Tetrahedron 68 (2012) 7456–7462

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and arylation of unprotected sulfonimidamides

Matías Funes Maldonado [a,†], Fernando Sehgelmeble [a], Fanny Bjarnemark [a], Mats Svensson [a], Jens Åhman [a], Per I. Arvidsson [b,c,d,*]

[a] Medicinal Chemistry, iScience, CNSP iMed, AstraZeneca R&D Södertälje, S-151 85, Södertälje, Sweden
[b] Project Management, CNSP iMed, AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden
[c] Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Centre, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden
[d] School of Pharmacy and Pharmacology, Westville Campus, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa

ARTICLE INFO

Article history:
Received 18 February 2012
Received in revised form 28 May 2012
Accepted 18 June 2012
Available online 26 June 2012

Keywords:
Sulfonimidamides
Arylation
Isostere
C–N coupling
Pd catalysis

ABSTRACT

Herein we evaluate different methodologies for the synthesis of unprotected sulfonimidamides. Three different procedures that allow orthogonal deprotection of the imine nitrogen under acidic, nucleophilic, and basic conditions were established. Moreover, we present a highly efficient methodology for functionalization of the imine nitrogen through Pd-catalyzed C–N arylation. RuPhos ligand was shown to allow short reaction time, excellent yields, and allowed coupling of both aryl halides and heteroaryl bromides.

1. Introduction

Sulfonimidamides are aza-analogs of sulfonamides, in which one oxygen atom has been replaced by a nitrogen group. This structural modification creates a stereogenic sulfur center and thereby offers the possibility of introducing additional structural diversity around this functional group. We recently disclosed that sulfonimidamides represent an interesting bioisostere of sulfonamides, a widely used functional group in medicinal chemistry.[1]

So far, the sulfonimidamide motif has received little attention in the chemical literature. Such compounds were first described in the 1960s by Levechenko et al.[2] However it was only during the last years that some research has focused on their applications in organic synthesis and their biological activity. The use of sulfonimidamides as reagent in organic synthesis has been studied by Malacriaet al.[3] Sulfonimidamides have been applied in the iminations of sulfides,[4a] aziridination of olefins,[4b,c] and C–H aminations of hydrocarbons[4d,5,6] by Dodd, Dauban, and others. Bolm et al. explored the application of sulfonimidamides as organocatalyst in asymmetric reactions,[7] as chiral ligands in asymmetric metal catalysis,[8] and more recently their use in iridium-catalyzed asymmetric hydrogenation of cyclic enamides.[9] The use of sulfonimidamides as a functional group in biologically active compounds is less explored. Researchers from Lilly Research Laboratories explored their use as analogs of oncolytic sulfonylureas,[10] while the use of sulfonimidamide as a transition state analog for aspartic acid and metallo-proteases was explored by Schloss.[11]

The synthesis of *N*-protected sulfonimidamides has been described by Bolm et al.;[12] however, only few synthetic approaches for their preparation have been reported. A patent application was published describing the synthesis and the use of sulfonimidamides as pesticidal agents, especially against insects and acaridae.[13] The synthesis of unprotected sulfonimidamides, i.e., R^4=H Fig. 1, has initially been investigated by Johnson and Lavergne.[14] From a pharmaceutical standpoint it is important to be able to access

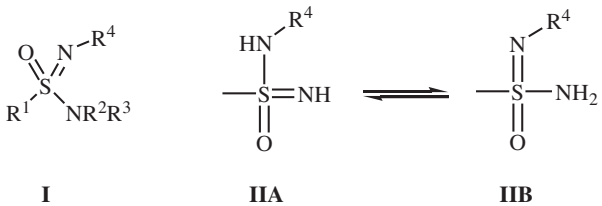


Fig. 1. Structure of sulfonimidamides **I** (1° R^2, R^3=H; 2° R^2=H, $R^3 \neq$H; 3° R^2, $R^3 \neq$H). Tautomerism of sulfonimidamides **II** (**IIA** most stable (1.0 kcal/mol) when R^4=Me, while **IIB** most stable (4.2 kcal/mol) when R^4=acyl).

* Corresponding author. Tel.: +46 8 553 25923; e-mail addresses: Per.Arvidsson@astrazeneca.com, Per.Arvidsson@orgfarm.uu.se (P.I. Arvidsson).
† Current address: Department of Chemistry, Faculty of Mathematics and Natural Sciences, Oslo University, 0371 Oslo, Norway.

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.06.072

N–H sulfonimidamides, i.e., R^4=H, as these would be the closest analogs of sulfonimidamides and serve as versatile precursors for the substituted (R^4=Alk, Ar) analogs. The present work aims to develop such N–H derivatives, and also explore novel methodology for their functionalization by arylation of the imine nitrogen.

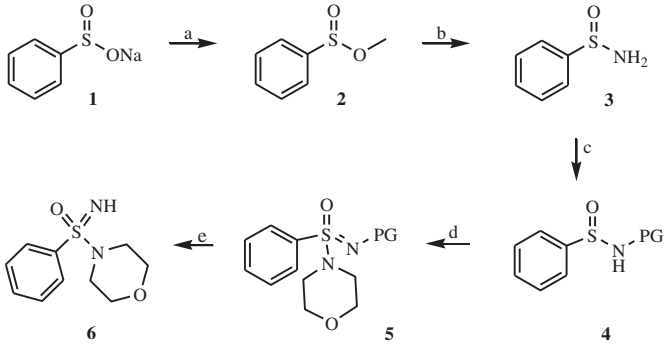
2. Results and discussion

Sulfonamides and sulfonimidamides can be primary (1°), secondary (2°) or tertiary (3°), (structure **I**, Fig. 1). Primary and secondary sulfonimidamides represent interesting structures, as they may undergo tautomerization by migration of a proton from one nitrogen atom to another (i.e., structure **II**, Fig. 1). We undertook some initial theoretical calculations on this tautomeric equilibrium. Our results confer that tautomer **IIA** is more stable by 1.0 kcal/mol (when R^4=Me), while the tautomer **IIB** is more stable by 4.2 kcal/mol (when R^4=COMe) (for computational details see Section 5 in the experimental part).[15]

This tautomerism of sulfonimidamides was described in 1979 by Johnson et al., who demonstrated rapid proton exchange on the NMR time scale.[16] Tautomerization can be avoided by having an acyl-protecting group on the imine nitrogen, thus making tautomer **IIB** more stable. Similarly, tertiary sulfonimidamides will not undergo tautomerization. In order to avoid the complexity of tautomeric equilibrium, we decided to focus on tertiary substituted sulfonimidamide, i.e., R^2, $R^3 \neq$ H, Fig. 1.

