DDQ-Promoted C–S Bond Formation: Synthesis of 2-Aminobenzothiazole Derivatives under Transition-Metal-, Ligand-, and Base-Free Conditions

Rui Wang,*[a] Wen-juan Yang,[a] Liang Yue,[a] Wei Pan,[a] Hong-yao Zeng[b]

[a] School of Pharmacy & Bioengineering, Chongqing University of Technology, Chongqing 400054, P. R. of China
Fax +86(23)62563182; E-mail: wangrx1022@163.com

[b] Department of Chemistry and Life Sciences, Leshan Normal University, Leshan 614000, P. R. of China

Received: 07.03.2012; Accepted after revision: 16.04.2012

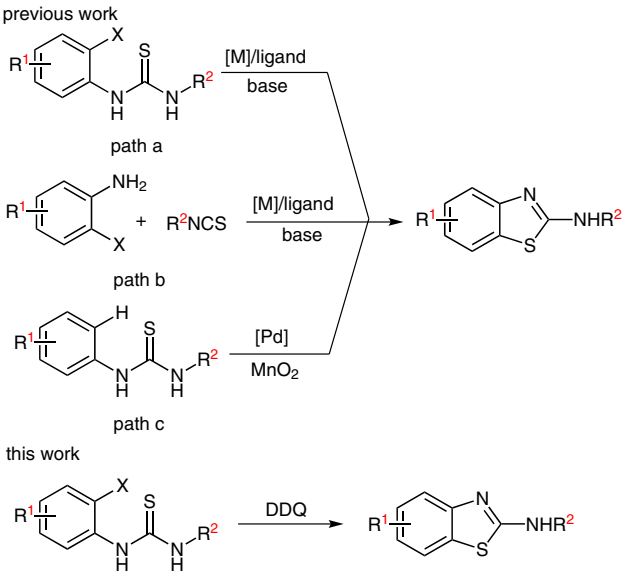
Abstract: A transition-metal-free method for the intramolecular S-arylation of *o*-halobenzothiaoureas via DDQ-mediated leading to the 2-aminobenzothiazole derivatives is reported. The reactions are performed at room temperature under ligand- and base-free conditions with good to excellent yields.

Key words: 2-aminobenzothiazoles, transition-metal-free, ligand-free, DDQ, S-arylation

2-Aminobenzothiazoles, an important topical benzothiazole scaffold, are broadly found in bioorganic and medicinal chemistry[1] with applications in drug discovery and development for the treatment of various diseases, such as diabetes,[2] epilepsy,[3] and tuberculosis.[4] Therefore, much attention has been paid to the development of efficient methods for preparing 2-aminobenzothiazole derivatives. Recent strategies for the synthesis of 2-aminobenzothiazoles based on transition-metal-catalyzed reactions nicely complement the traditional synthetic approaches – the oxidative cyclization of thiobenzanilides.[5] The transition-metal-catalyzed, particularly palladium or copper, even iron, intramolecular cyclization of 2-halobenzothiaoureas[6a–d] that were generated in situ or pre-synthesized from suitable isothiocyanates and 2-haloanilines, and tandem addition–C–S coupling[6e–i] are the most common and efficient methods (path a and path b in Scheme 1). On the other hand, recent advances in the metal-mediated C–H functionalization provide a complementary and potentially more efficient methodology to heteroaromatic compounds, because additional preactivation steps can be avoided (path c in Scheme 1).[6j] However, using excess amounts of toxic reagents or transition metals is a major drawback of these methods. Moreover the high cost of palladium and the required especially suitable ligands, as well as the stoichiometric base and low functional-group tolerance, led to a need to explore the more practical approaches for such coupling reactions. Therefore, in order to avoid the use of transition metals, the development of new efficient strategy appears very appealing in view of so-called green and sustainable chemistry.

SYNLETT 2012, 23, 1643–1648
Advanced online publication: 11.06.2012
DOI: 10.1055/s-0031-1291159; Art ID: ST-2012-W0196-L

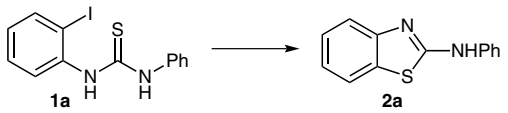
Herein we report a practical, cheap, and highly efficient coupling reaction mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) without using any transition metal, base, and ligand (this work in Scheme 1).



