation of these quinone imides **11** and, without isolation, the subsequent condensation with the azadiene. Indeed, according to this one-pot protocol, we were able to isolate the corresponding 2,3-dihydrobenzofurans, albeit in poor yields (Table 2, entries 5–7).[22]

With two of these substrates (Table 2, entries 6 and 7), the one-pot reaction was inefficient with Ag_2CO_3 in either toluene or ethanol[23] and required the use of PIFA under basic conditions to obtain the desired products.

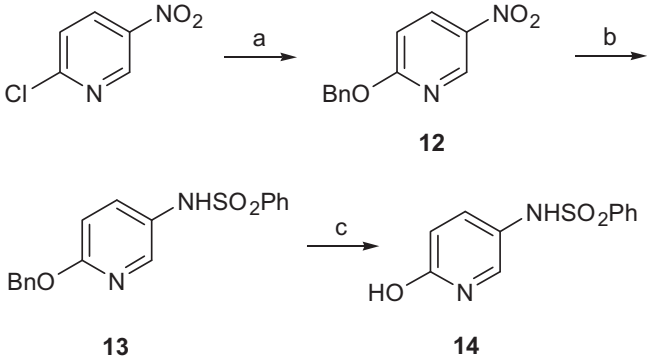
Following the same one-pot procedure, better results were observed with 4-hydroxysulfonamides substrates as 2,3-dihydrobenzofurans having various *N*-5 substitutions (phenyl-, trimethylsilylethyl-,[24] methyl- or trifluoromethyl-sulfonyl) were obtained in moderate to excellent yields (Table 2, entries 1–4).

The absence of an electron-withdrawing group on the nitrogen atom seems to be deleterious for the second cycloaddition step as we were not able to obtain the corresponding 2,3-dihydrobenzofuran under the previously described conditions. In fact, although the corresponding quinone imide was prepared in good yield after either Ag_2CO_3 or PIFA oxidation (Table 1, entry 7), the reaction mixture did not evolve anymore after the azadiene addition. Nevertheless, when the reaction was carried out with PIFA, in the absence of K_2CO_3, the desired product was isolated with a 61% yield (Table 2, entry 8). This last result suggests that the acidic conditions of the reaction, due to the released trifluoroacetic acid (after the oxidation step) might favour the [3+2] cycloaddition, as previously noticed.[9]

2.3. Effect of ring modification

To study the scope of the reaction further, we decided to carry out this one-pot procedure with other sulfonylated *para*-aminophenols and we then envisaged aromatic ring modifications, either by substitution on it or by introduction of a nitrogen atom into this ring.

2.3.1. Synthesis of the starting materials. Whereas the preparation of some ring-substituted quinone imide precursors implies a sulfonylation reaction on commercially available products or compounds described in the literature, we have designed a three step sequence for the synthesis of *N*-(6-hydroxy-pyridin-3-yl)-benzene sulfonamide **14**, starting from 2-chloro-5-nitropyridine (Scheme 7). After nucleophilic substitution of the chlorine atom with benzyl alcohol,[25] the nitro group in **12** was then reduced and, without purification of the corresponding amino compound, a sulfonylation under classical conditions ($PhSO_2Cl$ in pyridine) allowed the introduction of the sulfonamide group in **13**. The last step of this sequence has consisted

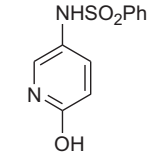
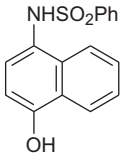
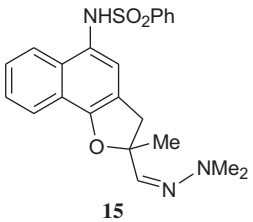
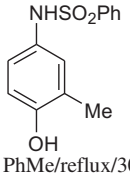
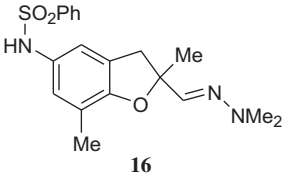
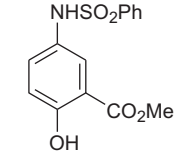
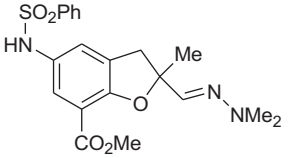
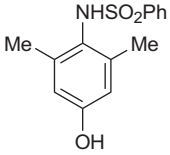
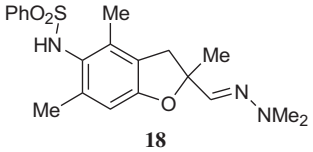


Scheme 7. Reagents and conditions: (a) BnOH, KOH, 18-C-6, toluene, reflux, 30 min, 74%. (b) (1) H_2 5 bars, Pd/C, AcOEt, rt, 6 h. (2) $PhSO_2Cl$, pyridine, rt, 16 h, 84% over the two steps. (c) H_2 5 bars, Pd/C, EtOH, rt, 6 h, quantitative.

in an hydrogenolysis to remove the benzyl protecting group of the pyridinol and this was done in a quantitative yield (Scheme 7).

2.3.2. Tentative one-pot synthesis of 2,3-DHBF starting from pyridine derivative ***14****.* Unfortunately, the one-pot oxidation/cycloaddition procedure carried out on substrate **14** failed as we never managed to obtain the corresponding 2,3-dihydrobenzofuran, whatever the oxidative agent we used: Ag_2CO_3 on Celite, PIFA, $Pb(OAc)_4$, PhIO, supported $NaIO_4$, or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[26] in various solvents (toluene, EtOH, *i*-PrOH, acetonitrile, glacial acetic acid, chloroform of ethyl acetate) (Table 3, entry 1).

Table 3
One-pot synthesis of ring-substituted 2,3-dihydrobenzofurans

Entry	Substrate and conditions[a]	Product	Yield %
1		—	—
2	 EtOH/reflux/30 min Toluene/reflux/1 h	 **15**	50 53
3	 PhMe/reflux/30 min	 **16**	62
4	 PhMe/rt/30 min	 **17**	Trace[b]
5	 PhMe/reflux/30 min	 **18**	50

[a] Reactions carried out with 2.1 equiv Ag_2CO_3 on Celite: after the oxidation step (10–30 min at the indicated temperature, monitored by TLC), the mixture was cooled to 0 °C, 2 equiv of azadiene **9** were added and the resulting mixture stirred for the indicated time.

[b] Reaction carried out with 1.2 equiv PIFA and 2.4 equiv K_2CO_3. Product **17** was characterized on the base of ^1H NMR and HRMS, together with an unidentified side-product. No reaction was observed with Ag_2CO_3 on Celite.

