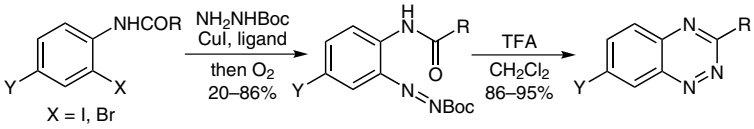
Synlett Y. Zhou et al. Letter

Synthesis of 1,2,4-Benzotriazines via Copper(I) Iodide/1*H*-Pyrrole-2-carboxylic Acid Catalyzed Coupling of *o*-Haloacetanilides and *N*-Boc Hydrazine

Yijun Zhou[a]
Zhigao Zhang[b]
Yongwen Jiang[b]
Xianhua Pan[*a]
Dawei Ma[*b]

[a] School of Perfume and Aroma Technology, Shanghai Institute of Technology, No. 120 Cao Bao Road, Shanghai 200235, P. R. of China
[b] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. of China
madw@mail.sioc.ac.cn



Received: 06.03.2015
Accepted after revision: 07.05.2015
Published online: 08.06.2015
DOI: 10.1055/s-0034-1378708; Art ID: st-2015-b0153-l

Abstract Coupling of *o*-haloacetanilides and *N*-Boc hydrazine proceeded at room temperature under the catalysis of CuI/1*H*-pyrrole-2-carboxylic acid. The coupling products underwent oxidation to afford the azo compounds, which were subjected to deprotection with TFA and in situ cyclization to give 1,2,4-benzotriazines.

Key words coupling, cyclization, copper, catalysis, 1,2,4-benzotriazine

The 1,2,4-benzotriazine and its analogues are an important class of pharmaceutical heterocycles that display a wide range of biological properties. Recent examples include 1,2,4-benzotriazine 1,4-dioxide **1** that acts as hypoxia selective cytotoxin,[1] 3-amino-substituted 1,2,4-benzotriazine **2** that possesses significant antitumor activity by inhibiting Src kinase,[2] PARP inhibitor **3**,[3] microbiocide **4**,[4] sodium-glucose co-transporter 2 (SGLT2) inhibitor **5** that has been used for prevention and treatment of metabolic disorders,[5] as well as selective A3 adenosine receptor antagonist **6** (Figure 1).[6] In addition, compounds with 1,2,4-benzotriazine core structure have been utilized as fluorescent brighteners,[7] herbicides,[8] and dyes.[9]

The typical method for preparing 1,2,4-benzotriazines involves the initial formation of 1,2-dihydro-1,2,4 benzotriazines precursors through an acylation–reduction–cyclization process from 2-nitrophenylhydrazine.[10] Another method starts with *o*-nitroanilines and requires a four-step sequence to afford the core structures.[11] These methods suffer from a limited number of available starting materials for diversity synthesis. Recently, a copper-catalyzed coupling of 2-haloanilines and hydrazides was found to give 1,2,4-benzotriazines, but only 3-aryl-substituted products could be obtained.[12] As such, development of an alternative route to construct 1,2,4-benzotriazines and related heterocycles would be highly valuable.

