Tetrahedron xxx (2014) 1–6

Contents lists available at ScienceDirect

Tetrahedron

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

$Cu(OAc)_2$ promoted Chan–Evans–Lam C–N cross coupling reactions on the *N*- and *N′*-nitrogen atoms of sulfonimidamides with aryl boronic acids

Ganesh C. Nandi [a], Sudhakar R. Kota [a], Thavendran Govender [a], Hendrik G. Kruger [a], Per I. Arvidsson [a,b,*]

[a] *Catalysis and Peptide Research Unit, University of KwaZulu-Natal, Durban, South Africa*
[b] *Science for Life Laboratory, Drug Discovery & Development Platform & Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden*

ARTICLE INFO

Article history:
Received 5 April 2014
Received in revised form 13 June 2014
Accepted 30 June 2014
Available online xxx

Keywords:
Sulfonimidamides
Aryl boronic acid
C–N cross coupling reactions
$Cu(OAc)_2$
Triethylamine

ABSTRACT

We report a highly efficient and mild protocol for Chan–Evans–Lam C–N cross coupling of sulfonimidamides and aryl boronic acids using $Cu(OAc)_2$ as mediator, triethylamine (TEA) as base and acetonitrile as solvent. The reaction proceeds at room temperature and provides high to excellent yields for a variety of boronic acids, allowing *N*-arylation of both *N*-protected (*N*-amine nitrogen) and *N*-deprotected (*N′*-imine nitrogen) sulfonimidamides.

1. Introduction

Although Levchenko et al.[1] reported on the aza analogues of sulfonamides, i.e., sulfonimidamides, already in 1962, this class of compounds has received very little attention in the literature.[2] This is surprising given the interesting properties sulfonimidamides might entail; replacement of one of the oxygen atoms in the sulfonamide functional group with a nitrogen atom generates a stereogenic sulfur centre and brings about the possibility of introducing additional structural diversity around the widely used sulfonamide functional group.

Although sparse, some research during the past decades has focused on the applications of sulfonimidamides in organic synthesis, as well as their biological activity. The research groups of Malacria and Dodd independently explored sulfonimidamides as reagents in organic synthesis via iminations of sulfides, aziridination of olefins, and C–H aminations of hydro-carbons.[3] Bolm et al. used sulfonimidamides as organocatalysts,[4] and as chiral ligands in asymmetric reactions,[5] most recently in the iridium-catalyzed asymmetric hydrogenation of cyclic enamides.[6] Sulfonimidamides has also been utilized as analogues of oncolytic sulfonylureas by Lilly Research Laboratories[7] and Schloss evaluated sulfonimidamides as transition state analogues for aspartic acid and metalloproteases.[8] Our group recently reported the first in vivo application of a sulfonimidamide as a potential bioisostere of the, in drug leads, widespread sulfonamide.[9]

In view of their increasing medicinal and synthetic applicability, it is important to develop more general, efficient, and mild routes to synthesize *N′*- and *N*-functionalized sulfonimidamides. Previously, the Bolm research group[10] reported the stoichiometric copper mediated arylation of *N′*-protected sulfonimidamides with aryl halides. Independently, Malacriand co-workers[11] described the copper catalyzed arylation of *N′*-protected sulfonimidamides with aryl iodides under microwave heating. Both of these reports are restricted to functionalization of the primary amine functionality in *N′*-protected sulfonimidamides and they required high temperatures and provided moderate to good yields. Correspondingly, we described the arylation of the imine nitrogen in *N′*-deprotected sulfonimidamides using a Pd catalyst under high temperature microwave conditions.[12] During the course of our study on Chan–Evans–Lam reaction, Battula et al.[12b] reported the copper catalyzed *N′*-arylation of sulfonimidamides using aryl boronic acid at room temperature; the reported method produces high yield of product although with longer reaction times.

* Corresponding author. E-mail addresses: Per.Arvidsson@ki.se, Per.Arvidsson@scilifelab.se (P.I. Arvidsson).

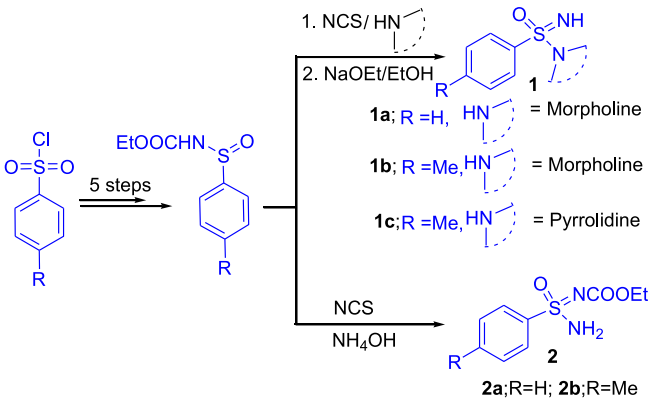
http://dx.doi.org/10.1016/j.tet.2014.06.122
0040-4020/

As a part of our ongoing medicinal and synthetic research program on sulfonimidamides,[13] we were interested to find a general route to sulfonimidamide derivatives that would hopefully work under mild conditions and allow functionalization of both the primary nitrogen (*N*-) in protected sulfonimidamides and the imine nitrogen (*N*′-) of unprotected sulfonimidamides. Herein we report the so-called Chan–Evans–Lam cross coupling between sulfonimidamides and aryl boronic acids at room temperature using $Cu(OAc)_2$ as mediator, TEA as base, and acetonitrile as solvent.