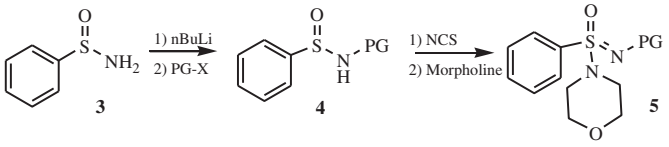
Our synthesis strategy for the *N*–H sulfonimidamide was based on finding an appropriate *N*-protecting group that allows for synthesis and manipulation of the core combined with a late stage deprotection to release the N–H functionality. It was important to find protecting groups with orthogonal removal conditions to allow for a wide variety of structures to be made.

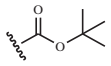
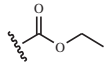
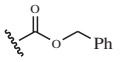
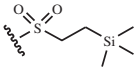
We based our synthesis of *N*-protected sulfonimidamides on Bolm's approach (Scheme 1): first, sodium benzenesulfinate salt **1** was treated with thionyl chloride to convert it into methyl ester **2** in up to 96% yield via the treatment of the corresponding sulfinic acid chloride with methanol. Next, ester **2** was reacted with lithium hexamethyldisilazide (LiHMDS), which upon hydrolysis gave benzenesulfinamide **3** in 90% yield after recrystallization.[17] Protection of sulfinamide **3** with 2.5 equiv of *n*-BuLi, followed by the addition of the corresponding anhydride[18] afforded the *N*-acylsulfinamide **4** (Table 1); alternatively, the reaction of the corresponding sulfinic acid chloride with 2-(trimethylsilyl)ethanesulfonamide or benzylamine provided sulfinamides **4e** and **4f**, respectively (Table 1, entries 5 and 6). Oxidative chlorination using *N*-chlorosuccinimide[12]



Scheme 1. Synthesis of unprotected sulfonimidamide **6**. (a) $SOCl_2$ (3 equiv), DCM, 0 °C→rt, 3 h; concentrated in vacuum, then methanol 0 °C, triethylamine (3 equiv), rt, overnight, 96%; (b) LiHMDS (1.5 equiv), THF, −78 °C→RT, 1.5 h; then satd aq NH_4Cl, rt, overnight, recrystallization from hexane/ethyl acetate 2:1, 90%; (c) *n*-butyl lithium (2.5 equiv), corresponding anhydride (1.2 equiv), THF, −78 °C→rt, overnight; (d) NCS (3 equiv), acetonitrile, rt, 2 h; then morpholine (3 equiv), 43 h; (e) conditions summarized in Table 2.

Table 1
Summary of protection and oxidation steps for the synthesis of sulfonimidamides



Entry	PG	Product[a] **4**	Yield[b] (%)	Product[c] **5**	Yield[b] (%)
1		**4a**	45	**5a**	61
2		**4b**	77	**5b**	79
3		**4c**	74	**5c**	87
4		**4d**	63	**5d**	75
5		**4e**[d]	Not isolated	**5e**	18
6		**4f**[e]	94	**5f**	8

[a] Reaction conditions: *n*-butyl lithium (2.5 M in hexane, 2.5 equiv), corresponding anhydride (1.2 equiv), THF, −78 °C, overnight.
[b] Isolated yield determined after column chromatography.
[c] Reaction conditions: NCS (3 equiv), morpholine (3 equiv), MeCN, rt, 17–43 h.
[d] NaH (1.2 equiv), 2-(trimethylsilyl)ethanesulfonamide (1.2 equiv), benzenesulfinic chloride (1.1 equiv).
[e] Benzylamine (1.1 equiv), Et_3N (1.5 equiv), benzenesulfinic chloride (1.0 equiv).

(NCS) in acetonitrile and treatment of the resulting sulfonimidoyl chloride with 3.0 equivalents of morpholine afforded *N*-substituted sulfonimidamide **5** in moderate to good yield 8–87% (Table 1).

The best result for the protection step was obtained with *N*-benzyl (94%, Table 1, entry 6), which provided product **4f** that was readily purified through recrystallization. Reaction of *N*-benzoyl and ethyl carbamate derivative also gave the desired products **4b** and **4c** in good yields (77 and 74%, respectively; Table 1, entries 2 and 3). Other carbamate protecting groups, i.e., *N*-benzyl and *tert*-butyl, gave the desired products **4d** and **4a** in slightly lower yields (63 and 45%, respectively; Table 1, entries 4 and 1). Product **4e** was not isolated due to decomposition during column chromatography; instead this product was used directly in the next step.

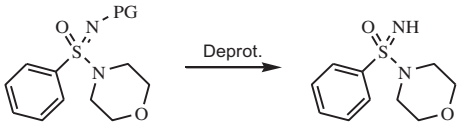
The reactivity of the protected sulfinamides **4a**–**4f** during the oxidation step can be compared in Table 1. For this reaction the best result was obtained with *N*-ethyl carbamate sulfinamide **4c** (87%, Table 1, entry 3). However, reaction of *N*-benzoyl and *N*-benzyl carbamate sulfinamide **4b** and **4d** also gave the desired products **5b** and **5d** in good yields (79%, 75%, entries 2, 4, respectively). Further evaluation of the cleavage of these protecting groups was necessary in order to determine, which would be the methodology of choice.

Bolm's group,[12] as well as internal work at AstraZeneca, has only explored electron-withdrawing protecting groups for sulfinamides **4**. In order to evaluate the electronic influence of the nitrogen-protecting group on the subsequent chlorination and substitution, we employed *N*-benzyl sulfinamide **4f**. The use of this non electron-withdrawing group led to the formation of **5f** in only 8% yield (Table 1, entry 6), thus demonstrating the need for an electron-

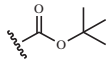
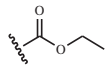
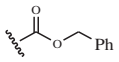
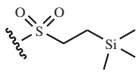
withdrawing substituent for the oxidative chlorination step to proceed smoothly.