In situ mass spectroscopy studies were then carried out to understand the behaviour of this starting material under our oxidative conditions. A stoichiometric mixture of substrate **14**, potassium carbonate and PIFA in ethanol was then stirred (ultrasonic conditions) at rt: the mixture gradually turned to blue then violet and was periodically (15 s, 1 and 12 min) analyzed by using Electron Spray Ionization High Resolution Mass Spectroscopy. The resulting Mass Spectrum (after 15 s) showed a very fast consumption of the starting material **14** (no more detected after a 1 min reaction time) and the appearance of a major peak at m/z=365.0566 ($[M1K]^+$, 100% abundance, intermediate also detected in the negative polarity, at m/z=325.0882 for $[M1-H]^-$), which identity could not be assigned (Fig. 2). The abundance of this peak significantly dropped

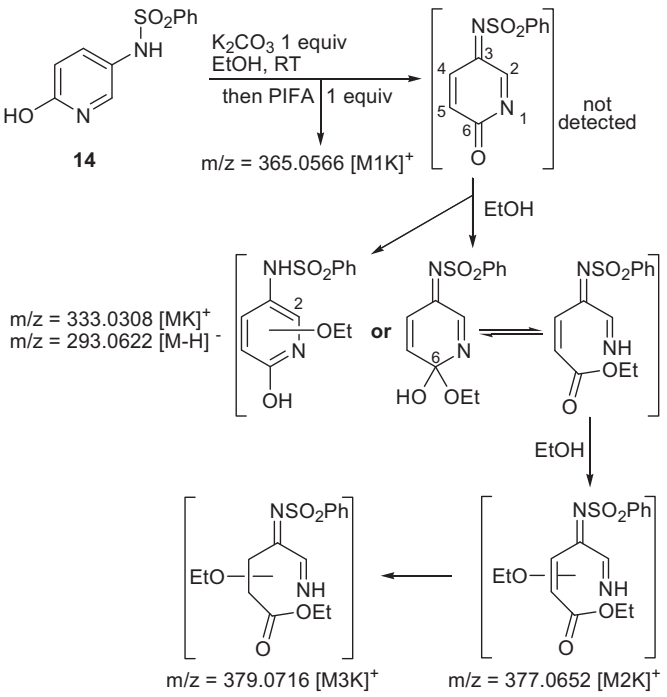


Fig. 2. Mass spectroscopy study of pyridine **14** oxidation reaction.

to 47% after 1 min reaction time and two other major intermediates were detected at m/z=377.0562 ($[M2K]^+$, 36% abundance) and m/z=379.0716 ($[M3K]^+$, 100% abundance): these two intermediates derived from the direct oxidation product of **14**.

Indeed, the aza-quinone imide derivative was not detected itself (Fig. 2) but through its ethanol adducts. First, an ethanol molecule could add on this quinoid structure, as shown by the detection of a peak at m/z=333.0308, but this could happen according to two different possibilities: either through a conjugated addition (most probably at position 2) and aromatization or after the hemi-acetal formation at position 6.

This ketal should be in equilibrium with an open form, which could be favoured, in this case, owing to the electronegativity of the nitrogen atom (Fig. 2). This intermediate is able to act as a Michael acceptor for an other ethanol molecule, finally giving a new compound, measured as its potassium adduct, at m/z=379.0716. After a 12 min reaction time, this peak remained the most abundant one, accompanied with the peak at m/z=333.0308 (abundance=17%).

Unfortunately, every attempt to isolate this compound failed. However, this experiment showed that the oxidation of pyridine substrate **14** took place but, regarding to the structure of such nitrogen derivative, side-reactions occurred, and the formal [3+2] cycloaddition with the azadiene **9** did not take place to give the expected 2,3-dihydrobenzofuran.

2.3.3. One-pot synthesis of ring-substituted 2,3-dihydrobenzofurans. The substitution on the aromatic ring was then studied: the one-pot reaction proceeded well with fused aryl- (i.e., *para*-

sulfonamido α-naphthol substrate) (Table 3, entry 2) and alkyl-substituted derivatives (Table 3, entries 3 and 5).

In contrast, the presence of an ester afforded 2,3-dihydrobenzofuran **17** as trace amount after PIFA oxidation (Table 3, entry 4). Although it is necessary to have an electron-withdrawing group on the nitrogen atom of amino-phenols or naphthols (such as a sulfonyl group), it seems that the presence of such group is deleterious for the formation of the desired heterocycle.

3. Conclusion

The new one-pot version of the [3+2] cycloaddition reaction between *N*-substituted *para*-aminophenols and an azadiene appears to be useful to prepare various substituted 2,3-dihydrobenzofurans, and allows the condensation with unstable quinone imides derived from carboxamides, though in lower yields in this latter case.

We are convinced that our one-pot method will be helpful for medicinal chemists wishing to prepare such interesting heterocyclic structures.

4. Experimental

4.1. General

All reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points were measured on a Barnstead Electrothermal 9200 or Büchi B-540 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker ALS300, DRX300 and DRX400 Fourier transform spectrometers, using an internal deuterium lock, operating at 300 or 400 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_H=0.00; $CDCl_3$, δ_H=7.26 and DMSO-d_6, δ_H=2.50).[27] Data are presented as follows: chemical shift (δ, ppm), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad), coupling constant (reported in Hz), assignment. Atom numbering refers to naphthalene, pyridine and benzofuran nomenclatures. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AC200, ALS300, DRX300 or DRX400 Fourier transform spectrometers, using an internal deuterium lock, operating at 50, 75 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_C=0.00; $CDCl_3$, δ_C=77.16 and DMSO-d_6, δ_C=39.52). Carbon multiplicities (indicated in parentheses) were determined by DEPT experiments. ^{19}F NMR spectra were recorded on a Bruker ALS300 spectrometer, operating at 282 MHz, relative to $CFCl_3$. Electron-Spray low-resolution mass spectra were recorded on a Thermo ALCQ Advantage spectrometer. High-resolution mass spectra were recorded on a Bruker MicroTOF Q or Thermoquest Finnigan MAT 95 XL spectrometer (for chemical ionisations, isobutane was used).

Analytical Thin Layer Chromatography was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F_{254}, with visualization by ultraviolet and anisaldehyde stain solution.

Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40–63 μm). Pyridine (analytical grade), *N*,*N*-dimethylformamide (DMF, analytical grade), toluene (analytical grade), ethyl acetate (AcOEt, analytical grade) and absolute ethanol (analytical grade) were used as received without purification. Dichloromethane was distilled over calcium hydride prior to use. All other chemical reagents were used as received.