2. Results and discussion

The original Chan–Evans–Lam C–N/O cross coupling reaction, described in 1998 in three consecutive publications by Chan,[14] Lam[15] and Evans,[16] utilized boronic acids as electrophilic agents and amines/alcohols as nucleophilic agents. Since then, several applications have been developed, rendering this arylation protocol as a useful tool for various $C(sp^2)$-N bond formations in organic synthesis.[17]

We synthesized tertiary *N*′-deprotected sulfonimidamides **1a–c** and the protected primary sulfonimidamides **2a** and **2b** following a similar approach as that described by Bolm's group[18] and outlined in detail in our previous report (Scheme 1).[12]



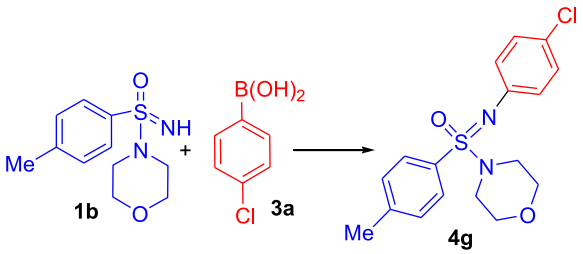
Scheme 1. Synthetic routes to sulfonimidamides.

First, we attempted the synthesis of 4-(*S*-*p*-tolyl-*N*-(4-chlorophenylsulfonimidoyl)morpholine) **4g**. *S*-(*p*-Tolylsulfonimidoyl)morpholine **1b** (1.0 equiv) was reacted with 4-chloro-phenylboronic acid **3a** (2.5 equiv) as a test substrate to optimize the reaction conditions (Table 1). Initially, the model reaction was carried out in MeOH with 10 mol % of $Cu(OAc)_2$ catalyst at room temperature. Only 20% product was formed after 24 h of stirring with a lot of unreacted starting materials remaining (Table 1, entry 1). Attempt to heat the reaction mixture at 60 °C gave the sulfinamide **5** as major product (Table 1, entry 2, Scheme 2)—a side-reaction previously reported by Malacria.[11]

Other copper catalysts, such as CuBr and CuI were also evaluated (Table 1, entries 3 & 4); CuBr provided 16% of the desired product together with the diarylated product **6** (Scheme 3), which was obtained by the homocoupling of the boronic acid; CuI yielded trace amounts of the product in a complex reaction mixture.

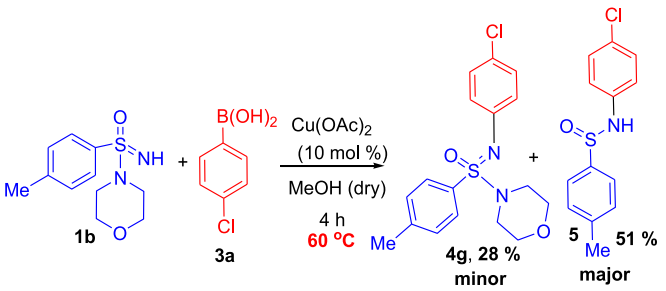
Thereafter, we decided to increase the amount of $Cu(OAc)_2$ until all of the starting materials was consumed. The reaction was therefore performed with 100 mol % of $Cu(OAc)_2$, but only 42% of the product was obtained (Table 1, entry 5). Our efforts to complete the sulfonimidamide during the reaction was successful only when 150 mol % and 200 mol % of $Cu(OAc)_2$ were used, leading to 72% and 70% yield of product, respectively (Table 1, entries 5 & 6). Employing 150 mol % of copper acetate as mediator, we next screened various solvents, such as DCM, dioxane,

Table 1
Optimization of Chan–Evans–Lam *N*-arylation of the *N*′-imine nitrogen of sulfonimidamide **1b** with 4-chlorophenyl boronic acid **3a**

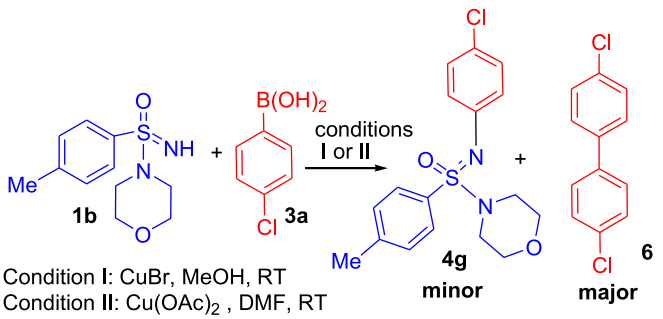


Entry	Catalyst (mol %)	Solvent	Base (equiv)	Yield[a] (%)	Time (h)
1.	$Cu(OAc)_2$ (10)	MeOH	—	20[b]	24
2.	$Cu(OAc)_2$ (10)	MeOH	—	28	5
3.	CuBr (10)	MeOH	—	16[c]	24
4.	CuI (10)	MeOH	—	Trace	24
5.	$Cu(OAc)_2$ (100)	MeOH	—	42[b]	24
6.	$Cu(OAc)_2$ (200)	MeOH	—	70	24
7.	$Cu(OAc)_2$ (150)	MeOH	—	72	24
8.	$Cu(OAc)_2$ (150)	THF	—	78	24
9.	$Cu(OAc)_2$ (150)	DMF	—	43[c]	12
10.	$Cu(OAc)_2$ (150)	DCM	—	81	24
11.	$Cu(OAc)_2$ (150)	Dioxane	—	84	24
12	$Cu(OAc)_2$ (150)	EtOH	—	62[b]	48
13.	$Cu(OAc)_2$ (150)	MeCN	—	92	14
14.	$Cu(OAc)_2$ (50)	MeCN	—	73[b]	24
15.	$Cu(OAc)_2$ (100)	MeCN	—	81	24
16.	$Cu(OAc)_2$ (200)	MeCN	—	91	14
17.	$Cu(OTf)_2$ (100)	MeCN	—	13[d]	24
18.	$Cu(OAc)_2$ (50)	MeCN	TEA (1)	82	10
19.	$Cu(OAc)_2$ (100)	MeCN	TEA (1)	92[e]	5
20.	$Cu(OAc)_2$ (150)	MeCN	TEA (1)	90	5
21.	$Cu(OAc)_2$ (100)	MeCN	TEA (1.5)	91	5
22.	$Cu(OAc)_2$ (100)	MeCN	TEA (0.5)	88	8
23.	$Cu(OAc)_2$ (100)	MeCN	Pyridine (1.0)	86	7

[a] Isolated yield.
[b] Starting materials were still in the reaction.
[c] Biaryls were formed through self-coupling of boronic acid.
[d] A number of spots were generated.
[e] The same results were obtained with 1.5 and 2.0 equiv of boronic acid.