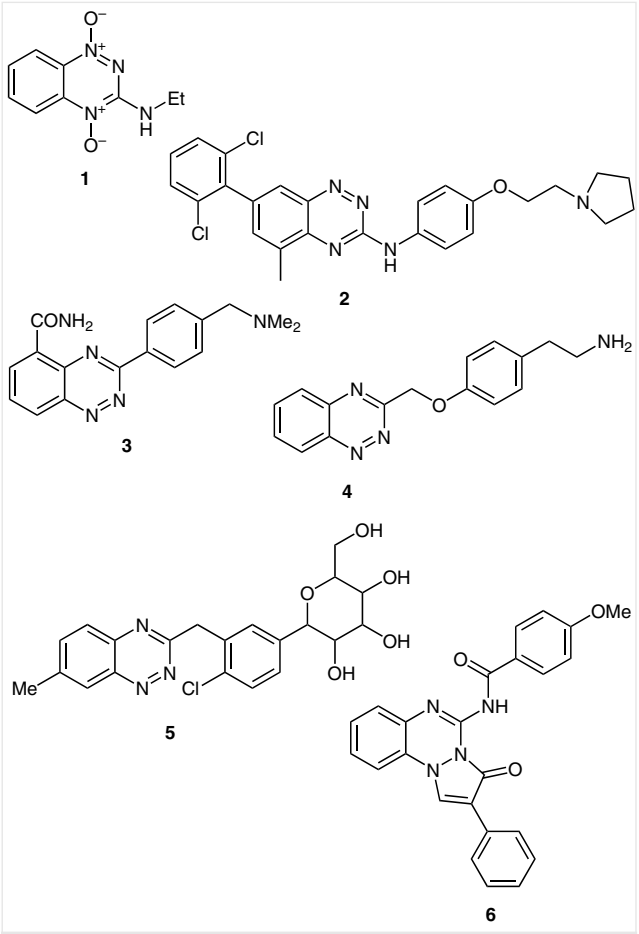
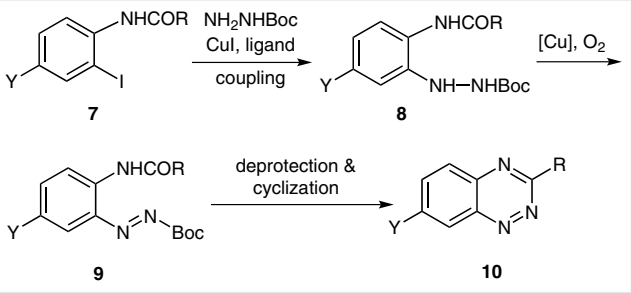


Figure 1 Representative compounds

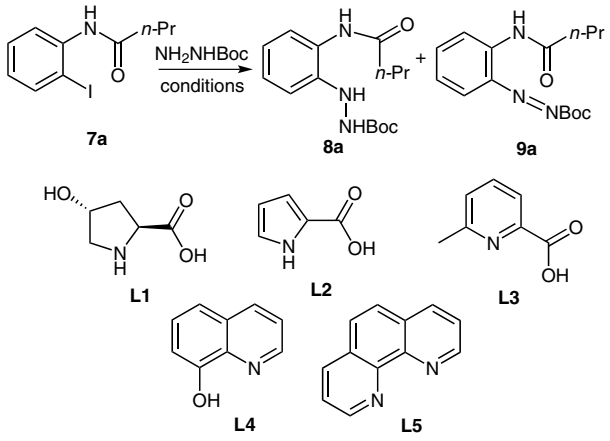
Based on the copper (I)–amino acid promoted Ullmann-type coupling reactions, we have developed a series of cascade and one-pot processes for assembling heterocycles[13] such as benzofurans, indoles, benzimidazoles, benzothiazoles, and phenothiazines. As an extension of this study, we tried the coupling reaction of *o*-haloacetanilides and *N*-Boc hydrazine, and found that *N*′-arylated products **8** formed selectively, which easily underwent oxidation to deliver azo compounds **9** (Scheme 1).[14] Interestingly, treatment of **9** with TFA provided 1,2,4-benzotriazines in excellent yields. Herein, we wish to report our result.