2-Methylacrolein *N*,*N*′-dimethylhydrazone **9** was synthesized via an acidic condensation between 2-methylacrolein and *N*,*N*′-dimethylhydrazine (CAUTION: these two chemicals are known to be highly toxic/carcinogenic compounds).[28] Methyl 5-aminosalicylate[29] and 4-amino-3,5-dimethyl phenol[21b] were prepared from commercially available 5-aminosalicylic acid and 3,5-dimethylphenol, according to literature procedures. Trimethylsilyl ethanesulfonyl chloride was prepared according to a modified protocol[30] of Weinreb's initial conditions.[31] Ag_2CO_3 on Celite was prepared according to Fétizon's protocol.[19]

4.2. *N*-Substituted *para*-aminophenols 8

Compound **8h** (R^4=Ph) was purchased by Alfa Aesar Chemicals. Some of the *para*-aminophenols **8** were prepared from 4-aminophenol according to literature protocols: sulfonylation reaction with trifluoromethanesulfonic anhydride for compound **8d** (R^4=SO_2CF_3)[32] or N-protection using Boc_2O in water for compound **8g** (R^4=COO*t*-Bu).[33] Compounds **8a**–**c**, **8e**,**f** and ring-substituted *para*-sulfonamidophenols were prepared according to the following procedures.

*4.2.1. General procedure 1. Sulfonylation of para-aminophenol: preparation of N-(4-hydroxyphenyl)-benzenesulfonamide **8a** (R^4=SO_2Ph).* To a cooled (0 °C) solution of *para*-aminophenol (10,9 g, 100 mmol) in DMF (20 mL) was added pyridine (20 mL) and then dropwise (over a 10 min period) benzenesulfonyl chloride (12,8 mL, 100 mmol). The mixture was allowed to warm to rt and was stirred for one additional hour. After this time, water (150 mL) and EtOAc (100 mL) were added. After decantation, the aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were washed with water (150 mL), 5% w/w aqueous solution of copper sulfate (150 mL) and brine (150 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to afford compound **8a** (19.22 g, 77%) as a white solid; mp 160 °C (lit.[13] 156 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.59 (2H, d, *J*=9.0, Ar*H*), 6.82 (2H, d, *J*=9.0, Ar*H*), 7.51 (2H, m, SO_2(*m*-Ar*H*)), 7.59 (1H, m, SO_2(*p*-Ar*H*)), 7.63–7.67 (2H, m, SO_2(*o*-Ar*H*)), 9.31 (1H, very br s, N*H*SO_2Ph or O*H*), 9.71 (1H, very br s, O*H* or N*H*SO_2Ph).

*4.2.2. 2-Trimethylsilanyl-ethanesulfonic acid (4-hydroxyphenyl)-amide **8b** (R^4=$SO_2CH_2CH_2SiMe_3$).* According to general procedure 1, scale: *para*-aminophenol (1.09 g, 10 mmol), DMF (20 mL), pyridine (10 mL), trimethylsilyl ethanesulfonyl chloride (2.01 g, 10 mmol), reaction time at rt=2 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to afford compound **8b** (2.144 g, 79%) as a beige solid; mp 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=−0.02 (9H, s, Si*Me*$_3$), 0.99–1.05 (2H, m, $CH_2CH_2SiMe_3$), 2.93–2.99 (2H, m, $CH_2CH_2SiMe_3$), 6.09 (1H, very br s, N*H* or O*H*), 6.78 (2H, d, *J*=8.9, Ar*H*), 6.82 (1H, s, O*H* or N*H*), 7.09 (2H, d, *J*=8.9, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ=−1.9 (CH_3), 10.6 (CH_2), 47.4 (CH_2), 116.5 (CH), 125.2 (CH), 128.9 (C), 154.5 (C). HRMS (ESI^+): *m*/*z* calcd for $C_{11}H_{19}NNaO_3SSi$: 296.0747 [MNa^+]; found: 296.0750.

*4.2.3. N-(4-Hydrophenyl)-methanesulfonamide **8c** (R^4=SO_2Me).* According to general procedure 1, scale: *para*-aminophenol (5.45 g, 50 mmol), DMF (20 mL), pyridine (10 mL), methanesulfonyl chloride (3.87 mL, 50 mmol), reaction time at rt=2 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 50:50) to afford compound **8c** (4.40 g, 48%) as a pale pink solid; mp 155–157 °C (lit.[13] 154.5–155.5 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.84 (3H, s, SO_2CH_3), 6.72 (2H, d, *J*=8.3, Ar*H*), 7.03 (2H, d, *J*=8.3, Ar*H*), 9.24 (1H, very br s, N*H*SO_2Me or O*H*), 9.31 (1H, very br s, O*H* or

N*H*SO_2Me). Spectral data were in agreement to those reported in the literature.[34]

4.2.4. 2,2,2-Trifluoro-N-(4-hydroxyphenyl)-acetamide ***8e*** *(R^4=$COCF_3$).* To a suspension of *para*-aminophenol (1.09 g, 10 mmol) in dichloromethane (20 mL) at 0 °C was slowly added trifluoroacetic anhydride (6.9 mL, 50 mmol). The resulting mixture was then stirred for 2 h at 0 °C. After removal of the volatiles under reduced pressure, the solid residue was taken in a 2 M $NaHCO_3$ aqueous solution (75 mL): this solution was extracted with EtOAc (4×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/EtOAc 70:30) to afford compound **8e** (1.04 g, 51%) as a white solid; mp 170–172 °C (lit.[35] 169–170 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.77 (2H, d, J=8.7, Ar*H*), 7.43 (2H, d, J=8.7, Ar*H*), 9.51 (1H, very br s, N*H*$COCF_3$ or O*H*), 10.99 (1H, very br s, O*H* or N*H*$COCF_3$). ^{19}F NMR (282 MHz, DMSO-d_6): δ=−74.2 (s, $COCF_3$).