Scheme 1 Comparison of previous works with this work

Our initial investigations were carried out using a series of oxidants for the model reaction of 2-iodobenzothiaourea **1a**, which can easily be synthesized by the reaction of commercially available 2-iodoaniline and phenyl isothiocyanate.[7] To our delight, experimental data showed that the DDQ could promote the reaction more effectively than other types of oxidants, with conversions of up to 61% after 24 hours under transiton-metal-free, ligand-free, and base-free reaction conditions at room temperature (Table 1, entry 1). However, only a trace amount of **2a** was detected when inorganic oxidants were used instead of DDQ, such as K_2S2O_8, CAN, Ag_2O, CAN/H_2O_2,[8] I_2, and $KBrO_3$ were no longer the effective oxidants in the reaction, and no desired **2a** was isolated under transiton-metal-free, ligand-free, and base-free reaction conditions at room temperature (Table 1, entries 2–4). Meanwhile, replacing DDQ with stronger oxidant, $KMnO_4/SiO_2$,[9] only the intermediate of *o*-iodobenzothiaourea was detected, the use of Dess–Martin periodinane[10] resulted in a much lower reaction efficiency (Table 1, entries 5 and 6). Based

Table 1 Screening Conditions for the Synthesis of 2-Aminobenzothiazole[a]



Entry	Oxidant	Solvent	Yield (%)[b]
1	DDQ	CH_2Cl_2	61
2	$K_2S_2O_8$/CAN/Ag_2O	CH_2Cl_2	trace
3	CAN/H_2O_2[c]	CH_2Cl_2	trace
4	I_2/$KBrO_3$	CH_2Cl_2	trace
5	$KMnO_4$/SiO_2[d]	CH_2Cl_2	n.d.
6	DMP[e]	CH_2Cl_2	<50
7	DDQ	THF	trace
8	DDQ	DMF	78
9	DDQ	DMSO	92
10	DDQ	DMSO	86[f]
11	DDQ	DMSO	80[g]

[a] Reaction conditions: *o*-iodobenzothiaourea (**1a**, 1.0 mmol), oxidant (1.2 mmol), solvent (3.0 mL), r.t.
[b] Yield of isolated product after column chromatography.
[c] Conditions: 30% aq H_2O_2 (4 equiv) and CAN (0.1 equiv).
[d] $KMnO_4$/SiO_2 (0.90 g, 2.5 mmol) was added.
[e] Dess–Martin periodinane.
[f] Conditions: DDQ (1.5 mmol).
[g] Conditions: DDQ (1.0 mmol).

on these promising initial results we decided to further optimize the reaction conditions, especially improving the solubility of the intermediates *o*-iodobenzothiaourea. Further optimization of these preliminarily obtained conditions showed that the solvent DMSO was far more superior to DMF, affording **2a** in 92% yield even under room temperature (Table 1, entries 8 and 9) and proved to be the solvent of choice. Furthermore, both increase and decrease the amount of DDQ and reduced the yield (Table 1, entries 10 and 11). Only *o*-iodobenzothiaourea was detected without DDQ.