Scheme 1 A new route for syntheses of 1,2,4-benzotriazines

As summarized in Table 1, we began our investigation with conducting the coupling reaction of the *N*-(2-iodophenyl)butyramide (**7a**) and *N*-Boc hydrazine. Our previous study indicated the *o*-amide functional group may facilitate the coupling reactions,[13] and therefore initial reaction conditions could be set at 35 °C. Firstly, a number of ligands were tested. To our delight, most of the tested ligands could directly deliver simple coupling product **8a** and azo compound **9a**, while 1*H*-pyrrole-2-carboxylic acid (**L2**) was our best ligand (Table 1, entries 1–5). This result indicated that the C–N coupling took place selectively on the *N*′-position of *N*-Boc hydrazine, which is different with the coupling reaction of simple aryl halides with *N*-Boc hydrazine.[15,16] Different solvents were then compared (Table 1, entries 6–8). Although NMP gave a similar result (Table 1, entry 7), toluene and acetonitrile almost produced no desired coupling or cyclization products but the deiodonation compound and unreacted starting material. Moreover, it was proved that addition of NaI could dramatically increase the reaction rate, resulting in that comparable efficiency could also be obtained even with lower catalyst and ligand loading (Table 1, entries 9 and 10).[17] As we observed, the coupling product could be partially converted into the corresponding azo compound in situ, which might result from copper-catalyzed oxidation with air.[14] To further promote the oxidation, we decided to introduce oxygen into the reaction mixture after consumption of *o*-iodoanilide **7a**, and found that the yield of **9a** could be increased to 83% (Table 1, entry 11). Taking together, we conclude that the optimal conditions were using 1*H*-pyrrole-2-carboxylic acid as the ligand, DMSO as the solvent, and promoting the oxidation by addition of oxygen.

Table 1 Optimization of Reaction Conditions[a]



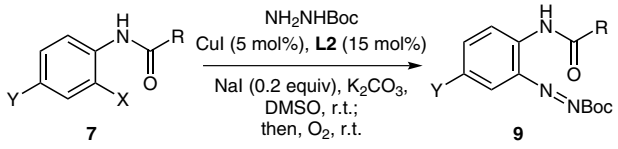
Entry	Ligand	Solvent	Additive	Yield of **8a** (%)[b]	Yield of **9a** (%)[b]
1	**L1**	DMSO	–	22	10
2	**L2**	DMSO	–	51	16
3	**L3**	DMSO	–	18	7
4	**L4**	DMSO	–	40	16
5	**L5**	DMSO	–	10	7
6[c]	**L2**	PhMe	–	–	–
7[c]	**L2**	NMP	–	30	7
8[c]	**L2**	MeCN	–	–	–
9[d]	**L2**	DMSO	–	56	–
10[e]	**L2**	DMSO	–	55	17
11[f]	**L2**	DSMO	O_2	–	83

[a] Reaction conditions: **7a** (0.5 mmol), *N*-Boc hydrazine (0.53 mmol), CuI (10 mol%), ligand (20 mol%), K_2CO_3 (1.0 mmol), solvent (1.5 mL), 35 °C, 36 h.
[b] Isolated yield.
[c] Reaction conditions: 25 °C, 36 h.
[d] Reaction conditions: CuI (5 mol%), **L2** (15 mol%), NaI (0.5 mmol), 25 °C, 10 h.
[e] Reaction conditions: CuI (5 mol%), **L2** (15 mol%), NaI (0.1 mmol), 25 °C, 24 h.
[f] Oxygen was added into the reaction mixture after coupling reaction, 25 °C, 3 h.

With the optimized conditions in hand, we then explored the scope and limitations of this novel transformation, and the results are summarized in Table 2.[17] Our conditions complied well with different steric hindered substituents, such as *i*-propyl, *t*-butyl, cyclopropyl groups (Table 2, entries 2–5). A pyran-derived substrate and two other substrates with additional functional groups could also afford the desired azo products in 58–74% yields (Table 2, entries 6–8). Aromatic substitution (phenyl and thiophene) was also tested while only moderate yields could be achieved (Table 2, entries 9, 10). The relatively low yields in these cases might be caused by deiodination because the

corresponding side products were determined, and further study is needed to fix this problem. Furthermore, the electronic effect on the phenyl ring was investigated (Table 2, entries 11–15). It was found that the substrates with electron-donating groups could deliver the azo compounds in excellent yields (Table 2, entries 11 and 12), while those with electron-withdrawing functional groups gave the desired azo products in only moderate yields (Table 2, entries 13–15). Additionally, we found that *o*-bromoacetanilide coupling partners were less reactive coupling partners than *o*-iodoacetanilides, giving the corresponding products in only 20–28% yields (Table 2, entries 16–19).