The cleavage of the protecting groups was one of the most important steps in our synthesis because it will lead us to the unprotected sulfonimidamide **6** that is of interest on its own, but also offers the possibility for further functionalization through arylation in this position. Sulfonimidamide **5a** was treated with 5 equiv of trifluoroacetic acid (TFA) in DCM at room temperature to yield the 'free' sulfonimidamide **6** in excellent yield (87%, Table 2, entry 1). A

Table 2
Optimized conditions for deprotection of sulfonimidamides



5 6

Entry	Substrate	PG	Conditions	Yield[a] (%)	Overall yield[b] (%)
1	**5a**		TFA/DCM	87	21
2	**5b**		HCl	53	28
3	**5c**		C_2H_5ONa/EtOH	91	51
4	**5d**		Pd/H_2	64	36
5	**5e**		TBAF	85	9

[a] Isolated yield determined after column chromatography.
[b] Overall yield of the synthesis of 4-(phenylsulfonimidoyl)morpholine **6** starting from **1**.

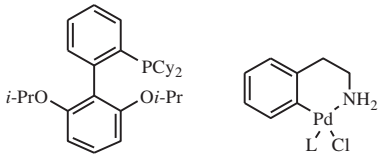
simple procedure for cleavage of the *N*-benzoyl protecting group with borane tetrahydrofuran complex was reported by Bolm in a paper related to the α-arylation of sulfoximines;[19] however, employing this methodology to sulfonimidamides did not prove satisfactory results, due to competing benzoyl to benzyl reduction. Instead, exposing **5b** to acidic conditions (1.0 M HCl in dioxane) at room temperature afforded 4-(phenylsulfonimidoyl)morpholine **6** in moderate yield (53%, Table 2, entry 2). The cleavage of the protecting groups on sulfonimidamides **5c**–**5e** was based on a procedure reported in a patent related to the synthesis of sulfoximines.[20] Sulfonimidamide **5c** was deprotected under basic conditions, using a solution of sodium ethoxide in ethanol and stirring at room temperature for 21 h, to afford the desired product **6** in excellent yield (91%, Table 2, entry 3). The treatment of sulfonimidamide **5d** in an H-cube continuous-flow hydrogenation reactor using a cartridge of palladium 10% in carbon at room temperature cleaved the benzyl carbamate group, giving the unprotected sulfonimidamide in moderate yield (64%, Table 2, entry 4). Finally, **5e** was treated with tetrabutylammonium fluoride in THF at 40 °C to give **6** in excellent yield (85%, Table 2, entry 5).

The best overall yield for the whole reaction sequence from **1** was obtained when using ethyl carbamate group (51%, Table 2, entry 3) and therefore was the *N*-protecting group of choice for this methodology. Benzyl carbamate also looks promising, especially for those compounds that are not stable under basic conditions, since it is cleaved under very mild conditions using heterogeneous palladium on carbon (Pd/C) catalyst in the presence of hydrogen gas. Finally, benzoyl group gave good yields in all the synthesis steps except for the deprotection, since this is a difficult group to remove that sometimes require harsh conditions.

Bolm previously reported the arylation of *N*-protected sulfonimidamides using aryl halides and stoichiometric amounts of copper.[21] Later, Malacria et al.[22] developed an efficient copper-catalyzed method for introducing aryl substituents on the amino end of sulfonimidamides. We decided to explore functionalization of unprotected sulfonimidamides through arylation of the imine nitrogen.

Our first attempt at the arylation step was to use copper-mediated reactions, since they provide a low-cost alternative compared to palladium cross-couplings. Unsatisfactory results were obtained when using stoichiometric amounts of copper salts with iodo-, bromo-, and chlorobenzene as precursors, decomposition of starting material was observed and only a small amount of the desired product was observed by LC–MS and HPLC when iodobenzene was used as the aryl halide. We tried to improve this reaction by using a catalytic amount of copper in presence of a ligand. Malacria successfully used *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand for introducing aryl substituents on the amino end of sulfonimidamides[22] and Buchwald also reported good results when using this ligand for the amidation of aryl halides,[23] but when attempting these conditions for the arylation of the imine nitrogen of sulfonimidamides it did not provide satisfactory results. A recent publication by Jiang et al.[24] reported 8-hydroxyquinolin-*N*-oxide as a superior ligand for CuBr catalyzed coupling reactions, but again no C–N cross-coupling reaction was observed when attempting this with sulfonimidamides under the reported conditions.

We finally attempted the arylation using Pd-catalyzed C–N coupling reaction. As ligand of choice we tried RuPhos ligand, which is commercially available, easy to handle, air stable, and was reported by Buchwald as the ligand of choice for secondary alkyl amines.[25] Buchwald reaction also offers low catalyst loading and short reaction times.[26] The Pd source was a Pd(II) amine complex (Fig. 2), which undergoes reduction of Pd(II) to Pd(0) before entry into the catalytic cycle. The amine nitrogen is deprotonated and the resulting intermediate undergoes a reductive elimination generating indoline and the active monoligated Pd(0) complex.



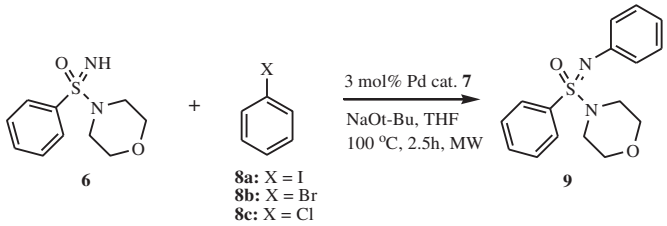
L RuPhos RuPhos precatalys **7**

Fig. 2. Structure of RuPhos ligand (**L**) and precatalyst **7** used in C–N cross-coupling.

We were pleased to see that the desired arylation of the imine nitrogen of sulfonimidamides did indeed proceed under these conditions (Table 3). The coupling of unprotected sulfonimidamide **6** with iodo-, bromo-, and chlorobenzene at catalyst loading of 3 mol %, using sodium *tert*-butoxide (NaO*t*-Bu) as base in THF and 2.5 h under microwave irradiation gave the desired product in excellent yields 88–95%. Even the less reactive aryl chloride gave the expected product in 95% yield (Table 3, entry 3).