4.2.5. N-(4-Hydroxyphenyl)-benzamide ***8f*** *(R^4=COPh).* According to general procedure 1, scale: *para*-aminophenol (5.45 g, 50 mmol), DMF (20 mL), pyridine (10 mL), benzoyl chloride (5.8 mL, 50 mmol), reaction time at rt=3 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to afford compound **8f** (8.2 g, 77%) as a white solid; mp 208–210 °C (lit.[36] 207–209 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.74 (2H, d, J=9.0, Ar*H*), 7.47–7.59 (5H, m, Ar*H* and CO*Ph*), 7.93 (2H, m, CO*Ph*), 9.26 (1H, very br s, N*H*COPh or O*H*), 10.02 (1H, br s, O*H* or N*H*COPh). Spectral data were in agreement to those reported in the literature.[36]

4.2.6. N-(4-Hydroxy-naphthalen-1-yl)-benzene sulfonamide. According to general procedure 1, scale: *para*-hydroxy-α-aminonaphthol hydrochloride (978 mg, 5 mmol), DMF (4 mL), pyridine (6 mL), benzenesulfonyl chloride (0.65 mL, 5 mmol), reaction time at rt=2 h. After addition of 1 M hydrochloric acid (10 mL), EtOAc (50 mL) and decantation, the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/EtOAc 70:30) to afford the *title compound* (880 mg, 59%) as a pale brown solid; mp 203–204 °C (lit.[37] 201–203 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.70 (1H, d, J=8.1, Ar*H*2), 6.85 (1H, d, J=8.1, Ar*H*3), 7.37 (2H, m, Ar*H*6 and Ar*H*7), 7.47 (2H, m, SO_2(*m*-Ar*H*)), 7.57 (1H, m, SO_2(*p*-Ar*H*)), 7.62 (2H, dd, J=7.0–1.7, SO_2(*o*-Ar*H*)), 7.62 (1H, dd, J=7.0–2.3, Ar*H*8), 8.07 (1H, dd, J=7.2–2.3, Ar*H*5), 9.80 (1H, br s, N*H*SO_2Ph or O*H*), 10.26 (1H, br s, O*H* or N*H*SO_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ=107.3 (CH), 122.1 (CH), 123.0 (C), 123.2 (CH), 124.8 (CH), 124.9 (C), 125.8 (CH), 126.2 (CH), 126.8 (CH), 129.0 (CH), 131.6 (C), 132.5 (CH), 140.2 (C), 152.5 (C).

4.2.7. N-(4-Hydroxy-3-methyl-phenyl)-benzene sulfonamide. According to general procedure 1, scale: 4-amino-2-methyl phenol (1.23 g, 10 mmol), DMF (4 mL), pyridine (2 mL), benzenesulfonyl chloride (1.27 mL, 10 mmol), reaction time at rt=2 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 70:30) to give the *title compound* (1.63 g, 62%) as a pale pink solid; mp 200–202 °C (lit.[13] 198–199 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.98 (3H, s, CH_3), 6.58 (1H, d, J=8.5, Ar*H*), 6.65 (1H, d, J=8.5, Ar*H*), 6.73 (1H, s, Ar*H*2), 7.49–7.61 (3H, m, SO_2(*m*-Ar*H*) and SO_2(*p*-Ar*H*)), 7.66 (2H, J=7.2, SO_2(*o*-Ar*H*)), 9.19 (1H, br s, N*H*SO_2Ph or O*H*), 9.67 (1H, br s, O*H* or N*H*SO_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ=16.0 (CH_3), 114.7 (CH), 121.2 (CH), 124.4 (C), 125.2 (CH), 126.7 (CH), 128.3 (C), 129.0 (CH), 132.6 (CH), 139.7 (C), 153.0 (C).

4.2.8. 5-Benzenesulfonylamino-2-hydroxy-benzoic acid methyl ester. According to general procedure 1, scale: methyl 5-aminosalicylate (440 mg, 2.63 mmol), DMF (1.0 mL), pyridine (0.5 mL), benzenesulfonyl chloride (0.34 mL, 2.63 mmol), reaction time at rt=4 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 65:35) to give the *title compound* as a white solid (700 mg, 87%); mp 143–145 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.84 (3H, s, CH_3), 6.88 (1H, d, J=9.0, Ar*H*5), 7.20 (1H, dd, J=9.0–2.6, Ar*H*6), 7.48 (1H, d, J=2.6, Ar*H*2), 7.50–7.63 (3H, m, SO_2(*m*-Ar*H*) and SO_2(*p*-Ar*H*)), 7.67–7.71 (2H, m, SO_2(*o*-Ar*H*)), 10.05 (1H, very br s, N*H*SO_2Ph or O*H*), 10.28 (1H, very br s, O*H* or N*H*SO_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ=52.6 (CH_3), 113.2 (C), 118.3 (CH), 123.2 (CH), 126.7 (CH), 129.0 (C), 129.2 (CH), 129.9 (CH), 132.9 (CH), 139.2 (C), 157.2 (C), 168.4 (C). HRMS (ESI$^+$): m/z calcd for $C_{14}H_{13}NNaO_5S$: 330.0407 [MNa^+]; found: 330.0407.

4.2.9. N-(4-Hydroxy-2,6-dimethyl-phenyl)-benzene sulfonamide.- According to general procedure 1, scale: 4-amino-3,5-dimethyl phenol (1.0 g, 7.3 mmol), DMF (4 mL), pyridine (2 mL), benzenesulfonyl chloride (0.93 mL, 7.3 mmol), reaction time at rt=1 h. The crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to give the *title compound* (1.763 g, 87%) as a yellow solid; mp 164–165 °C (lit.[38] 163 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.81 (6H, s, 2C*H*3), 6.37 (2H, s, Ar*H*3 and Ar*H*5), 7.55 (2H, m, SO_2(*m*-Ar*H*)), 7.62–7.66 (3H, m, SO_2(*m*-Ar*H*) and SO_2(*p*-Ar*H*)), 9.01 (1H, very br s, N*H*SO_2Ph or O*H*), 9.27 (1H, br s, O*H* or N*H*SO_2Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ=18.5 (CH_3), 114.8 (CH), 124.5 (C), 126.4 (CH), 129.2 (CH), 132.4 (CH), 138.9(C), 141.9 (C), 155.9 (C).

4.3. Pyridine derivatives

4.3.1. 2-Benzyloxy-5-nitropyridine ***12.*** In a round-bottomed flask fitted with a Dean Stark apparatus and a condenser were successively introduced 2-chloro-5-nitropyridine (6.34 g, 40 mmol), toluene (50 mL), benzyl alcohol (2.5 mL, 24 mmol), KOH (4.52 g, 80.6 mmol) and 18-C-6 (80 mg, 0.3 mmol). The mixture was stirred under reflux for 30 min and, after cooling to rt, water (40 mL) was then added. After decantation, the aqueous phase was extracted with EtOAc (3×40 mL). The combined organic phases (toluene and EtOAc) were washed with brine (1×120 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the orange residue was purified by flash chromatography (cyclohexane/EtOAc 90:10) to afford compound **12** (4.08 g, 74%) as a pale yellow solid; mp 105–106 °C (lit.[39] 107–108 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.49 (2H, s, CH_2 benzyl group), 6.88 (1H, d, J=9.0, *H*3), 7.35–7.48 (5H, m, Ar*H* benzyl group), 8.37 (1H, dd, J=9.0, 3.0, *H*4), 9.10 (1H, d, J=3.0, *H*6). Spectral data were identical to those reported in the literature.[40]