Table 2 Syntheses of Aromatic Azo Compounds via CuI/**L2**-Catalyzed Coupling/Oxidation Process[a]



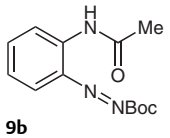
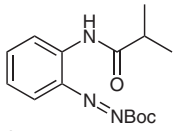
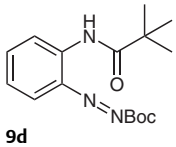
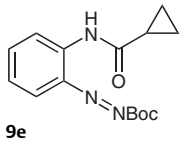
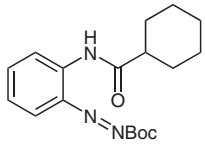
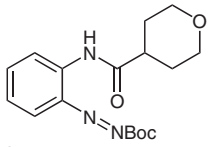
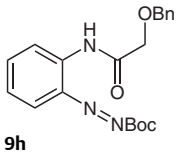
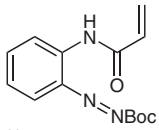
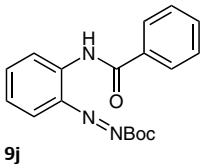
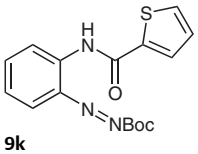
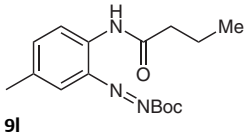
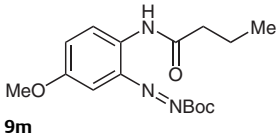
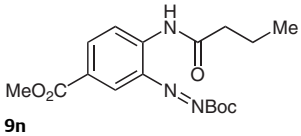
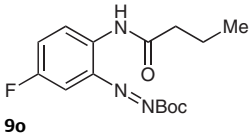
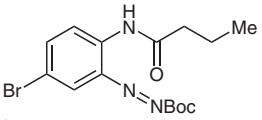
Entry	X	Product	Yield (%)[b]
1	I	 **9b**	67
2	I	 **9c**	78
3	I	 **9d**	72
4	I	 **9e**	78
5	I	 **9f**	78

Table 2 (continued)

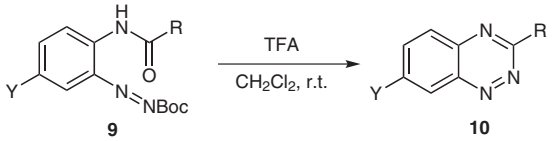
Entry	X	Product	Yield (%)[b]
6	I	 **9g**	69
7	I	 **9h**	74
8	I	 **9i**	58
9	I	 **9j**	42
10	I	 **9k**	42
11	I	 **9l**	86
12	I	 **9m**	81
13	I	 **9n**	49
14	I	 **9o**	57

Entry	X	Product	Yield (%)[b]
15	I	 **9p**	51
16[c]	Br	**9a**	24
17[c]	Br	**9f**	20
18[c]	Br	**9l**	28
19[c]	Br	**9m**	23

[a] Reaction conditions: **7** (0.5 mmol), *N*-Boc hydrazine (0.53 mmol), CuI (5 mol%), ligand (15 mol%), K_2CO_3 (1 mmol), solvent (1.5 mL), 25 °C, 24–30 h; then oxygen was added at r.t. for 3–5 h.
[b] Isolated yield.
[c] Time for coupling step was 48 h.