Encouraged by the good results obtained with this novel methodology we next attempted coupling of heteroaryl halides. Heteroaryl halides are typically more challenging substrates than

Table 3
Pd-catalyzed cross-coupling of sulfonimidamide **6** and aryl halides[a]



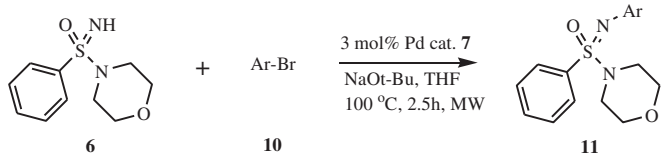
6 + **8a:** X = I, **8b:** X = Br, **8c:** X = Cl → **9**

Entry	Aryl halide	Yield[b] (%)
1	**8a**	88
2	**8b**	87
3	**8c**	95

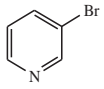
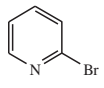
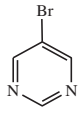
[a] Reaction conditions: sulfonimidamide (1.0 equiv), aryl halide (1.5 equiv), NaO*t*-Bu (1.2 equiv), 3 mol % Pd cat. in THF at 100 °C, 2.5 h in microwave.
[b] Isolated yield determined after column chromatography.

aryl halides in Pd-catalyzed C–N cross-coupling reactions;[26] but the obtained products are often of larger interest in the pharmaceutical industry. Nevertheless, this catalyst system even allows the coupling of electron-poor heteroaryl bromides with excellent yields (86%, Table 4, entry 2). All reactions were extremely clean and gave the desired product in excellent yield 86–98% with relatively low catalyst loading (3–6 mol %) and short reaction times. Table 4 summarizes these results.

Table 4
Pd-catalyzed cross-coupling of sulfonimidamide **6** and heteroaryl bromides[a]



6 + Ar-Br (**10**) → **11**

Entry	Aryl bromide	Product	Yield[b] (%)
1	 **10a**	**11a**	98
2	 **10b**	**11b**	86
3[c]	 **10c**	**11c**	86

[a] Reaction conditions: sulfonimidamide (1.0 equiv), aryl halide (1.5 equiv), NaO*t*-Bu (1.2 equiv), 3 mol % Pd cat. in THF at 100 °C, 2.5 h in microwave.
[b] Determined after column chromatography.
[c] Pd cat. (6 mol %).

3. Conclusion

We have established a synthesis of unprotected sulfonimidamides from three different precursors that allows orthogonal protecting group removal, i.e., acidic, nucleophilic, and hydrogenation, to give N–H sulfonimidamide in excellent to good overall yield. *N*-Ethyl carbamate group gave the desired product **6** in excellent overall yields and was therefore chosen as the best *N*-protecting group for this methodology. Next, we developed an efficient Pd-catalyzed C–N coupling methodology that allows the imine nitrogen of tertiary sulfonimidamides to be functionalized through arylation with both aryl and heteroaryl groups. To the best of our knowledge, this is the first time sulfonimidamides have been employed as substrates in these kinds of reactions. Work to extend this methodology to primary and secondary sulfonimidamides has so far proven to be challenging, but additional work is on-going.

4. Experimental

4.1. General

NMR spectra were recorded on a 500 MHz NMR spectrometer from Bruker fitted with a probe of suitable configuration. Spectra were recorded at ambient temperature unless otherwise stated. Chemical shifts are given in parts per million. The following reference signals were used: TMS δ 0.00, or the residual solvent signal of DMSO-d_6 δ 2.49, or $CDCl_3$ δ 7.26 (unless otherwise indicated). Resonance multiplicities are denoted s, d, t, q, m, br, and app for singlet, doublet, triplet, quartet, multiplet, broad, and apparent, respectively. IR spectra were recorded by a Thermo Nicolet 4700 spectrometer using an attenuated total reflection (ATR) unit. High-resolution mass spectra (HRMS) were recorded on a Waters Synapt-G2 mass spectrometer as described in detail in Supplementary data. Column chromatography was performed by manual flash chromatography (wet packed silica, 0.04–0.063 mm) or by automated column chromatography on Isco CombiFlash system using pre-packed RediSep™ columns. Microwave reactions were performed in a Biotage Initiator reactor with fixed hold time. All reagents were purchased from commercial suppliers and used without further purification.

4.2. Methyl benzenesulfinate 2[27]

Sodium benzenesulfinate **1** (5.00 g, 30.3 mmol) was dissolved in dichloromethane (80 mL). The solution was cooled down to 0 °C and kept under argon atmosphere. Thionyl chloride (6.60 mL, 90.8 mmol) was added dropwise at 0 °C. After 20 min the ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 3 h and then concentrated in vacuum to give benzenesulfinic chloride. Benzenesulfinic chloride was then dissolved in a small amount of dry dichloromethane and added to a round bottom flask with dry methanol (200 mL) at 0 °C, after 10 min triethylamine (12.5 mL, 89.7 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and then dissolved in dichloromethane, washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give methyl benzenesulfinate **2** (4.49 g, 96%) as a pale yellow oil. MS (ES^+), *m*/*z*: 156.9 [$(M+H)^+$]. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.44 (s, 3H), 7.60–7.69 (m, 3H), 7.69–7.75 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 50.1, 125.1, 129.3, 132.5, 143.6.

4.3. Benzenesulfinamide 3

To a solution of methyl benzenesulfinate **2** (4.48 g, 28.7 mmol) in anhydrous THF (60 mL), lithium bis(trimethylsilyl)amide (43 mL, 43 mmol) was added dropwise over 10 min at −78 °C. The mixture was stirred for 10 min at −78 °C and 1.5 h at room temperature. Then a saturated sol of NH_4Cl (100 mL) was added and the mixture stirred overnight at room temperature. The reaction mixture was diluted by addition of ethyl acetate, the organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product was recrystallized from hexane/ethyl acetate 2:1. Benzenesulfinamide **3** (3.66 g,

90%) was isolated as colorless crystals. MS (ES^+), *m/z*: 141.9 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 6.25 (s, 2H), 7.45–7.60 (m, 3H), 7.60–7.72 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 125.3, 128.6, 130.2, 148.1. Data in accordance with literature values.[28]

4.4. *tert*-Butyl phenylsulfinylcarbamate 4a

Benzenesulfinamide **3** (0.40 g, 2.80 mmol) was dissolved in dry THF (12 mL) and cooled down to −78 °C in a round bottom flask. The mixture was stirred for 10 min at −78 °C and *n*-butyl lithium (2.80 mL, 7.10 mmol) was added dropwise over 10 min. The mixture was stirred for 10 more minutes at −78 °C, followed by rapid addition of di-*tert*-butyl dicarbonate (0.742 g, 3.40 mmol), stirring was continued for 10 min at −78 °C and then overnight at room temperature. A saturated solution of $NaHCO_3$ was added to the reaction mixture and diluted with dichloromethane. The water phase was extracted with dichloromethane, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography using dichloromethane as eluent yielded **4a** (0.306 g, 45%) as a white solid. MS (ES-), *m/z*: 240 [$(M-H)^-$]. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.53 (s, 9H), 6.63 (br s, 1H), 7.54–7.59 (m, 3H), 7.73–7.80 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 27.8, 81.5, 124.9, 125.5, 129.0, 131.3, 143.4.