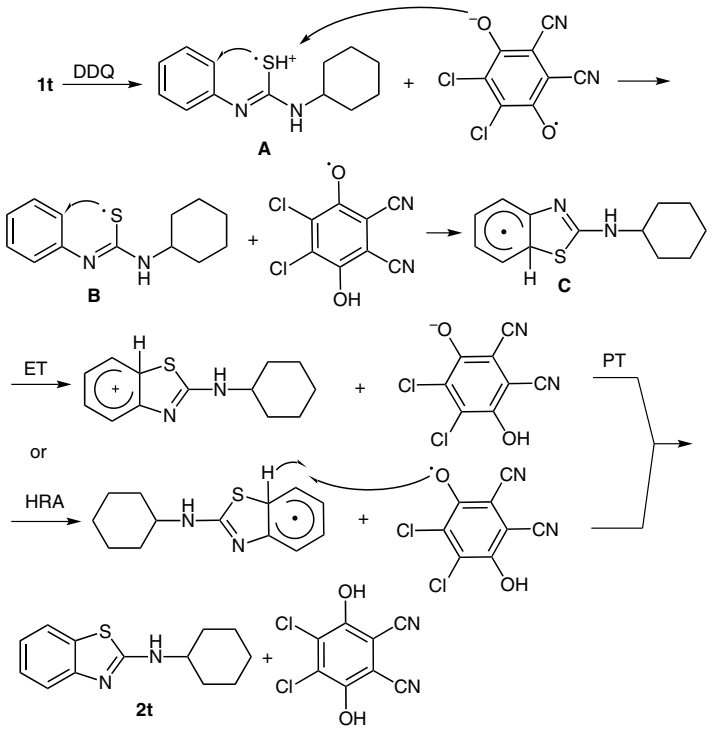
With the optimized conditions in hand, the generality of this transformation was examined by using various *o*-halobenzothiaoureas, and the corresponding results are listed in Table 2. This method is efficient for the synthesis of a number of 2-aminobenzothiazole derivatives in good to excellent yields. The nature of the *ortho*-substituted halogen on the aniline moiety was very important to the reaction outcome. (*o*-Iodoaryl)thiaoureas or (*o*-bromoaryl) thiaoureas can smoothly be converted into the desired products in synthetic acceptable to excellent yields, however, the use of *o*-chloro-substituted substrates to effect such transformations proved unsuccessful under these conditions that probably attributed to their poorer tendency to leave than their iodo or bromo analogues (Table 2, entries 1–3). Regarding the R^1 moiety, several functional groups including electron-donating (Me and OMe) and electron-withdrawing (NO_2 and CF_3) substituents even halogens (F and Cl, Table 2, entries 13–18) were tolerated well. In the case of the electronic nature of the aromatic motifs, such as 4-methyl-*o*-iodoaniline, containing an electron-donating substituent, increased yields of products were obtained, and the effect is the reverse as with electron-withdrawing substituents.

For aryl iodides, we were pleased to find that the electronic nature of the phenyl isothiocyanate moiety seems to have little influence on the reaction, which is evident from the fact that a variety of substituents, such as Me, OMe, NO_2, Cl, or Br can give satisfactory results. It is worth noting that C–Br or C–Cl compatible with reaction conditions are particularly appealing, since these substituents offer great opportunity for further preparing more complex 2-substituted benzothiazoles by further operations (Table 2, entries 5, 6, 9, and 10).

In addition, 2-alkyl aminobenzothiazole can also be obtained in good yield (Table 2, entry 22). The requirement for an *ortho*-halo-substituted precursor could be eliminated through a direct cyclization using anilines as aryl-alkyl thiaoureas provided another access to 2-aminobenzothiazoles. Whereas it is important to note that this methodology could not be applied to the aryl isothiocyanate substrates, two isomers were observed (Table 2, entry 23). As far as aryl isothiocyanate substrates are concerned, using aryl iodides, which act as directing group, could avoid the formation of isomers.

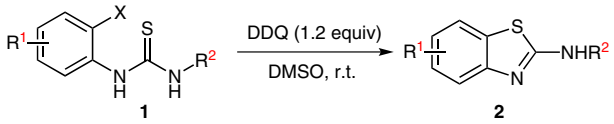
When 1,1-diphenylethylene or TEMPO, which are both known to be effective radical scavengers, was added to the reaction mixture, the reaction progress was significantly decreased under the present DDQ-promoted C–S bond-forming process, and only poor product yields were obtained, even after longer reaction times (48 h, yield <20%), suggesting that our present oxidative C–S bond-forming reaction involves radical intermediates. However, further studies are needed to unambiguously establish the reaction mechanism. A tentative mechanism for the coupling is proposed in Scheme 2. A single electron transfer from the aryl thiaoureas to DDQ generates a radical cation and a DDQ radical anion. The anionic oxygen of DDQ radical anion then abstracts the hydrogen cation from the radical cation and generates sulfanyl radical **B**. Subsequently, Oxidation of an intermediate cyclohexadienyl radical **C** can occur by electron transfer (ET) to give a cyclohexadienyl cation, followed by proton transfer (PT) gives 2-aminobenzothiazole derivatives. This result does not exclude an alternative pathway, which involves C–H bond cleaving hydrogen radical abstraction (HRA) as a single-step transformation.