4.3.2. N-(6-Benzyloxy-pyridin-3-yl)-benzenesulfonamide ***13.*** To a solution of 2-benzyloxy-5-nitropyridine **12** (2.30 g, 10 mmol) in EtOAc (50 mL) was added 10% Pd/C (125 mg, 0.118 mmol). The resulting mixture was submitted to a 5 bars hydrogen pressure in a Parr hydrogenation reactor vessel and stirred for 6 h at rt. The reactor vessel was then opened, flushed with argon and benzenesulfonyl chloride (1.28 mL, 10 mmol) was added dropwise to the reaction mixture. After a 16 h additional stirring time, the mixture was filtered on a 2 cm thick silica gel pad, washing with EtOAc. The filtrate was evaporated under reduced pressure and the yellow liquid residue was purified by flash chromatography (cyclohexane/EtOAc 70:30) to afford compound **13** (2.863 g, 84%) as a white solid; mp 125 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=5.24 (2H, s, CH_2 benzyl group), 6.79 (1H, d, J=8.9, *H*5), 7.30–7.42 (6H, m, Ar*H* benzyl group and *H*4), 7.55 (2H, m, SO_2(*m*-Ar*H*)), 7.63 (1H, m, SO_2(*p*-Ar*H*)), 7.68–7.71 (2H, m, SO_2(*o*-Ar*H*)), 7.79 (1H, d, J=2.6, *H*2), 10.11 (1H, very br s, N*H*SO_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ=67.2 (CH_2), 111.0 (CH), 126.7 (CH),

127.7 (CH), 127.9 (CH), 128.1 (C), 128.3 (CH), 129.3 (CH), 133.0 (CH), 134.4 (CH), 137.1 (C), 139.0 (C), 140.6 (CH), 160.5 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{16}N_2NaO_3S$: 363.0774 [MNa$^+$]; found: 363.0775.

*4.3.3. N-(6-Hydroxy-pyridin-3-yl)-benzenesulfonamide **14**.* To a solution of compound **13** (2.00 g, 5.88 mmol) in absolute ethanol (50 mL) was added 10% Pd/C (73 mg, 0.069 mmol). The resulting mixture was submitted to a 5 bars hydrogen pressure in a Parr hydrogenation reactor vessel during 6 h. The mixture was filtered on a 1 cm thick silica gel pad, washing with EtOAc. The filtrate was evaporated under reduced pressure to give compound **14** as an off-white solid; mp 200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.24 (1H, d, *J*=9.6, *H*5), 6.96 (1H, d, *J*=3.0, *H*2), 7.08 (1H, dd, *J*=9.6–3.0, *H*4), 7,54–7.71 (5H, m, SO_2Ar*H*), 9.62 (1H, s, O*H* or N*H*SO_2Ph), 10.42 (1H, very br s, N*H*SO_2Ph or O*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ=117.2 (C), 119.4 (CH), 126.9 (CH), 129.3 (CH), 131.7 (CH), 133.0 (CH), 138.8 (C), 139.5 (CH), 161.1 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{11}N_2O_3S$: 251.0485 [MH$^+$]; found: 251.0484.

4.4. Quinone monoimides 11

*4.4.1. General procedure 2 for the synthesis of quinone monoimides using Ag_2CO_3 on Celite: preparation of compound **11a** (R^4=SO_2Ph).* To a cold (0 °C) solution of **8a** (25 mg, 0.1 mmol) in toluene (5 mL) was added Ag_2CO_3/Celite (60 mg, 0.1 mmol) in one portion. The resulting mixture was vigorously stirred for 30 min at 0 °C. The reaction mixture was then filtered on a 1 cm thick pad of Celite, washing with toluene. The filtrate was evaporated under reduced pressure to give quinone imide **11a** (24.2 mg, 98%) as a yellow solid; mp 132–133 °C (lit.[13] 134 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.70 (2H, m, alkene), 6.99 (1H, dd, *J*=10.0–3.0, alkene), 7.59 (2H, m, SO_2(*m*-Ar*H*)), 7.68 (1H, m, SO_2(*p*-Ar*H*)), 8.02 (2H, m, SO_2(*o*-Ar*H*)), 8.21 (1H, dd, *J*=10.0–3.0, alkene).

*4.4.2. Preparation of compound **11b** (R^4=$SO_2CH_2CH_2SiMe_3$).* According to general procedure 2, scale: aminophenol **8b** (55 mg, 0.2 mmol), Ag_2CO_3/Celite (120 mg, 0.21 mmol), toluene (10 mL), reaction time at 110 °C=30 min. Quinone imide **11b** was obtained as a yellow powder (52 mg, 95%); mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.10 (9H, s, Si*Me*$_3$), 1.13–1.19 (2H, m, $CH_2CH_2SiMe_3$), 3.22–3.28 (2H, m, $CH_2CH_2SiMe_3$), 6.64 (1H, dd, *J*=10.6–2.3), 6.72 (1H, dd, *J*=10.2–2.3), 7.03 (1H, dd, *J*=10.2–2.6), 8.01 (1H, dd, *J*=10.6–2.6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ=−1.9 (CH_3), 9.8 (CH_2), 51.5 (CH_2), 130.7 (CH), 135.0 (CH), 135.7 (CH), 140.2 (CH), 164.8 (C), 185.9 (C). HRMS (CI): *m*/*z* calcd for $C_{11}H_{18}NO_3SSi$: 272.0777 [MH+]; found: 272.0778.

*4.4.3. Preparation of compound **11c** (R^4=SO_2Me).* According to general procedure 2, scale: aminophenol **8c** (0.094 g, 0.5 mmol), Ag_2CO_3/Celite (300 mg, 0.53 mmol), toluene (20 mL), reaction time at rt=30 min. Quinone imide **11c** was obtained as a yellow solid (64 mg, 69%); mp 132–135 °C (lit.[13] 134 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.28 (3H, s, SO_2*Me*), 6.65 (1H, dd, *J*=10.2–2.3, alkene), 6.73 (1H, dd, *J*=10.4–2.3, alkene), 7.02 (1H, dd, *J*=9.8–2.6, alkene), 7.96 (1H, dd, *J*=10.6–2.6, alkene).

*4.4.4. Preparation of compound **11h** (R^4=Ph).* According to general procedure 2, scale: aminophenol **8h** (0.370 g, 2.0 mmol), Ag_2CO_3/Celite (1.2 g, 2.11 mmol), toluene (80 mL), reaction time at rt=30 min. Quinone imide **11h** was obtained as an orange solid (364 mg, 99%); mp 101–102 °C (lit.[19] 102–103 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.54 (1H, dd, *J*=10.2–2.3, alkene), 6.70 (1H, dd, *J*=9.8–2.3, alkene), 6.86–6.90 (2H, m, *o*-Ar*H*), 7.09 (1H, dd, *J*=10.2–2.6, alkene), 7.24 (1H, m, *p*-Ar*H*), 7.31 (1H, dd, *J*=10.2–2.6, alkene), 7.41 (2H, m, *m*-Ar*H*).