4.5. *N*-(Phenylsulfinyl)benzamide 4b

The same procedure as described for **4a** was used with the exception of use of benzoic anhydride (0.77 g, 3.40 mmol) instead of di-*tert*-butyl dicarbonate. The product was recrystallized from hexane/ethyl acetate (2:1) to obtain **4b** (0.533 g, 77 %) as a white solid. MS (ES-), *m/z*: 245.9 [$(M-H)^-$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 7.47–7.55 (m, 2H), 7.59–7.68 (m, 4H), 7.73–7.84 (m, 2H), 7.86–7.95 (m, 2H), 11.65 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 125.5, 128.4, 128.5, 129.1, 131.4, 131.9, 132.9, 143.5, 168.1. Data in accordance with literature values.[29]

4.6. Ethyl phenylsulfinylcarbamate 4c

The same procedure as described for **4a** was used with the exception of use of diethyl dicarbonate (0.50 mL, 3.40 mmol) instead of di-*tert*-butyl dicarbonate. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **4c** (0.446 g, 74 %) as a white solid. MS (ES^+), *m/z*: 213.9 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.22 (t, *J*=7.1 Hz, 3H), 4.17 (q, *J*=7.1 Hz, 2H), 7.58–7.61 (m, 3H), 7.67–7.70 (m, 2H), 10.78 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 14.2, 63.2, 124.7, 129.4, 132.0, 143.4, 153.6.

4.7. Benzyl phenylsulfinylcarbamate 4d

The same procedure as described for **4a** was used with the exception of use of dibenzyldicarbonate (0.973 g, 3.40 mmol) instead of di-*tert*-butyl dicarbonate. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield benzyl phenylsulfinylcarbamate **4d** (0.492 g, 63.1%) as a white solid. MS (ES^-), *m/z*: 274 [$(M-H)^-$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 5.20 (s, 2H), 7.32–7.44 (m, 5H), 7.57–7.62 (m, 3H), 7.67–7.73 (m, 2H), 10.93 (s, 1H).

4.8. *N*-(Phenylsulfinyl)-2-(trimethylsilyl)ethanesulfonamide 4e

Sodium benzenesulfinate **1**(0.30 g, 1.82 mmol) was dissolved in dichloromethane (8.60 mL), the solution was cooled down to 0 °C and kept under argon atmosphere. Thionyl chloride (0.50 mL, 7.30 mmol) was added dropwise at 0 °C and after 20 min the ice bath was removed. The reaction mixture was stirred for 2 h at room temperature and then concentrated under vacuum to give benzenesulfinic chloride. A slurry of sodium hydride (0.088 g, 2.20 mmol) in dichloromethane (9.50 mL) was cooled down to 0 °C under argon atmosphere. 2-(Trimethylsilyl)ethanesulfonamide (0.388 g, 2.10 mmol) was dissolved in a small amount of DCM and added to the slurry at 0 °C and stirred for 1 h. Benzenesulfinic chloride was dissolved in a small amount of DCM and added dropwise to the mixture at 0 °C, which was stirred overnight at room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted with DCM. The combined organic phases were dried in $MgSO_4$ and concentrated under reduced pressure to give a crude yellow oil, the product was not isolated. MS (ES^-), *m/z*: 304 [$(M-H)^-$].

4.9. *N*-Benzylbenzenesulfinamide 4f[30]

Sodium benzenesulfinate **1** (1.00 g, 6.10 mmol) was dissolved in dichloromethane (20 mL). The solution was cooled down to 0 °C and kept under argon atmosphere. Thionyl chloride (1.30 mL, 18.2 mmol) was added dropwise at 0 °C. After 20 min the ice bath was removed and the solution allowed to warm to room temperature. The reaction mixture was stirred for 2 h and then concentrated in vacuum to give benzenesulfinic chloride, which was dissolved again in DCM (20 mL) and phenylmethanamine (0.70 mL, 6.70 mmol) was added dropwise, subsequently triethylamine (1.30 mL, 9.10 mmol) was added to the reaction mixture and everything went into solution, the reaction mixture was stirred overnight. The reaction mixture was concentrated in vacuum to remove all the solvents and then diluted in DCM and washed with a saturated solution of NH_4Cl. The organic layers were dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give *N*-benzylbenzenesulfinamide **4f** (1.307 g, 93%). MS (ES^+), *m/z*: 231.9 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 3.69 (dd, *J*=14.3, 7.1 Hz, 1H), 4.00 (dd, *J*=14.3, 5.0 Hz, 1H), 7.10 (dd, *J*=6.7, 5.5 Hz, 1H), 7.20–7.26 (m, 3H), 7.26–7.31 (m, 2H), 7.51–7.60 (m, 3H), 7.66–7.70 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 43.2, 125.9, 127.0, 128.2, 129.9, 130.6, 138.6, 144.5.