In summary, we have successfully developed a straightforward, high efficient, and mild DDQ-promoted method for the intramolecular S-arylation providing 2-aminobenzothiazole ring system derivatives under transition-metal-, ligand-, and base-free conditions. In the near future we would like to establish another methodology for this transformation under transition-metal-free conditions.



Scheme 2 Proposed reaction mechanism

Table 2 Effect of Substituents on 2-Aminobenzothiazoles Formation[a]



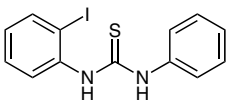
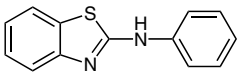
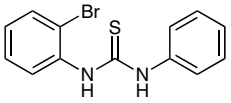
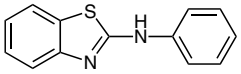
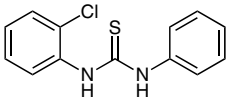
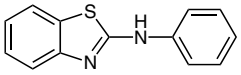
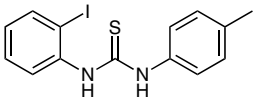
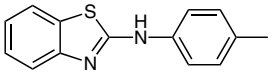
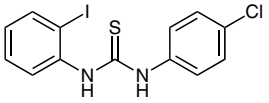
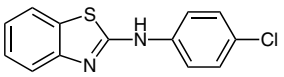
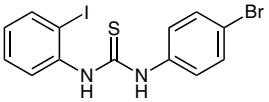
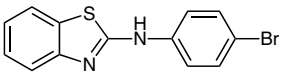
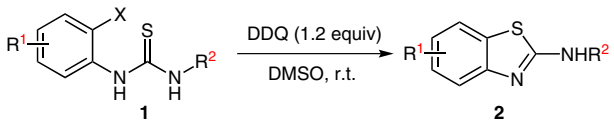
Entry	Substrate	Product	Yield (%)[b]
1		 **2a**	92
2		 **2a**	74
3		 **2a**	–
4		 **2b**	88
5		 **2c**	89
6		 **2d**	90

Table 2 Effect of Substituents on 2-Aminobenzothiazoles Formation[a] (continued)



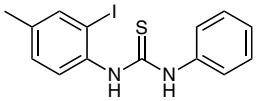
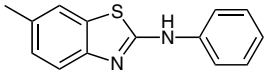
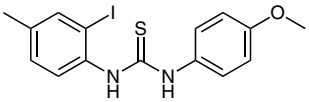
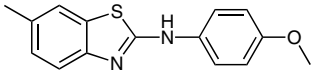
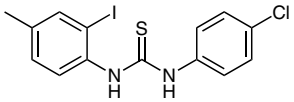