Scheme 2. Reaction of *N*′-deprotected sulfonimidamide with 4-chlorophenyl boronic acid at 60 °C.



Scheme 3. Formation of diarylated product via homocoupling of 4-chlorophenyl boronic acid.

THF, EtOH and MeCN to identify the solvent of choice (Table 1, entries 8–13). It was established that MeCN provides the best result by yielding 92% of the expected product in 14 h (Table 1, entry 13). In DMF, again the self condensed biarylated product **6** was obtained as a major product (Table 1, entry 9; Scheme 3). The reaction was also conducted with 50 mol % and 100 mol % of $Cu(OAc)_2$ in MeCN but with lower yield (Table 1, entries 14 & 15). In an attempt to decrease reaction times, we added triethylamine (TEA) or pyridine as base to the reaction with MeCN as solvent. After several attempts (Table 1, entries 18–23), the best yields were obtained with 100 mol % of $Cu(OAc)_2$ and 1.0 equiv of TEA in MeCN; these conditions gave 92% of isolated product in 5 h reaction time (Table 1, entry 19). To verify the optimum amount of boronic acid needed, the reaction was investigated with 1.0, 1.5 and 2.0 equiv of boronic acid with 100 mol % of $Cu(OAc)_2$ and 1.0 equiv of TEA. The use of 1.0 equiv of boronic acid provided lesser yields and took longer reaction times than the use of 1.5 and 2.0 equiv of boronic acid. Overall, the best reaction conditions were obtained when the sulfonimidamide (1.0 equiv) was reacted with boronic acid (1.5 equiv) in the presence of $Cu(OAc)_2$ (100 mol %), TEA (1.0 equiv) in MeCN at room temperature (Table 1, entry 19). The experiment to review the catalytic activity of $Cu(OTf)_2$ was unsuccessful for this transformation (Table 1, entry 17).

It should be noted that, in our hands, the Chan–Evans–Lam coupling on the imine nitrogen of sulfonimidamides did not work efficiently under catalytic conditions, as recently reported by Battula et al. (10 mol % $Cu(OAc)_2$, MeOH, 24 h, rt).[12b] The reason for this discrepancy is unclear; we ran the reaction under atmospheric conditions, but did not make any special arrangements for copper re-oxidation that might have been beneficial for a catalytic process.

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. Both electron withdrawing and electron donating substituents on the aryl ring of the boronic acid worked well in the reactions, offering products in good to excellent yields (Chart 1). Also fused aryl boronic acids showed good reactivity (Chart 1, **4d**,**j**). In addition, modification of the sulfonimidamide partner was well tolerated as shown by replacing the morpholine moiety with a pyrrolidine, to offer the products **4k**–**m** (Chart 1) in similar yields and at comparable reaction rates. Heteroaromatic 2-thienylboronic acid yielded the corresponding product **4n**; in this case TEA was not tolerated as additive (led to a complex reaction mixture) and thus the reaction was performed with $Cu(OAc)_2$ only that resulted lower yield and longer reaction time 13 h.

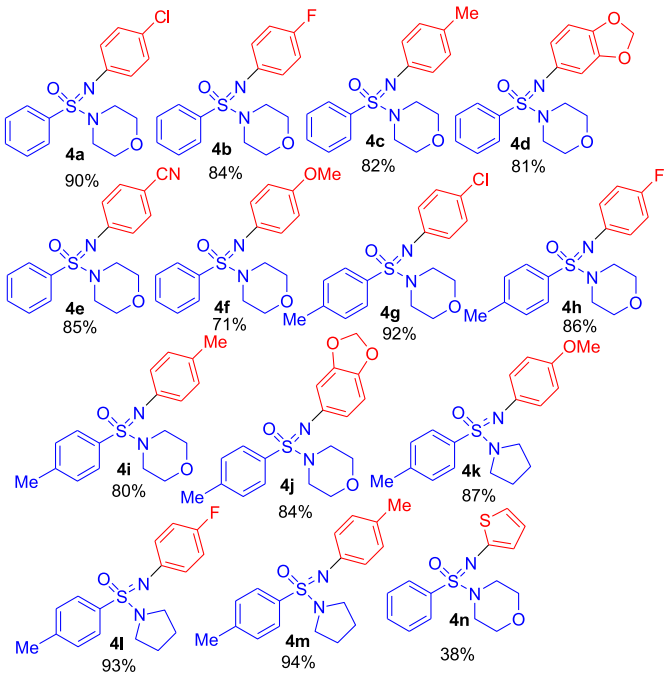
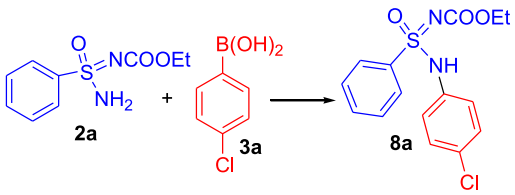


Chart 1. Substrate scope for the Chan–Evans–Lam *N*′-functionalization of sulfonimidamides with aryl boronic acids.