Upon deprotection of the Boc group in the azo compounds **9** with TFA in dichloromethane, exclusive formation of 1,2,4-benzotriazines were observed. The mechanism for this transformation is still unclear, and further studies are required to address this issue. As shown in Table 3, a number of 1,2,4-benzotriazines could be obtained in excellent yields. It is notable that this novel reaction was proved to be compatible with a variety of functional groups, including alkyl groups (Table 3, entries 1–6), aromatic substituents (Table 3, entries 7 and 8), and electron-rich/poor substrates (Table 3, entries 9 and 10).[18]

Table 3 Syntheses of 1,2,4-Benzotriazines[a]



9 **10**

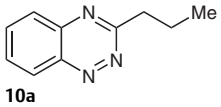
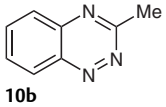
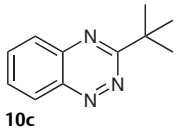
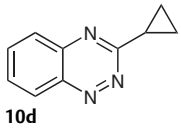
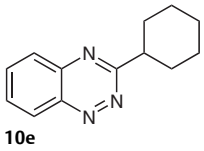
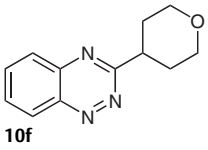
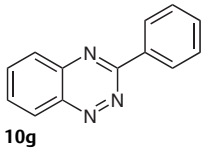
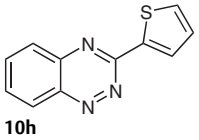
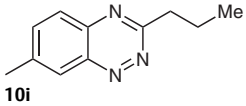
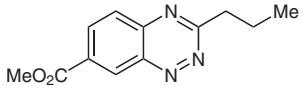
Entry	Product	Yield (%)[b]
1	 **10a**	91
2	 **10b**	90
3	 **10c**	95
4	 **10d**	89

Table 3 (continued)

Entry	Product	Yield (%)[b]
5	 **10e**	96
6	 **10f**	88
7	 **10g**	92
8	 **10h**	91
9	 **10i**	93
10	 **10j**	86

[a] Reaction conditions: **9** (0.2 mmol), TFA (0.5 mL), CH_2Cl_2 (2 mL), r.t., 2 h.
[b] Isolated yields.

In conclusion, we have developed a novel method for assembling 1,2,4-benzotriazines, which relies on a one-pot CuI–1*H*-pyrrole-2-carboxylic acid catalyzed coupling of *o*-iodoacetanlides and *N*-Boc hydrazine and subsequent aerobic oxidation. Noteworthy is that a considerable number of *o*-iodoacetanlides with different functionalized groups worked well under the present conditions, and thereby allowing diverse synthesis of these special heterocycles.

Acknowledgment

The authors are grateful to Chinese Academy of Sciences and the National Natural Science Foundation of China (grant 21132008 & 21372240) for their financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378708.