4.10. *tert*-Butyl[morpholin-4-yl(oxido)phenyl-λ^6-sulfanylidene]carbamate 5a

Under an inert atmosphere of argon, *N*-chlorosuccinimide (0.083 g, 0.62 mmol) was added to a solution of **4a** (0.05 g, 0.20 mmol) in dry acetonitrile (1.50 mL). After 2 h LC–MS showed no starting material. Morpholine (54 μL, 0.60 mmol) was added and the mixture stirred for 43 h (until no starting material was left checked by LC-MS). The reaction was stopped by addition of water (5 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **5a** (0.041 g, 61 %) as a white solid. Mp=104–105 °C. MS (ES^+), *m/z*: 327 [$(M+H)^+$]. IR (ATR): ν=1693, 1677, 1446, 1251, 1155, 1107, 1087, 1064, 929, 896, 777, 736, 526 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.41 (s, 9H), 3.09–3.17 (m, 4H), 3.73–3.78 (m, 4H), 7.55–7.60 (m, 2H), 7.62–7.67 (m, 1H), 7.85–7.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 27.9, 45.7, 66.1, 80.5, 127.8, 129.2, 133.2, 135.2, 156.2. HRMS (ESI) $C_{15}H_{22}N_2O_4S$ calcd $[M+H]^+$ 327.1379; found 327.1376.

4.11. *N*-[Morpholin-4-yl(oxido)phenyl-λ^6-sulfanylidene] benzamide 5b

The same procedure as described for **5a** but with **4b** (0.05 g, 0.2 mmol) as starting material was employed. The product was purified using flash chromatography by slowly increasing the

gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **5b** (0.053 g, 79%) as a white solid. MS (ES^+), *m/z*: 331 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 3.02–3.12 (m, 4H), 3.64–3.72 (m, 4H), 7.46–7.52 (m, 2H), 7.57–7.62 (m, 1H), 7.68–7.73 (m, 2H), 7.75–7.81 (m, 1H), 7.86–7.90 (m, 2H), 8.02–8.10 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 45.4, 65.3, 127.6, 128.3, 129.0, 132.4, 133.7, 134.3, 135.3, 171.4.

4.12. Ethyl[morpholin-4-yl(oxido)phenyl-λ^6-sulfanylidene] carbamate 5c

The same procedure as described for **5a** but with **4c** (0.05 g, 0.2 mmol) as starting material was employed. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **5c** (0.060 g, 87%) as a white solid. Mp=145–146 °C. MS (ES^+), *m/z*: 299 [$(M+H)^+$]. IR (ATR): ν=1666, 1448, 1275, 1110, 1089, 1065, 1020, 786, 748, 687, 611 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.11 (t, *J*=6.9 Hz, 3H), 2.94–2.99 (m, 4H), 3.60–3.65 (m, 4H), 3.91–4.01 (m, 2H), 7.66–7.72 (m, 2H), 7.74–7.83 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 14.5, 45.9, 61.5, 65.6, 127.9, 129.9, 134.0, 134.5, 156.9.HRMS (ESI) $C_{13}H_{18}N_2O_4S$ calcd $[M+H]^+$ 299.1066; found 299.1069.

4.13. Benzyl[morpholin-4-yl(oxido)phenyl-λ^6-sulfanylidene] carbamate 5d

The same procedure as described for **5a** but with **4d** (0.05 g, 0.18 mmol) as starting material was employed. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **5d** (0.049 g, 75%) as a white solid. MS (ES^+), *m/z*: 361 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.92–3.00 (m, 4H), 3.58–3.64 (m, 4H), 4.97–5.04 (m, 2H), 7.26–7.36 (m, 5H), 7.66–7.71 (m, 2H), 7.75–7.82 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 45.7, 66.0, 67.8, 127.8, 127.9, 128.2, 128.3, 129.3, 133.4, 134.6, 136.2, 157.0.

4.14. *N*-[Morpholin-4-yl(oxido)phenyl-λ^6-sulfanylidene]-2-(trimethylsilyl)ethanesulfonamide 5e

Under an inert atmosphere of argon, *N*-chlorosuccinimide (0.117 g, 0.87 mmol) was added to a crude solution of *N*-(phenylsulfinyl)-2-(trimethylsilyl)ethanesulfonamide (0.089 g) in dry acetonitrile (1.40 mL) and stirred for 2 h. Morpholine (76 μL, 0.87 mmol) was added and subsequently the solution was stirred overnight at room temperature. The reaction was stopped by addition of water, and the phases were separated. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **5e** (0.020 g, 18%) as a white solid. MS (ES^+), *m/z*: 391 [$(M+H)^+$]. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.02 (s, 9H), 0.92–1.02 (m, 2H), 2.94–3.02 (m, 2H), 3.02–3.12 (m, 4H), 3.61–3.69 (m, 4H), 7.72 (t, *J*=7.7 Hz, 2H), 7.81 (t, *J*=7.4 Hz, 1H), 7.85–7.91 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm -1.9, 10.0, 46.0, 52.4, 65.2, 127.5, 129.7, 134.2, 134.3.

4.15. 4-(Phenylsulfonimidoyl)morpholine 6 starting from 5a

To a solution of **5a** (0.01 g, 0.03 mmol) in dichloromethane (0.2 mL), trifluoroacetic acid (12 μL, 0.15 mmol) was added and the mixture was stirred overnight. The solvent was removed and the product was purified using preparative HPLC to yield **6** (6.00 mg, 87 %) as a white solid. Mp=103–105 °C. MS (ES^+), *m/z*: 227 [$(M+H)^+$]. IR (ATR): ν=1251, 1108, 1067, 992, 924, 722, 688, 600, 523 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.74–2.83 (m, 4H), 3.56–3.61 (m, 4H), 4.52 (s, 1H), 7.58–7.64 (m, 2H), 7.64–7.70 (m, 1H), 7.74–7.79 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 46.7, 65.6, 127.8, 128.8, 132.3, 135.5. HRMS (ESI) $C_{10}H_{14}N_2O_2S$ calcd $[M+H]^+$ 227.0854; found 227.0860.

4.16. 4-(Phenylsulfonimidoyl)morpholine 6 starting from 5b

To a solution of **5b** (0.02 g, 0.06 mmol) in ethanol (0.40 mL), hydrogen chloride 1 M sol in 1,4-dioxane (0.2 mL, 0.18 mmol) was added and stirred at room temperature until the starting material was consumed (monitored by LC–MS). The mixture was diluted with water and extracted with DCM, the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **6** (7.30 mg, 53.3 %) as a white solid. Analytical data as above.

4.17. 4-(Phenylsulfonimidoyl)morpholine 6 starting from 5c

A solution of **5c** (2.25 g, 7.54 mmol) in ethanol (67.5 mL) was treated with sodium ethoxide solution (7.90 mL, 21.12 mmol) and stirred at room temperature for 21 h (until no starting material was observed by LC–MS). The reaction mixture was diluted with ethyl acetate and brine. The resulting mixture was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product was purified using flash chromatography by slowly increasing the gradient from 100% heptane to 50:50 heptane/ethyl acetate to yield **6** (1.555 g, 91 %) as a white solid. Analytical data as above.