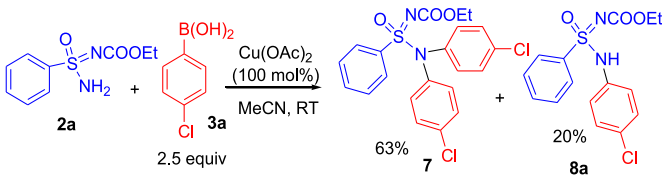
Encouraged by the successful *N*′-arylation of the imine nitrogen of *N*′-deprotected sulfonimidamides, we next attempted the reactions with the primary *N*-amino group of *N*′-protected sulfonimidamides (**2a**,**b**) with aryl boronic acids. We started our analysis by reacting sulfonimidamide **2a** (0.25 mmol) with 4-chlorophenyl boronic acid **3a** (2.5 equiv) in acetonitrile at room temperature by using $Cu(OAc)_2$ (100 mol %) as catalyst without any base; to our surprise we got diarylated product **7** as the main product along with the desired product **8a** (Table 2, entry 1; Scheme 4). To overcome this complexity, the reaction was performed with 1.0 equiv of boronic acid using 100 mol % of catalyst. The reaction was then completed within 7 h and gave 85% of isolated product (Table 2, entry 2). Interestingly, the use of TEA as a basic additive was found to lower the reaction times, enhance the yields, and helped to reduce the catalyst loading for the reaction (Table 2, entries 3–5). Thus, the best yields, shortest reaction times, and overall best condition for the arylation of the primary amine functionality of protected sulfonimidamides was observed when 1.0 equiv of each starting material was stirred with 50 mol % of $Cu(OAc)_2$ and 1.0 equiv of TEA in MeCN at room temperature (Table 2, entry 4).

Table 2
Optimization of Chan–Evans–Lam *N*-arylation of the *N*-amine functionality of sulfonimidamide **2a**[a]



Entry	Catalyst (mol %)	Base (equiv)	Yield[b] (%)	Time (h)
1.	$Cu(OAc)_2$ (100)	—	20[c]	5
2.	$Cu(OAc)_2$ (100)	—	85[d]	7
3.	$Cu(OAc)_2$ (100)	TEA (1.0)	91[d]	2
4.	$Cu(OAc)_2$ (50)	TEA (1.0)	93[d]	2
5.	$Cu(OAc)_2$ (25)	TEA (1.0)	73[d]	4

[a] All reactions were performed at room temperature.
[b] Isolated yield.
[c] Diarylated product **7** was formed as the major one (2.5 equiv of boronic acid was used).
[d] 1.0 equiv of each substrate was used.



Scheme 4. Reaction of *N*′-protected sulfonimidamide **2a** with excess 4-chlorophenyl boronic acid **3a**.

On the basis of the above optimized reaction conditions, the scope and generality of this protocol was next examined by using various sulfonimidamides **2** and substituted aryl boronic acids **3**.

Electron-rich, as well as electron-deficient, substituents on the aryl boronic acids were well tolerated for this transformation (Chart 2, **8a**–**e**). In addition, the benzofused boronic acid was also nicely tolerated to yield the corresponding *N*-arylated sulfonimidamide (**8f**). Notably, the replacement of phenyl group with tolyl group in the sulfonimidamide scaffold provides parallel yields (**8d**,**e**).

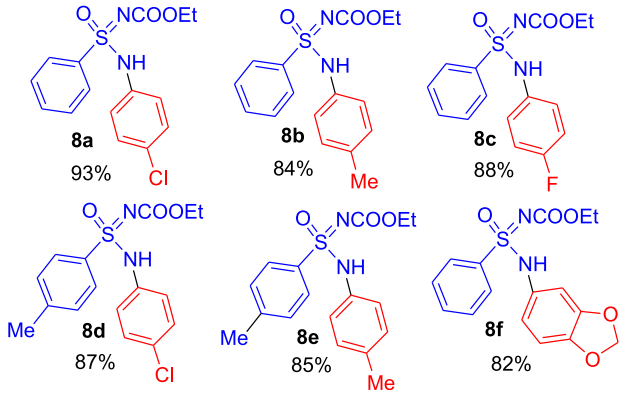


Chart 2. Substrate scope for the reactions of *N*-deprotected sulfonimidamides and aryl boronic acids.

We find that addition of TEA increase the reactivity of both the *N*-amine and *N*′-imine sulfonimidamide nucleophiles in our stoichiometric implementation of the Chan–Evans–Lam coupling. Although a more comprehensive study would be required to understand the full reaction mechanism, it is likely that the added base facilitates N–H deprotonation and coordination to the copper centre.[17]

3. Conclusion

In summary, we have developed a general, convenient, and mild copper mediated approach for sulfonimidamide arylation based on the Chan–Evans–Lam protocol. The reported methodology can be applied for *N*-arylation of both the primary *N*-amine of *N*′-protected sulfonimidamides, as well as on the *N*′-imine nitrogen of tertiary sulfonimidamides. The reaction proceeds at room temperature and provide high to excellent yields with short times using a low cost catalyst and base. The methodology works well with a variety of boronic acids. Considering an increased interest of the sulfonimidamide moiety in the area of drug design, and the structural diversity offered by this group as compared to the widely used sulfonamide, we anticipate that this new protocol will find broad application for the synthesis of various kinds of sulfonimidamide derivatives with so far unidentified properties and opportunities.

4. Experimental section

4.1. General

The starting material sulfonimidamides were synthesized following the reported method.[12,18] The aryl boronic acids, $Cu(OAc)_2$ and triethylamine were purchased from commercial suppliers and used as received. ^1H and ^{13}C NMR spectra were recorded on Bruker TOPSPIN 2.1 spectrometer operating at 400 and 100 MHz, respectively. IR spectra of selected compounds (**4e**, **4i**, **8b**, **8c** and **8d**) were recorded on BRUKER-ALPHA spectrophotometer. HRMS were recorded on BRUKER micrOTOF-Q-II spectrometer. Melting points were uncorrected.