*4.4.5. Preparation of compound **11a** (R^4=SO_2Ph) using a PIFA mediated oxidation.* To a cold (0 °C) solution of **8a** (25 mg, 0.1 mmol) in toluene (5 mL) was added K_2CO_3 (33 mg, 0.24 mmol) and PIFA (52 mg, 0.12 mmol). The resulting mixture was stirred for 30 min at 0 °C. The reaction mixture was then filtered on a 1 cm thick pad of Celite, washing with toluene and the filtrate was evaporated under reduced pressure to give quinone imide **11a** (24.2 mg, 98%) as a yellow-orange solid; mp 133 °C (lit.[13] 134 °C).

4.5. 2,3-Dihydrobenzofurans 7a–h, 15–18

*4.5.1. General procedure 3 for the 2,3-dihydrobenzofurans synthesis with Ag_2CO_3 on Celite mediated oxidation: preparation of compound **15**.* To a solution of *N*-phenylsulfonyl *para*-hydroxy α-naphthylamine (299 mg, 1.0 mmol) in 40 mL of absolute ethanol was added Ag_2CO_3 on Celite (600 mg, 1.05 mmol). The colourless solution turned to yellow and the mixture was stirred under reflux until the complete consumption of the starting material (30 min), then cooled to 0 °C. A solution of azadiene **9** (224 mg, 2.0 mmol) in 4 mL of absolute ethanol was then added in one portion. The solution turned to dark green and the resulting mixture allowed to stir for 30 min. After filtration on a pad of Celite (1 cm thick), washing with ethanol, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **15** as a beige solid (202 mg, 50%); mp 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.68 (3H, s, C*H*$_3$), 2.82 (6H, s, N*Me*$_2$), 3.09 (1H, d, *J*=15.4, *H*3), 3.77 (1H, d, *J*=15.4, *H*3′), 6.67 (1H, s, *H*C=N–NMe$_2$), 6.74 (1H, br s, N*H*SO_2Ph), 7.21 (1H, s, *H*4), 7.23–7.27 (1H, m, Ar*H*), 7.32–7.37 (3H, m, Ar*H*), 7.48 (1H, tt, *J*=7.2, 1.2, SO_2(*p*-Ar*H*)), 7.59 (1H, d, *J*=8.4, Napth*H*), 7.70 (2H, dd, *J*=8.4–1.2, Ar*H*), 7.90 (1H, d, *J*=7.6, Napth*H*). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=26.0 (CH_3), 40.6 (CH_2), 42.9 (CH_3), 90.1 (C), 119.7 (C), 120.8 (C), 122.2 (CH), 122.4 (CH), 123.1 (C), 123.9 (CH), 125.5 (CH), 126.3 (CH), 127.5 (CH), 129.0 (CH), 130.6 (C), 132.8 (CH), 139.7 (C), 153.8 (C). HRMS (ESI$^-$): *m*/*z* calcd for $C_{22}H_{22}N_3O_3S$: 408.1387 [M−H$^-$]; found: 408.1392.

*4.5.2. General procedure 4 for the 2,3-dihydrobenzofurans synthesis with PIFA mediated oxidation: preparation of compound **7a**.* To a solution of *N*-phenylsulfonyl *para*-aminophenol **8a** (125 mg, 0.5 mmol) in 20 mL of toluene were added dried K_2CO_3 (166 mg, 1.2 mmol) and PIFA (258 mg, 0.6 mmol) and the resulting mixture was heated up at 110 °C (oil bath). The colourless solution, which turned to orange, was stirred for 5 min at this temperature, and then cooled to 0 °C. A solution of azadiene **9** (112 mg, 1.0 mmol) in 2 mL of toluene was then added in one portion. The solution turned to dark red and the resulting mixture allowed to stir for 5 min. Without evaporation, the reaction mixture was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 80:20) to give the 2,3-dihydrobenzofuran **7a** (R^4=SO_2Ph) as a yellow viscous oil (102 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.54 (3H, s, C*H*$_3$), 2.77 (6H, s, N*Me*$_2$), 2.88 (1H, d, *J*=16.1, *H*3), 3.56 (1H, d, *J*=16.1, *H*3′), 6.52 (1H, d, *J*=8.4, *H*7), 6.61 (1H, s, *H*C=N–NMe$_2$), 6.68 (1H, dd, *J*=8.4–2.3, *H*6), 6.95 (1H, br d, *J*=2.3, *H*4), 7.09 (1H, br s, N*H*SO_2Ph), 7.41 (2H, t, *J*=7.4, SO_2(*m*-Ar*H*)), 7.51 (1H, t, *J*=7.4, SO_2(*p*-Ar*H*)), 7.71–7.75 (2H, m, SO_2(*o*-Ar*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): 25.7 (CH_3), 39.7 (CH_2), 42.8 (CH_3), 89.2 (C), 109.5 (CH), 122.1 (CH), 124.4 (CH), 127.4 (CH), 128.4 (C), 128.5 (C), 129.0 (CH), 132.8 (CH), 135.7 (CH), 139.1 (C), 157.0 (C). HRMS (EI): calcd for $C_{18}H_{21}N_3O_3S$ [M$^{+\bullet}$]: 359.1304; found: 359.1303.

*4.5.3. Compound **7b**.* According to general procedure 3, scale: *para*-aminophenol **8b** (137 mg, 0.5 mmol), Ag_2CO_3 on Celite (300 mg,

0.53 mmol), absolute ethanol (20 mL) and reaction time at 0 °C=1 h. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of absolute ethanol and reaction time at 0 °C=15 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 80:20) to give compound **7b** as a pale yellow oil (177 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.00 (9H, s, SiMe_3), 1.01–1.07 (2H, m, $CH_2CH_2SiMe_3$), 1.58 (3H, s, CH_3), 2.79 (6H, s, NMe_2), 2.91–2.99 (3H, m, $CH_2CH_2SiMe_3$ and *H*3), 3.66 (1H, d, *J*=15.8, *H*3′), 6.59 (1H, s, *H*C=N–NMe$_2$), 6.64 (1H, br s, N*H*SO$_2$CH$_2$CH$_2$SiMe$_3$), 6.67 (1H, d, *J*=8.7, *H*7), 6.93 (1H, dd, *J*=8.7–2.6, *H*6), 7.10 (1H, d, *J*=2.6, *H*4). ^{13}C NMR (50 MHz, $CDCl_3$): δ=−2.0 (CH_3), 10.5 (CH_2), 25.7 (CH_3), 39.8 (CH_2), 42.7 (CH_3), 46.8 (CH_2), 89.2 (C), 109.8 (CH), 121.2 (CH), 123.4 (CH), 128.8 (C), 129.0 (C), 135.7 (CH), 156.8 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{17}H_{30}N_3O_3SSi$: 384.1772 [MH$^+$]; found: 384.1776.