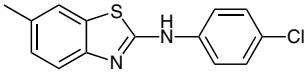
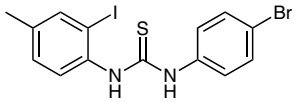
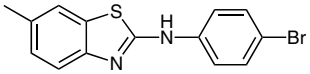
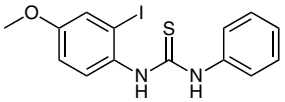
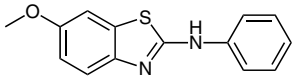
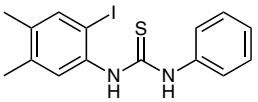
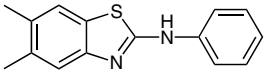
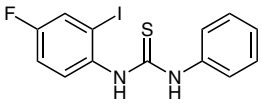
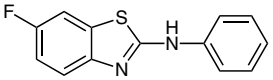
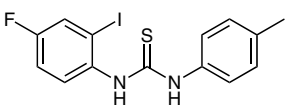
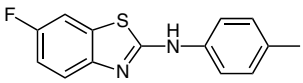
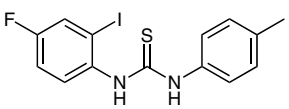
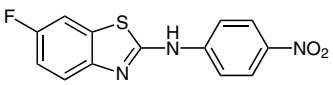
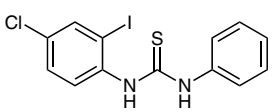
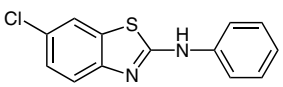
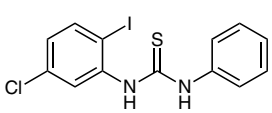
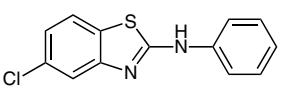
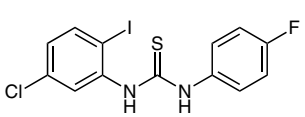
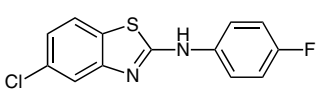
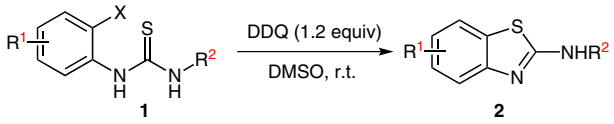
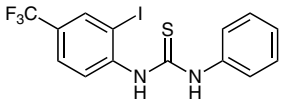
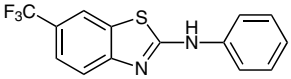
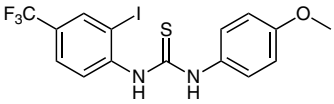
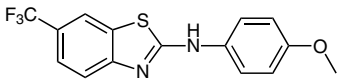
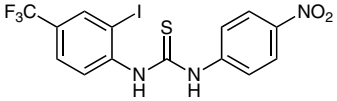
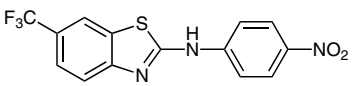
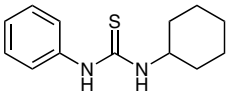
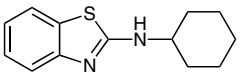
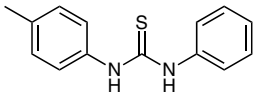
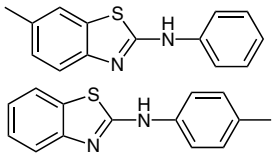
Entry	Substrate	Product	Yield (%)[b]
7		 **2e**	95
8		 **2f**	88
9		 **2g**	92
10		 **2h**	95
11		 **2i**	92
12		 **2j**	95
13		 **2k**	83
14		 **2l**	80
15		 **2m**	89
16		 **2n**	84
17		 **2o**	86
18		 **2p**	88