4.2. General procedure for functionalization of the *N*′-imine nitrogen of sulfonimidamides with aryl boronic acids for the synthesis of *N*′-arylated sulfonimidamides (4a–n)[†]

To a 0.5 ml acetonitrile solution of *N*-deprotected sulfonimidamide (imine nitrogen) (0.25 mmol) and aryl boronic acid (1.5 equiv), $Cu(OAc)_2$ (100 mol %) followed by TEA (1.0 equiv) were added and the whole reaction mixture was stirred for the stipulated period of time at room temperature. After completion of the reaction (checked by TLC), sodium bicarbonate solution was added to it and extracted with ethyl acetate (2×10 ml). The organic layer was washed with water followed by brine solution. Then the ethyl acetate layer was dried (Na_2SO_4), evaporated and purified by column chromatography using 5–6% of ethyl acetate in hexane as eluent. All the compounds were characterized by ^1H NMR, ^{13}C NMR and mass spectrometry.

*4.2.1. 4-(S-Phenyl-N′-(4-chlorophenylsulfonimidoyl)morpholine) (**4a**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 90%. R_f=0.4 (1:10 EtOAc/Hexane); mp 109–111 °C. IR (ATR): ν=2974, 2914, 2855, 1589, 1442, 1256, 790. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95–7.93 (m, 2H), 7.62–7.56 (m, 3H), 7.20 (d, J=6.3 Hz, 2H), 7.16 (d, J=6.3 Hz, 2H), 3.68–3.58 (m, 4H), 3.07–2.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.1, 134.9, 133.0, 129.2, 129.1, 128.1, 127.3, 124.9, 66.3, 46.7. HRMS (ESI) calcd for $C_{16}H_{17}ClN_2O_2S$ $[M+H]^+$ 337.0772, found 337.0762.

*4.2.2. 4-(S-Phenyl-N′-(4-fluorophenylsulfonimidoyl)morpholine) (**4b**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 84%. R_f=0.4 (1:10 EtOAc/Hexane); mp 95–96 °C. IR (ATR): ν=2975, 2889, 2854, 1726, 1493, 1284, 741. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95–7.93 (m, 2H), 7.61–7.55 (m, 3H), 7.19–7.16 (m, 2H), 6.92 (t, J=8.6 Hz, 2H), 3.64–3.59 (m, 4H), 3.06–2.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6 (d, J=239 Hz), 139.3, 135.1, 132.9, 129.1, 128.1, 124.7 (d, J=8.0 Hz), 115.7 (d, J=22 Hz), 66.3, 46.7. HRMS (ESI) calcd for $C_{16}H_{17}FN_2O_2S$ $[M+H]^+$ 321.1067, found 321.1068.

*4.2.3. 4-(S-Phenyl-N′-(p-tolylsulfonimidoyl)morpholine) (**4c**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 82%. R_f=0.4 (1:10 EtOAc/Hexane); mp 85–86 °C. IR (ATR): ν=2981, 2909, 2861, 1606, 1501, 1258, 741. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.97–7.95 (m, 2H), 7.60–7.53 (m, 3H), 7.13 (d, J=8.2 Hz, 2H), 7.04 (d, J=8.2 Hz, 2H), 3.67–3.57 (m, 4H), 3.07–2.95 (m, 4H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 135.4, 132.7, 131.5, 129.7, 129.0, 128.2, 123.6, 66.5, 46.9, 21.0. HRMS (ESI) calcd for $C_{17}H_{20}N_2O_2S$ $[M+H]^+$ 317.1318, found 317.1357.

*4.2.4. 4-(S-Phenyl-N′-(benzo[d][1,3]dioxoylsulfonimidoyl)morpholine) (**4d**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 81%. R_f=0.3 (1:10 EtOAc/Hexane); mp 91–92 °C. IR (ATR): ν=2971, 2918, 2874, 1608, 1474, 1256, 743. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.85–7.83 (m, 2H), 7.50–7.43 (m, 3H), 6.71 (s, 1H), 6.59 (d, J=0.9 Hz, 2H), 5.81 (d, J=1.3 Hz, 2H), 3.57–3.49 (m, 4H), 2.94–2.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.0, 143.0, 137.5, 135.1, 132.8, 129.1, 128.2, 116.0, 108.4, 105.6, 101.0, 66.3, 46.9.

[†] For **4n**, TEA was not added.

Please cite this article in press as: Nandi, G. C.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.122

HRMS (ESI) calcd for $C_{17}H_{18}N_2O_4S$ $[M+H]^+$ 347.1060, found 347.1054.

*4.2.5. 4-(S-Phenyl-N′-(4-cyanophenylsulfonimidoyl)morpholine) (**4e**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 85%. R_f=0.4 (1:10 EtOAc/Hexane); mp 90–91 °C. IR (ATR): ν=2956, 2899, 2851, 2222, 1598, 1497, 1232. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J=7.3 Hz, 2H), 7.65 (t, J=7.3 Hz, 1H), 7.59 (t, J=7.8 Hz, 2H), 7.51 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 3.69–3.60 (m, 4H), 3.09–2.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.7, 134.4, 133.3, 133.2, 129.3, 128.1, 123.9, 119.7, 104.8, 66.2, 46.7. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_3S$ $[M+H]^+$ 328.1114, found 328.1164.