4.5.4. Compound ***7c****.* According to general procedure 3, scale: *para*-aminophenol **8c** (94 mg, 0.5 mmol), Ag_2CO_3 on Celite (300 mg, 0.53 mmol), absolute ethanol (20 mL) and reaction time at rt=30 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of absolute ethanol and reaction time at 0 °C=15 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60:40) to give compound **7c** as a pale yellow oil (120 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60 (3H, s, CH_3), 2.81 (6H, s, NMe_2), 2.95 (3H, s, SO_2CH_3), 2.98 (1H, d, *J*=15.8, *H*3), 3.68 (1H, d, *J*=15.8, *H*3′), 6.30 (1H, br s, *H*C=N–NMe$_2$), 6.67 (1H, very br s, N*H*SO$_2$Me), 6.69 (1H, d, *J*=8.3, *H*7), 6.96 (1H, dd, *J*=8.7–2.3, *H*6), 7.12 (1H, d, *J*=2.3, *H*4). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.9 (CH_3), 38.9 (CH_3), 39.8 (CH_2), 42.8 (CH_3), 89.4 (C), 109.9 (CH), 121.7 (CH), 124.0 (CH), 128.7 (C), 129.0 (C), 135.7 (CH), 157.3 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{13}H_{20}N_3O_3S$: 298.1220 [MH$^+$]; found: 298.1220.

4.5.5. Compound ***7d****.* According to general procedure 3, scale: *para*-aminophenol **8d** (24 mg, 0.1 mmol), Ag_2CO_3 on Celite (60 mg, 0.1 mmol), toluene (4 mL) and reaction time at rt=15 min. Azadiene **9** (22.4 mg, 0.2 mmol) in 1 mL of toluene and reaction time at 0 °C=30 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **7d** as a pale brown oil (21 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.59 (3H, s, CH_3), 2.80 (6H, s, NMe_2), 2.97 (1H, d, *J*=16.0, *H*3), 3.67 (1H, d, *J*=16.0, *H*3′), 6.66 (1H, s, *H*C=N–NMe$_2$), 6.69 (1H, d, *J*=8.7, *H*7), 6.99 (1H, dd, *J*=8.7–2.3, *H*6), 7.09 (1H, m, *H*4). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−75.51 (s, SO_2CF_3). HRMS (ESI$^+$): *m*/*z* calcd for $C_{13}H_{17}F_3N_3O_3S$: 352.0937 [MH$^+$]; found: 352.0935.

4.5.6. Compound ***7e****.* According to general procedure 3, scale: *para*-aminophenol **8e** (205 mg, 1.0 mmol), Ag_2CO_3 on Celite (600 mg, 1.05 mmol), toluene (40 mL) and reaction time at 110 °C=1 h. Azadiene **9** (224 mg, 2.0 mmol) in 4 mL of toluene and reaction time at 0 °C=15 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 75:25) to give compound **7e** as a viscous green oil (50 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.60 (3H, s, CH_3), 2.80 (6H, s, NMe_2), 3.00 (1H, d, *J*=15.8, *H*3), 3.69 (1H, d, *J*=15.8, *H*3′), 6.67 (1H, br s, *H*C=N–NMe$_2$), 6.72 (1H, d, *J*=8.7, *H*7), 7.14 (1H, dd, *J*=8.7–2.3, *H*6), 7.47 (1H, d, *J*=2.3, *H*4), 7.79 (1H, br s, N*H*COCF$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.8 (CH_3), 39.8 (CH_2), 42.8 (CH_3), 89.5 (C), 109.7 (CH), 118.7 (CH), 121.2 (CH), 127.7 (C), 128.7 (C), 135.4 (CH), 156.9 (C) (quaternary carbons CO and CF_3 not detected, due to ^{13}C–^{19}F couplings). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−76.05 (s, $COCF_3$). HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{17}F_3N_3O_2$: 316.1267 [MH$^+$]; found: 316.1284.

4.5.7. Compound ***7f****.* According to general procedure 4, scale: *para*-aminophenol **8f** (106 mg, 0.5 mmol), PIFA (258 mg, 0.6 mmol), K_2CO_3 (166 mg, 1.2 mmol), absolute ethanol (20 mL) and reaction time at rt=15 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of absolute ethanol and reaction time at 0 °C=1 h. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **7f** as a pale beige oil (29 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.61 (3H, s, CH_3), 2.80 (6H, s, NMe_2), 3.02 (1H, d, *J*=15.8, *H*3), 3.66 (1H, d, *J*=15.8, *H*3′), 6.70 (1H, br s, *H*C=N–NMe$_2$), 6.72 (1H, d, *J*=8.5, *H*7), 7.15 (1H, dd, *J*=8.5–2.3, *H*6), 7.44–7.56 (3H, m, Ar*H*), 7.58 (1H, br s, Ar*H*), 7.77 (1H, very br s, N*H*COPh), 7.85 (2H, m, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.7 (CH_3), 40.2 (CH_2), 42.8 (CH_3), 89.1 (C), 109.5 (CH), 118.9 (CH), 121.0 (CH), 127.1 (CH), 128.1 (C), 128.8 (CH), 130.7 (C), 131.7 (CH), 135.2 (C), 136.1 (CH), 155.7 (C), 165.9 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{22}N_3O_2$: 324.1707 [MH$^+$]; found: 324.1705.

4.5.8. Compound ***7g****.* According to general procedure 4, scale: *para*-aminophenol **8g** (106 mg, 0.5 mmol), PIFA (258 mg, 0.6 mmol), K_2CO_3 (166 mg, 1.2 mmol), absolute ethanol (20 mL) and reaction time at rt=30 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of absolute ethanol and reaction time at 0 °C=15 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **7g** as an orange oil (30 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.50 (9H, s, C(C*H*$_3$)$_3$), 1.57 (3H, s, C*H*$_3$), 2.78 (6H, s, N*Me*$_2$), 2.97 (1H, d, *J*=15.8, *H*3), 3.60 (1H, d, *J*=15.8, *H*3′), 6.34 (1H, br s, *H*C=N–NMe$_2$), 6.64 (2H, br d, *J*=8.7, *H*7 and *H*4), 6.89 (1H, dd, *J*=8.7–2.3, *H*6), 7.31 (1H, very br s, N*H*COO*t*-Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.6 (CH_3), 28.5 (CH_3), 40.3 (CH_2), 42.8 (CH_3), 80.2 (C), 88.8 (C), 109.3 (CH), 117.4 (CH), 119.5 (CH), 128.0 (C), 131.1 (C), 136.3 (CH), 153.5 (C), 154.8 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{17}H_{26}N_3O_3$: 320.1969 [MH$^+$]; found: 320.1965.