Table 2 Effect of Substituents on 2-Aminobenzothiazoles Formation[a] (continued)



Entry	Substrate	Product	Yield (%)[b]
19		 **2q**	81
20		 **2r**	77
21		 **2s**	86
22		 **2t**	92[c]
23			96[d]

[a] Reaction conditions: *o*-halobenzothiaoureas **1** (1.0 mmol), DDQ (1.2 mmol), DMSO (3.0 mL), r.t., 24 h.[11]
[b] Yield of isolated product after column chromatography.
[c] Reaction time: 36 h.
[d] Product obtained as an 55:45 ratio of regioisomers as determined by ^{1}H NMR and (LC–MS) spectroscopic analysis of the unpurified reaction mixture.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (31170747) and Chongqing City Natural Science Foundation of China (No.cstc2011jjA10088) for financial support.

References and Notes

(1) (a) Paget, C. J.; Kisner, K.; Stone, R. L.; DeLong, D. C. *J. Med. Chem.* **1969**, *12*, 1016. (b) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. *J. Med. Chem.* **1988**, *31*, 656.
(2) Hays, S. J.; Rice, M. J.; Ortwine, D. F.; Johnson, G.; Schwartz, R. D.; Boyd, D. K.; Copeland, L. F.; Vartanian, M. G.; Boxer, P. A. *J. Pharm. Sci.* **1994**, *83*, 1425.
(3) Shirke, V. G.; Bobade, A. S.; Bhamaria, R. P.; Khadse, B. G.; Sengupta, S. R. *Indian Drugs* **1990**, *27*, 350.
(4) Suter, H.; Zutter, H. *Helv. Chim. Acta* **1967**, *50*, 1084.
(5) (a) Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48*, 669. (b) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (c) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2008**, *64*, 7741. (d) Xian, H.; Jing, T. *Tetrahedron* **2003**, *59*, 4851. (e) Garin, J.; Melendez, E.; Merchan, F. L.; Merino, P.; Orduna, J.; Tejero, T. *Synth. Commun.* **1990**, *20*, 2327.
(6) For metal-catalyzed intramolecular cyclizations of 2-halobenzothioureas, see: (a) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Wang, J.; Peng, F.; Jiang, J.; Lu, Z.; Wang, L.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467. (d) Benedí, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claver, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073. Tandem addition–C–S coupling reaction: (e) Pi, S.-S.; Zhang, X.-G.; Tang, R.-Y.; Li, J.-H. *Synlett* **2009**, 3032. See also: (f) Ding, Q. P.; He, X.-D.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587. See also: (g) Qiu, J.; Zhang, X.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 2319. See further: (h) Guo, Y.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Tetrahedron Lett.* **2010**, *51*, 649. See also: (i) Ding, Q. P.; Cao, B. P.; Liu, X. J.; Zong, Z.-Z.; Peng, Y. Y. J. *Green Chem.* **2010**, *12*, 1607. (j) Oxidative C–H bond functionalization: Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792.
(7) (a) Baltabaev, U. A.; Makhsumov, A. G.; Zakirov, U. B.; Babaev, I. D.; Shukurullaev, K. *Pharm. Chem. J.* **2002**, *36*, 77. (b) Belboukhari, N.; Cheriti, A.; Djafri, A.; Roussel, C. *Asian J. Chem.* **2008**, *20*, 2491. (c) Ramadas, K.; Srinivasan, N.; Narayanasamy, J. *Tetrahedron Lett.* **1993**, *34*, 6447.
(8) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835.

(9) Mohammadpoor-Baltork, I.; Ali Zolfigolb, M. A.; Abdollahi-Alibeika, M. *Tetrahedron Lett.* **2004**, *45*, 8687.
(10) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261.
(11) **Typical Procedure**
To a solution of (*o*-iodoaryl) thiaoureas (1.0 mmol) in DMSO (3 mL) were added DDQ in five equal portions. The mixture was stirred at r.t. for 24 h (TLC monitoring). After the reaction was completed, H_2O (10 mL) and a sat. aq $NaHCO_3$ solution (5 mL) were added, and then the aqueous solution was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated, and then the residue was purified by column chromatography [eluent: PE–EtOAc (5:1 to 7:1)] on silica gel to provide the desired product.
Compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.18 (m, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 8.3 Hz, 2 H), 7.50 (d, *J* = 7.7 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.5, 120.0, 120.8, 122.6, 124.3, 126.2, 129.6, 130.0, 139.7, 151.4, 164.1 ppm. ESI-HRMS: *m/z* calcd for $[C_{13}H_{10}N_2S + H]^+$: 227.0643; found: 227.0649.
Compound **2c**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.14 (t, *J* = 8.4 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.57 (d, *J* = 8 Hz, 2 H), 7.80 (d, *J* = 10 Hz, 2 H), 10.62 (br, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 119.6, 119.8, 121.6, 123.0, 125.8, 126.4, 129.3, 130.5, 140.0, 152.4, 161.7 ppm. ESI-HRMS: *m/z* calcd for $[C_{13}H_9ClN_2S + H]^+$: 260.0175; found: 260.0183.
Compound **2h**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 3 H), 7.14 (d, *J* = 8.2 Hz, 1 H), 7.49–7.54 (m, 3 H), 7.62 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 2 H), 10.53 (br, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 113.5, 119.5, 119.9, 121.5, 127.5, 130.5, 132.1, 132.3, 10.5, 150.3, 160.9 ppm. ESI-HRMS: *m/z* calcd for $[C_{14}H_{11}BrN_2S + H]^+$: 318.9905; found: 318.9937.
Compound **2t**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.41 (m, 5 H), 1.51–1.56 (m, 1 H), 1.67–1.73 (m, 2 H), 2.05–2.30 (m, 2 H), 2.66–2.69 (m, 1 H), 3.50 (br s, 1 H), 6.99 (t, *J* = 2.4, 9.3 Hz, 1 H), 7.27 (dd, *J* = 2.4, 7.8 Hz, 1 H), 7.42 (dd, *J* = 4.9, 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 25.5, 33.5, 57.6, 121.1, 121.3, 123.6, 128.9, 136.9, 152.4, 165.7 ppm. ESI-HRMS: *m/z* calcd for $[C_{13}H_{16}N_2S + H]^+$: 233.1112; found: 233.1140.