*4.2.6. 4-(S-Phenyl-N′-(4-methoxyphenylsulfonimidoyl)morpholine) (**4f**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 71%. R_f=0.4 (1:10 EtOAc/Hexane); mp 98–99 °C. IR (ATR): ν=2953, 2864, 2835, 1528, 1218, 916. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96–7.94 (m, 2H), 7.59–7.54 (m, 3H), 7.16 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.9 Hz, 2H), 3.77 (s, 3H), 3.63–3.59 (m, 4H), 3.03–2.98 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4, 136.3, 135.3, 132.7, 129.0, 128.1, 124.6, 114.4, 66.7, 55.6, 46.9. HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3S$ $[M+H]^+$ 333.1267, found 333.1209.

*4.2.7. 4-(S-p-Tolyl-N′-(4-chlorophenylsulfonimidoyl)morpholine) (**4g**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 82%. R_f=0.4 (1:10 EtOAc/Hexane); mp 103–104 °C. IR (ATR): ν=2961, 2922, 2824, 1722, 1591, 1484, 1228, 925, 714. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.9 Hz, 2H), 7.15 (d, J=9.0 Hz, 2H), 3.64–3.60 (m, 4H), 3.02–2.95 (m, 4H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 142.3, 131.9, 129.8, 129.1, 128.2, 127.1, 124.9, 66.3, 46.7, 21.6. HRMS (ESI) calcd for $C_{17}H_{19}ClN_2O_2S$ $[M+H]^+$ 351.0928, found 351.0917.

*4.2.8. 4-(S-p-Tolyl-N′-(4-fluorophenylsulfonimidoyl)morpholine) (**4h**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 86%. R_f=0.4 (1:10 EtOAc/Hexane); mp 113–114 °C. IR (ATR): ν=2922, 2848, 1494, 1257, 740. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J=8.2 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 7.18–7.15 (m, 2H), 6.92 (t, J=8.6 Hz, 2H), 3.64–3.57 (m, 4H), 3.04–2.94 (m, 4H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5 (d, J=248 Hz), 143.8, 139.6, 132.1, 129.7, 128.2, 124.7 (d, J=8.6 Hz), 115.6 (d, J=22 Hz), 66.3, 46.8, 21.6. HRMS (ESI) calcd for $C_{17}H_{19}FN_2O_2S$ $[M+H]^+$ 335.1224, found 335.1225.

*4.2.9. 4-(S-p-Tolyl-N′-(p-tolylsulfonimidoyl)morpholine) (**4i**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 80%. R_f=0.4 (1:10 EtOAc/Hexane); mp 98–100 °C. IR (ATR): ν=2953, 2924, 2854, 1507, 1107. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 7.03 (d, J=8.2 Hz, 2H), 3.67–3.57 (m, 4H), 3.05–2.94 (m, 4H), 2.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 140.9, 132.5, 131.5, 129.7, 129.6, 128.3, 123.6, 66.4, 46.8, 21.6, 20.9. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_2S$ $[M+H]^+$ 331.1474, found 331.1466.

*4.2.10. 4-(S-p-Tolyl-N′-(benzo[d][1,3]dioxoylsulfonimidoyl)morpholine) (**4j**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 84%. R_f=0.4 (1:10 EtOAc/Hexane); mp 124–125 °C. IR (ATR): ν=2974, 2887, 2852, 1599, 1480, 1260, 933, 521. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 6.80 (s, 1H), 6.68 (s, 2H), 5.90 (d, J=1.0 Hz, 2H), 3.65–3.61 (m, 4H), 3.04–2.94 (m, 4H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.9, 143.6, 142.8, 137.8, 132.2, 129.7, 128.3, 116.2, 108.4, 105.5, 101.0, 66.3, 46.8, 21.6. HRMS (ESI) calcd for $C_{18}H_{20}N_2O_4S$ $[M+H]^+$ 361.1216, found 361.1257.

*4.2.11. 1-(S-p-Tolyl-N′-(4-methoxyphenylsulfonimidoyl)pyrrolidine) (**4k**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 87%. R_f=0.3 (1:10 EtOAc/Hexane); mp 108–110 °C. IR (ATR): ν=3034, 2955, 2880, 1501, 980, 744. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.9 Hz, 2H), 3.76 (s, 3H), 3.26–3.20 (m, 2H), 3.18–3.12 (m, 2H), 2.42 (m, 3H), 1.67–1.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9, 143.0, 137.5, 134.1, 129.6, 128.1, 124.6, 114.4, 55.6, 48.4, 25.4, 21.6. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_2S$ $[M+H]^+$ 331.1474, found 331.1490.

*4.2.12. 1-(S-p-Tolyl-N′-(4-fluorophenylsulfonimidoyl)pyrrolidine) (**4l**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 93%; R_f=0.4 (1:10 EtOAc/Hexane); mp 96–97 °C. IR (ATR): ν=2972, 2949, 2874, 1594, 1492, 1209, 750. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, J=8.3 Hz, 2H), 7.32 (d, J=7.7 Hz, 2H), 7.18–7.15 (m, 2H), 6.91 (t, J=8.7 Hz, 2H), 3.26–3.20 (m, 2H), 3.16–3.11 (m, 2H), 2.43 (s, 3H), 1.69–1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5 (d, J=238 Hz), 143.2, 140.3, 133.8, 129.6, 128.1, 124.6 (d, J=8.0 Hz), 115.5 (d, J=21.9 Hz), 48.4, 25.3, 21.6. HRMS (ESI) calcd for $C_{17}H_{19}FN_2OS$ $[M+H]^+$ 319.1274, found 319.1269.