4.18. 4-(Phenylsulfonimidoyl)morpholine 6 starting from 5d

Sulfonimidamide **5d** (0.01 g, 0.03 mmol) was dissolved in methanol (1 mL). The resulting solution was treated in an H-cube continuous-flow hydrogenation reactor using a cartridge of palladium 10% on carbon at room temperature. The solvent was removed under reduced pressure to yield **6** (4.0 mg, 64%) as a white solid. Analytical data as above.

4.19. 4-(Phenylsulfonimidoyl)morpholine 6 starting from 5e

A solution of **5e** (0.01 g, 0.03 mmol) in THF (0.2 mL) was treated with 1 M solution of tetrabutylammonium fluoride (0.15 mL, 0.15 mmol) and stirred overnight. The reaction mixture was heated to 40 °C for 6 h to get full conversion (monitored by LC–MS). After cooling to room temperature, aqueous $NaHCO_3$ and brine were added and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by preparative HPLC to give yield **6** (4.90 mg, 85%) as a white solid. Analytical data as above.

4.20. General procedure for arylation of 6

An oven-dried microwave tube, which was equipped with a magnetic stir bar, was charged with sulfonimidamide **6** (0.05 g, 0.22 mmol, 1.0 equiv), NaO*t*-Bu (0.025 g, 0.27 mmol, 1.2 equiv), and chloro-(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl) [2-(2-aminoethyl)phenyl]palladium(II)/methyl-*tert*-butyl ether adduct **7** (3.0 mol % for aryl halides **8a**–**8c** and **10a**–**10b**) and (6.0 mol % for aryl bromide **10c**). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), then the aryl halide (1.5 equiv) or the heteroaryl halide (1.5 equiv) and THF (0.15 mL/mmol) were added under argon atmosphere (the heteroaryl halides that were solids at room temperature were added with

the precatalyst and base). The tube was degassed and sealed with a Teflon septum. The solution mixture was set in a microwave system (Biotage *Initiator 2.5* Power range 0–400 W from magnetron at 2.45 GHz) and was heated at 100 °C (external temperature) for 2.5 h. The reaction mixture was then diluted with ethyl acetate, washed with water, concentrated in vacuo, and purified with flash chromatography.

4.21. 4-(*N*,*S*-Diphenylsulfonimidoyl)morpholine 9

Following the general procedure for arylation, the product was purified with flash chromatography by slowly increasing the gradient from 100% heptane to 60:40 heptane/ethyl acetate to give 4-(*N*,*S*-diphenylsulfonimidoyl)morpholine **9**(0.059 g, 88%) as a white solid. Mp=110–112 °C. MS (ES^+), *m*/*z*: 303.1 [$(M+H)^+$]. IR (ATR): ν=1484, 1301, 1256, 1222, 1211, 1105, 1069, 1043, 1018, 921, 776, 736, 627, 534 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.83–2.94 (m, 4H), 3.47–3.52 (m, 2H), 3.53–3.59 (m, 2H), 6.95 (t, *J*=7.2 Hz, 1H), 7.13–7.16 (m, 2H), 7.22–7.26 (m, 2H), 7.66–7.70 (m, 2H), 7.73–7.76 (m, 1H), 7.91–7.94 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 46.4, 65.4, 121.8, 123.3, 127.8, 129.0, 129.2, 133.0, 134.4, 143.3; HRMS (ESI) $C_{16}H_{18}N_2O_2S$ calcd $[M+H]^+$ 303.1167, found 303.1174.

4.22. 4-[*S*-Phenyl-*N*-(pyridin-3-yl)sulfonimidoyl]morpholine 11a

Following the general procedure for arylation, the product was purified with flash chromatography by slowly increasing the gradient from 100% heptane to 5:95 heptane/ethyl acetate to give sulfonimidamide **11a** (0.066 g, 98 %) as a yellow oil. MS (ES^+), *m*/*z*: 304.3 [$(M+H)^+$]. IR (ATR): ν=1445, 1412, 1186, 1015, 997, 806, 598, 510 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.84–2.97 (m, 4H), 3.46–3.53 (m, 2H), 3.53–3.60 (m, 2H), 7.27 (dd, *J*=8.2, 4.41 Hz, 1H), 7.51–7.55 (m, 1H), 7.68–7.73 (m, 2H), 7.75–7.80 (m, 1H), 7.93–7.97 (m, 2H), 8.17 (dd, *J*=4.6, 1.10 Hz, 1H), 8.38 (d, *J*=2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 46.4, 65.3, 128.8, 127.8, 129.4, 129.6, 133.3, 133.8, 140.2, 142.7, 144.9; HRMS (ESI) $C_{15}H_{17}N_3O_2S$ calcd $[M+H]^+$ 304.1120, found 304.1110.

4.23. 4-[*S*-Phenyl-*N*-(pyridin-2-yl)sulfonimidoyl]morpholine 11b

Following the general procedure for arylation, the product was purified with flash chromatography by slowly increasing the gradient from 100% heptane to 5:95 heptane/ethyl acetate to give sulfonimidamide **11b** (0.058 g, 86 %) as a yellow oil. MS (ES^+), *m*/*z*: 305 [$(M+H)^+$]. IR (ATR): ν=1587, 1421, 1315, 1256, 1235, 1069, 1050, 922, 757, 732, 687, 599, 512 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.92–3.03 (m, 4H), 3.52–3.62 (m, 4H), 6.88 (ddd, *J*=7.2, 4.89, 0.79 Hz, 1H), 6.96 (d, *J*=8.2 Hz, 1H), 7.59–7.68 (m, 3H), 7.68–7.74 (m, 1H), 7.84–7.89 (m, 2H), 8.11 (dd, *J*=4.9, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 46.0, 65.4, 117.0, 117.1, 127.7, 129.3, 132.9, 135.4, 137.9, 148.0, 157.1; HRMS (ESI) $C_{15}H_{17}N_3O_2S$ calcd $[M+H]^+$ 304.1120, found 304.1116.