4.5.9. Compound ***7h****.* According to general procedure 4, scale: *para*-aminophenol **8h** (93 mg, 0.5 mmol), PIFA (258 mg, 0.6 mmol), toluene (20 mL) and reaction time at rt=30 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of toluene and reaction time at 0 °C=30 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 90:10) to give compound **7h** as a yellow oil (90 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.61 (3H, s, CH_3), 2.81 (6H, s, NMe_2), 2.99 (1H, d, *J*=15.8, *H*3), 3.63 (1H, d, *J*=15.8, *H*3′), 5.47 (1H, very br s, N*H*Ph), 6.69 (1H, d, *J*=8.3, *H*7), 6.75 (1H, br s, *H*C=N–NMe$_2$), 6.80 (1H, m, *p*-Ar*H*), 6.86–6.90 (3H, m, Ar*H* and *H*6), 6.98 (1H, m, *H*4), 7.20 (2H, m, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.7 (CH_3), 40.3 (CH_2), 42.8 (CH_3), 88.7 (C), 109.8 (CH), 115.4 (CH), 119.1 (CH), 119.2 (CH), 121.6 (CH), 128.3 (C), 129.3 (CH), 135.5 (C), 136.5 (CH), 145.8 (C), 154.5 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{22}N_3O$: 296.1757 [MH$^+$]; found: 296.1755.

4.5.10. Compound ***16****.* According to general procedure 3, scale: *N*-(4-hydroxy-3-methyl-phenyl)-benzene sulfonamide (131 mg, 0.5 mmol), Ag_2CO_3 on Celite (300 mg, 0. 53 mmol), toluene (20 mL) and reaction time at 110 °C=30 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of toluene and reaction time at 0 °C=30 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **16** as a yellow solid (115 mg, 62%); mp 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.55 (3H, s, CH_3), 2.06 (3H, s, C*H*$_3$), 2.80 (6H, s, N*Me*$_2$), 2.89 (1H, d, *J*=15.8, *H*3), 3.56 (1H, d, *J*=15.8, *H*3′), 6.29 (1H, br s, *H*C=N–NMe$_2$), 6.53 (1H, d, *J*=1.5, *H*6 or *H*4), 6.71 (2H, br s, *H*4 or *H*6 and N*H*SO$_2$Ph), 7.44 (2H, m, SO$_2$(*m*-Ar*H*)), 7.54 (1H, m, SO$_2$(*p*-Ar*H*)), 7.71–7.74 (2H, m, SO$_2$(*o*-Ar*H*)). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=15.4 (CH_3), 25.8 (CH_3), 40.1 (CH_2), 42.9 (CH_3), 88.7 (C), 119.3 (CH), 120.0 (C), 125.7 (CH), 127.4 (C), 127.5 (CH), 128.1 (C), 129.0 (CH), 132.8 (CH), 136.3 (CH, better detected when processing the FID signal with an LB value of 5 Hz), 139.3 (C), 155.7 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{24}N_3O_3S$: 374.1533 [MH$^+$]; found: 374.1542.

4.5.11. Compound ***17****.* According to general procedure 4, scale: 5-benzenesulfonylamino-2-hydroxy-benzoic acid methyl ester (31 mg, 0.1 mmol), PIFA (52 mg, 0.12 mmol), K_2CO_3 (33 mg,

0.24 mmol), toluene (4 mL) and reaction time at rt=30 min. Azadiene **9** (22.4 mg, 0.2 mmol) in 1 mL of toluene and reaction time at 0 °C=30 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **17** as a pale green oil (10 mg, contaminated with an inseparable side-product). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.62 (3H, s, C*H*$_3$), 2.80 (6H, s, N*Me*$_2$), 2.90 (1H, d, *J*=16.0, *H*3), 3.72 (1H, d, *J*=16.0, *H*3′), 3.81 (3H, s, OC*H*$_3$), 6.33 (1H, br s, *H*C=N–NMe$_2$), 6.68 (1H, very br s, N*H*SO$_2$Ph), 7.17 (1H, d, *J*=2.6, *H*6 or *H*4), 7.22 (1H, d, *J*=2.5, *H*4 or *H*6), 7.44 (2H, m, SO$_2$(*m*-Ar*H*)), 7.55 (1H, m, SO$_2$(*p*-Ar*H*)), 7.68–7.72 (2H, m, SO$_2$(*o*-Ar*H*)). HRMS (ESI$^+$): *m*/*z* calcd for $C_{20}H_{23}N_3NaO_5S$: 440.1251 [MH$^+$]; found: 440.1249.

4.5.12. Compound ***18****.* According to general procedure 3, scale: *N*-(4-hydroxy-2,6-dimethyl-phenyl)-benzene sulfonamide, Ag_2CO_3 on Celite (300 mg, 0. 53 mmol), toluene (20 mL) and reaction time at 110 °C=30 min. Azadiene **9** (112 mg, 1.0 mmol) in 2 mL of toluene and reaction time at 0 °C=30 min. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70:30) to give compound **18** as an orange solid (95 mg, 50%); mp 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ=1.58 (3H, s, C*H*$_3$), 1.81 (3H, s, C*H*$_3$), 2.00 (3H, s, C*H*$_3$), 2.80 (6H, s, N*Me*$_2$), 2.84 (1H, d, *J*=15.6, *H*3), 3.50 (1H, d, *J*=15.6, *H*3′), 5.92 (1H, br s, *H*C=N–NMe$_2$), 6.37 (1H, s, *H*7), 6.67 (1H, very br s, N*H*SO$_2$Ph), 7.46 (2H, m, SO$_2$(*m*-Ar*H*)), 7.57 (1H, m, SO$_2$(*p*-Ar*H*)), 7.73–7.76 (2H, m, SO$_2$(*o*-Ar*H*)). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=16.0 (CH_3), 19.0 (CH_3), 26.0 (CH_3), 39.5 (CH_2), 42.9 (CH_3), 89.1 (C), 109.0 (CH), 124.7 (C), 125.3 (C), 127.4 (CH), 129.1 (CH), 132.8 (CH), 135.4 (C), 138.0 (C), 140.9 (C), 157.4 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{20}H_{25}N_3NaO_3S$: 410.1509 [MNa$^+$]; found: 410.1503.

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