*4.2.13. 1-(S-p-Tolyl-N′-(p-tolylsulfonimidoyl)pyrrolidine) (**4m**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 5% EtOAc in Hexane as eluent. White solid; yield: 94%; R_f=0.4 (1:10 EtOAc/Hexane); mp 105–106 °C. IR (ATR): ν=3020, 2947, 2914, 1609, 1505, 1450, 812. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 7.02 (d, J=8.1 Hz, 2H), 3.25–3.21 (m, 2H), 3.18–3.13 (m, 2H), 2.42 (s, 3H), 2.27 (s, 3H), 1.67–1.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 141.6, 134.2, 131.1, 129.7, 129.6, 128.1, 123.5, 48.4, 25.4, 21.6, 20.9. HRMS (ESI) calcd for $C_{18}H_{22}N_2OS$ $[M+H]^+$ 315.1525, found 315.1570.

*4.2.14. 1-(S-Phenyl-N′-(2-thienylsulfonimidoyl)morpholine) (**4n**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 6% EtOAc in Hexane as eluent. White solid; yield: 38%. R_f=0.3 (1:10 EtOAc/Hexane); Pale yellow solid; mp 82–84 °C. IR (ATR): ν=3020, 2913, 2842, 1608, 1504, 295. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J=7.2 Hz, 2H), 7.61 (t, J=7.4 Hz, 1H), 7.58 (t, J=7.8 Hz, 2H), 6.81–6.79 (m, 1H), 6.75–6.73 (m, 1H), 6.60–6.58 (m, 1H), 3.70 (t, J=4.7 Hz, 4H), 3.07–3.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.9, 134.6, 133.1, 129.2, 128.1, 125.8, 116.8, 116.2, 66.3, 46.8. HRMS (ESI) calcd for $C_{14}H_{16}N_2O_2S_2$ $[M+H]^+$ 309.0725, found 309.0723.

4.3. General procedure for functionalization of the *N*-amine functionality of *N′*-protected sulfonimidamides with aryl boronic acids for the synthesis of *N*-arylated sulfonimidamides (8a–f)

To a 0.5 ml acetonitrile solution of *N′*-protected sulfonimidamide (0.25 mmol) and aryl boronic acid (1.0 equiv), $Cu(OAc)_2$ (50 mol %) followed by TEA (1.0 equiv) were added and the whole reaction mixture was stirred for the stipulated period of time at room temperature. After completion of reaction (checked by TLC),

Please cite this article in press as: Nandi, G. C.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.122

sodium bicarbonate solution was added to it and extracted with ethyl acetate (2×10 ml). The organic layer was washed with water followed by brine solution. Then the ethyl acetate layer was dried (Na_2SO_4), evaporated and purified by column chromatography using 12–15% of ethyl acetate in hexane as eluent. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry.

*4.3.1. N′-Carbethoxyphenylsulfonimid-N-(4-chlorophenyl)amide (**8a**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 12% EtOAc in Hexane as eluent. White solid; yield: 93%. R_f=0.5 (1:5 EtOAc/Hexane); mp 94–95 °C. IR (ATR): ν=3094, 2929, 2855, 1656, 1491, 1211. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.19 (br, 1H), 7.92 (d, J=7.6 Hz, 2H), 7.58 (t, J=7.4 Hz, 2H), 7.49 (t, J=7.7 Hz, 1H), 7.18 (d, J=8.6 Hz, 2H), 7.02 (d, J=8.6 Hz, 2H), 4.14 (q, J=7.1 Hz, 2H), 1.23 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 138.4, 134.3, 133.8, 131.5, 129.6, 129.4, 127.9, 124.0, 62.7, 14.5. HRMS (ESI) calcd for $C_{15}H_{15}ClN_2O_3S$ $[M+H]^+$ 339.0564, found 339.0562.

*4.3.2. N′-Carbethoxyphenylsulfonimid-N-(p-tolyl)amide (**8b**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 13% EtOAc in Hexane as eluent. White solid; yield: 84%. R_f=0.5 (1:5 EtOAc/Hexane); mp 116–118 °C. IR (ATR): ν=3243, 2955, 2922, 2853, 1725, 1613, 1363, 1266. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (br, 1H), 7.91–7.89 (m, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.48 (t, J=7.6 Hz, 2H), 7.03 (d, J=8.2 Hz, 2H), 6.94 (d, J=8.3 Hz, 2H), 4.17 (q, J=7.1 Hz, 2H), 2.26 (s, 3H), 1.28 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 138.7, 136.1, 133.5, 132.5, 130.1, 129.2, 127.9, 123.3, 62.5, 20.9, 14.4. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_3S$ $[M+H]^+$ 319.1110, found 319.1133.

*4.3.3. N′-Carbethoxyphenylsulfonimid-N-(4-fluorophenyl)amide (**8c**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 14% EtOAc in Hexane as eluent. White solid; yield: 88%. R_f=0.4 (1:5 EtOAc/Hexane); mp 86–87 °C. IR (ATR): ν=3107, 2953, 2922, 2850, 1671, 1507, 1258, 1203. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.16 (br, 1H), 7.92 (d, J=7.7 Hz, 2H), 7.57 (t, J=7.4 Hz, 1H), 7.48 (t, J=7.9 Hz, 2H), 7.10–7.07 (m, 2H), 6.92–6.88 (m, 2H), 4.15–4.09 (m, 2H), 1.20 (dt, $J1$=2.0 Hz, $J2$=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9 (d, J=244 Hz), 157.9, 138.2, 133.5, 131.0 (d, J=2.8 Hz), 129.2, 127.9, 125.7 (d, J=8.2 Hz), 116.2 (d, J=22 Hz), 62.4, 14.2. HRMS (ESI) calcd for $C_{15}H_{15}FN_2O_3S$ $[M+H]^+$ 323.0860, found 323.0865.