4.24. 4-[*S*-Phenyl-*N*-(pyrimidin-5-yl) sulfonimidoyl] morpholine 11c

Following the general procedure for arylation, the product was purified with flash chromatography by slowly increasing the gradient from 100% heptane to 5:95 heptane/ethyl acetate to give sulfonimidamide **11c** (0.058 g, 86%) as a yellow oil. MS (ES^+), *m*/*z*: 305 [$(M+H)^+$]. IR (ATR): ν=1541, 1412, 1293, 1257, 1234, 1124, 1068, 1045, 1015, 922, 738, 722, 637, 547 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.87–2.99 (m, 4H), 3.47–3.54 (m, 2H), 3.55–3.61 (m, 2H), 7.70–7.75 (m, 2H), 7.78–7.82 (m, 1H), 7.95–8.00 (m, 2H), 8.59 (s, 2H), 8.79 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 46.4, 65.3, 127.8, 129.5, 133.2, 133.7, 139.1, 150.6, 151.7; HRMS (ESI) $C_{14}H_{16}N_4O_2S$ calcd $[M+H]^+$ 305.1072, found 305.1065.

5. Computational details

The geometries were optimized in vacuo using the DFT functional B3LYP with a 6-31G** quality basis set. Solvent effects (water) were included using a PBF continuum available in the B3LYP functional with a 6-31+G** basis. All calculations were done using Jaguar.[15]

Acknowledgements

M.F. is grateful to the leadership team at Medicinal Chemistry, CNSP iMED, AstraZenca R&D Södertälje, Sweden, for allowing him to conduct his M.Sc. work there.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.072.

References and notes

1. Sehgelmeble, F.; Janson, J.; Ray, C.; Rosqvist, S.; Gustavsson, S.; Nilsson, L.; Minidis, A.; Holenz, J.; Rotticci, D.; Lundkvist, J.; Arvidsson, P. I. *ChemMedChem* **2012**, *7*, 396–399.
2. (a) Levechenko, E. S.; Derkach, N. Y.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1962**, *32*, 1208–1212; For reviews see: (b) Levchenko, E. S.; Markovskii, L. N.; Shermolovich, Y. G. *Russ. J. Org. Chem.* **2000**, *36*, 143–177; (c) Rashatasakhan, P.; Harmata, M. *Chemtracts: Org. Chem.* **2006**, *19*, 143–151.
3. (a) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573–3575; (b) Azzaro, S.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Synlett* **2008**, 2253–2256.
4. (a) Collet, F.; Dodd, R. H.; Dauban, P. *Org. Lett.* **2008**, *10*, 5473–5476; (b) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503–4505; (c) Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Müller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484–3487; (d) Lian, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343–350.
5. Tsushima, S.; Yamada, Y.; Oshima, K.; Chaney, M. O.; Jones, N. D.; Swartzendruber, J. K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1167–1178.
6. Collet, F.; Lescot, C.; Liang, C.; Dauban, P. *Dalton Trans.* **2010**, *39*, 10401–10413.
7. Worch, C.; Bolm, C. *Synlett* **2009**, 2425–2428.
8. Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310.
9. Patureau, F. W.; Worch, C.; Siegler, M. A.; Spek, A. L.; Bolm, C.; Reek, J. N. H. *Adv. Synth. Catal.* **2012**, *354*, 59–64.
10. Toth, J. E.; Grindey, G. B.; Ehlhardt, W.; Ray, J.; Boder, G. B.; Bewley, J. R.; Klingerman, K.; Gates, S.; Rinzel, S.; Schultz, R.; Weir, L.; Worzalla, J. *J. Med. Chem.* **1997**, *40*, 1018–1025.
11. Cathers, B.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1527–1531.
12. (a) Bolm, C.; Garcia Machenco, O. *Beilstein J. Org. Chem.* **2007**, *3*.
13. Paulini, R.; Breuninger, D.; Von Deyn, W.; Bastians, H.; Maria, M.; Beyer, C.; Anspaugh, D.; Oloumi-Sadeghi, H. (BASF SE) U.S. Patent WO 2009/156. 336 A1.
14. (a) Johnson, C. R.; Lavergne, O. *J. Org. Chem.* **1989**, *54*, 986–988; (b) Johnson, C. R.; Lavergne, O. *J. Org. Chem.* **1993**, *58*, 1922–1923.
15. *Jaguar, Version 7.8*; Schrödinger: New York, NY, 2007.
16. Johnson, C.; Jonsson, E.; Bacon, C. *J. Org. Chem.* **1979**, *44*, 2055–2061.
17. Worch, C.; Atodiresei, I.; Raabe, G.; Bolm, C. *Chem.—Eur. J.* **2010**, *16*, 677–683.
18. Ellman, J. A.; Dragoli, D. R.; Backers, B. J. *J. Org. Chem.* **1999**, *64*, 5472–5478.
19. Bolm, C.; Young, G. *Org. Lett.* **2005**, *7*, 1351–1354.
20. Lücking, U; Kettshau, G.; Biem, H.; Schwede, W.; Schäfer, M.; Thierauch, K.; Mann, M. (Shering Aktiengesellschaft) WO 2006/108695 A2.
21. Bolm, C.; Worch, C. *Synthesis* **2008**, *5*, 0739–0742.
22. Azarro, S.; Desage-El Murr, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Synlett* **2011**, 849–851.
23. Buchwald, S.; Huang, X.; Klapars, A. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
24. Jiang, S.; Wang, Z.; Li, Z.; Qiu, Y.; Yang, K. *J. Org. Chem.* **2011**, *76*, 3151–3159.
25. Surry, D.; Buchwald, S. *Chem. Sci.* **2011**, *2*, 27–50.
26. Maiti, D.; Fors, B.; Henderson, J.; Nakamura, Y.; Buchwald, S. *Chem. Sci.* **2011**, *2*, 57–68.
27. Douglass, I. B. *J. Org. Chem.* **1965**, *30*, 633–635.
28. Savile, C.; Magloire, V.; Kazluaskas, R. *J. Am. Chem. Soc.* **2005**, *127*, 2104–2113.
29. Kowalczyk, R.; Edmunds, A. J.; Hall, R.; Bolm, C. *Org. Lett.* **2011**, *13*, 768–771.
30. García Ruano, J.; Parra, A.; Marzo, L.; Yuste, F.; Mastranzo, V. M. *Tetrahedron* **2011**, *67*, 2905–2910.