*4.3.4. N′-Carbethoxy-p-tolylsulfonimid-N-(4-chlorophenyl)amide (**8d**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 12% EtOAc in Hexane as eluent. White solid; yield: 87%. R_f=0.5 (1:5 EtOAc/Hexane); mp 103–104 °C. IR (ATR): ν=3100, 2980, 1668, 1490, 1211. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, J=8.4 Hz, 2H), 7.27 (d, J=9.4 Hz, 2H), 7.17 (d, J=8.7 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 4.13 (q, J=7.1 Hz, 2H), 2.39 (s, 3H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0, 144.9, 135.2, 134.4, 131.3, 130.0, 129.6, 127.9, 123.9, 62.6, 21.7, 14.4. HRMS (ESI) calcd for $C_{16}H_{17}ClN_2O_3S$ $[M+H]^+$ 353.0721, found 353.0722.

*4.3.5. N′-Carbethoxy-4-tolylsulfonimid-N-4-tolylamide (**8e**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 12% EtOAc in Hexane as eluent. White solid; yield: 85%. R_f=0.5 (1:5 EtOAc/Hexane); mp 95–97 °C. IR (ATR): ν=3035, 2919, 2779, 1654, 1498, 1210. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (br, 1H), 7.79 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.5 Hz, 2H), 7.00 (d, J=8.3 Hz, 2H), 6.95 (d, J=8.4 Hz, 2H), 4.12 (q, J=7.1 Hz, 2H), 2.38 (s, 3H), 2.24 (s, 3H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 144.4, 135.8, 135.5, 132.7, 130.0, 129.8, 128.0, 123.2, 62.3, 21.7, 20.9, 14.4. HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3S$ $[M+H]^+$ 333.1267, found 333.1251.

*4.3.6. N′-Carbethoxy-4-phenylsulfonimid-N-(benzo[d][1,3]dioxoyl) amide (**8f**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 15% EtOAc in Hexane as eluent. White solid; yield: 82%. R_f=0.3 (1:5 EtOAc/Hexane); mp 97–98 °C. IR (ATR): ν=2983, 2920, 2851, 1685, 1481, 1240. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (br, 1H), 7.91 (d, J=7.4 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.49 (t, J=8.0 Hz, 2H), 6.65–6.62 (m, 3H), 5.92 (s, 2H), 4.14 (q, J=7.0 Hz, 2H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 148.2, 146.5, 138.4, 133.5, 129.2, 128.6, 128.0, 118.3, 108.4, 106.5, 101.7, 62.5, 14.4. HRMS (ESI) calcd for $C_{16}H_{16}N_2O_5S$ $[M+H]^+$ 349.0852, found 349.0850.

*4.3.7. N′-Carbethoxyphenylsulfonimid-N,N-di(4-chlorophenyl) amide (**7**).* The compound was purified via column chromatography (silica gel 100–200 mesh) using 12% EtOAc in Hexane as eluent. White solid; yield: 63%. R_f=0.7 (1:5 EtOAc/Hexane); mp 97–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92–7.90 (m, 2H), 7.66 (t, J=7.3 Hz, 1H), 7.53 (t, J=8.0 Hz, 2H), 7.27 (d, J=8.8 Hz, 4H), 7.22 (d, J=8.8 Hz, 4H), 4.13 (q, J=7.0 Hz, 2H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 139.8, 139.5, 134.2, 133.7, 130.2, 129.7, 129.4, 127.8, 62.3, 14.5. HRMS (ESI) calcd for $C_{21}H_{18}Cl_2N_2O_3S$ $[M+H]^+$ 449.0487, found 449.0481.

Acknowledgements

This work is based on the research supported in part by the National Research Foundation of South Africa for the Grant 87706. We are also grateful to UKZN for postdoctoral fellowships to G.C.N. and S.R.K. and for additional financial support.

References and notes

1. (a) Levchenko, E. S.; Sheinkman, I. E.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1960**, *30*, 1941; (b) Levchenko, E. S.; Derkach, N. Y.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1962**, *32*, 1208.
2. (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600; (b) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003; (c) Paitoon, R.; Harmata, M. *Chemtracts* **2006**, *19*, 143; (d) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061; (e) Carreno, M. C.; Hernandez-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129.
3. (a) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573; (b) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503; (c) Liang, C.; Robert-Peillard, F.; Fruit, C.; Muller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641.
4. Worch, C.; Bolm, C. *Synlett* **2009**, 2425.
5. Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301.
6. Patureau, F. W.; Worch, C.; Siegler, M. A.; Spek, A. L.; Bolm, C.; Reek, J. N. H. *Adv. Synth. Catal.* **2012**, *354*, 59.
7. 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.
8. Cathers, B.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1527.
9. Sehgelmeble, F.; Janson, J.; Ray, C.; Rosqvist, S.; Gustavsson, S.; Nilsson, L. I.; Minidis, A.; Holenz, J.; Rotticci, D.; Lundkvist, J.; Arvidsson, P. I. *ChemMedChem* **2012**, *7*, 396.
10. Worch, C.; Bolm, C. *Synthesis* **2008**, 739.
11. Azzaro, S.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Synlett* **2011**, 849.
12. (a) Maldonado, M. F.; Sehgelmeble, F.; Bjarnemark, F.; Svensson, M.; Ahman, J.; Arvidsson, P. I. *Tetrahedron* **2012**, *68*, 7456; (b) Battula, S. R. K.; Subbareddy, G. V.; Chakravarthy, I. E. *Tetrahedron Lett.* **2014**, *55*, 517.
13. Borhade, S. R.; Sandstrom, A.; Arvidsson, P. I. *Org. Lett.* **2013**, *15*, 1056.
14. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.
15. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.
16. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
17. For review see (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829; (b) Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735; (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400 For book; (d) Qiao, J. X.; Lam, P. Y. S. In *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH GmbH & KGaA: Weinheim, Germany, 2011; Vols. 1 and 2, http://dx.doi.org/10.1002/9783527639328; (e) King, A E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.
18. Bolm, C.; Garcia Machenco, O. *Beilstein J. Org. Chem.* **2007**, 3.