References and Notes

(1) Hay, M. P.; Hicks, K. O.; Pchalek, K.; Lee, H. H.; Blaser, A.; Pruijn, F. B.; Anderson, R. F.; Shinde, S. S.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **2008**, *51*, 6853.
(2) Noronha, G.; Barrett, K.; Cao, J.; Dneprovskaia, E.; Fine, R.; Gong, X.; Gritzen, C.; Hood, J.; Kang, X.; Klebansky, B.; Li, G.; Lose, D.; Mark, C.; McPherson, A.; Palanki, M.; Pathak, V.; Renick, J.; Soll, R.; Splittgerber, U.; Wrasidlo, W.; Zeng, B.; Zhao, N.; Zhou, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5546.
(3) Boyle, R. G.; Travers, S. WO 2008015429, **2008**.
(4) Zeller, M. WO 9838161, **1998**.
(5) Lee, J.; Lee, S.; Seo, H.; Kim, M.; Kang, S.; Kim, J.; Lee, S.; Jung, M.; Son, E.; Lee, J.; Song, K.; Kim, M. WO 2010147430, **2010**.
(6) Settimo, F. D.; Primofiore, G.; Taliani, S.; Marini, A. M.; La Motta, C.; Simorini, F.; Salerno, S.; Sergianni, V.; Tuccinardi, T.; Martinelli, A.; Cosimelli, B.; Greco, G.; Novellino, E.; Ciampi, O.; Trincavelli, M. L.; Martini, C. *J. Med. Chem.* **2007**, *50*, 5676.
(7) Fleck, F.; Balzer, H.; Aebli, H. FR 1411433, **1965**.
(8) Selby, T. US 5389600, **1995**.
(9) Leverenz, K.; Schuendehuette, K. DE 2241259, **1974**.
(10) (a) Riccardo, C.; Alessandro, B.; Fabio, S. *J. Heterocycl. Chem.* **1979**, *16*, 1005. (b) Reich, M.; Fabio, P.; Lee, V.; Kuck, N.; Testa, R. *J. Med. Chem.* **1989**, *32*, 2474.
(11) Bass, J. Y.; Caravella, J. A.; Chen, L.; Creech, K. L.; Deaton, D. N.; Madauss, K. P.; Marr, H. B.; McFadyen, R. B.; Miller, A. B.; Mills, W. Y.; Navas, F. III.; Parks, D. J.; Smalley, T. L. Jr.; Spearing, P. K.; Todd, D.; Williams, S. P.; Wisely, G. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1206.
(12) Guo, H.; Liu, J.; Wang, X.; Huang, G. *Synlett* **2012**, *23*, 903.
(13) (a) Chen, Y.; Ma, D. *Org. Lett.* **2006**, *8*, 6115. (b) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (c) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (d) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2598. (e) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 4222. (f) Ma, D.; Geng, Q.; Zhang, H.; Jiang, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 1291. (g) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200. (h) Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 1118. (i) Xu, L.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 1150.
(14) For copper-catalyzed oxidation of aryl hydrazines to azo compounds, see: Zhang, C.; Jiao, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6174.
(15) (a) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 4542. (b) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552.
(16) (a) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (b) Lam, M. S.; Lee, H. W.; Chan, A. C.; Kwong, F. Y. *Tetrahedron Lett.* **2008**, *49*, 6192.
(17) **General Procedure for the Preparation of 9**
A Schlenk tube was charged with iodide **7** (0.5 mmol), *N*-Boc hydrazine (70 mg, 0.53 mmol), CuI (5 mg, 0.025 mmol), 1*H*-pyrrole-2-carboxylic acid (9 mg, 0.08 mmol), NaI (15 mg, 0.1 mmol), and K_2CO_3 (138 mg, 1.0 mmol), evacuated, and backfilled with argon. DMSO (1.5 mL) was successively added. The reaction mixture was stirred at 25 °C for 24–30 h before oxygen was introduced. After the reaction mixture was stirred at 25 °C for 3–5 h, it was extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel to provide **9**.
Compound **9a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (s, 1 H), 8.70 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.74 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.54 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1 H), 7.09 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 2 H), 2.41 (t, *J* = 7.4 Hz, 2 H) 1.80–1.72 (m, 2 H), 1.65 (s, 9 H), 1.00 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.66, 160.23, 138.25, 138.05, 136.01, 123.11, 120.55, 119.36, 84.97, 40.16, 27.85 (3C), 18.75, 13.68. ESI-MS: *m/z* = 314.2 $[M + Na]^+$. ESI-HRMS:*m/z* calcd for $C_{15}H_{22}N_3O_3^+$ $[M + H]^+$: 292.1656; found: 292.1653.
Compound **9k**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.10 (s, 1 H), 8.83 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.95 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.71 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.62 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.59 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.22 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1 H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1 H), 1.71 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.30, 159.14, 139.74, 138.01, 136.45, 136.30, 131.71, 128.83, 127.88, 125.30, 123.50, 120.31, 84.95, 27.88 (3 C). ESI-MS: *m/z* = 354.2 $[M + Na]^+$. ESI-HRMS:*m/z* calcd for $C_{16}H_{18}N_3O_3S^+$ $[M + H]^+$: 332.1063; found: 332.1061.
(18) **Typical Procedure for the Prepration of 10**
To a solution of **9** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (0.5 mL). The solution was stirred at r.t. for 2 h before aq $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to provide **10**.
Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 7.9 Hz, 1 H), 7.96–7.90 (m, 1 H), 7.83–7.77 (m, 1 H), 3.35 (t, *J* = 9.6 Hz, 2 H), 2.08–1.97 (m, 2 H), 1.06 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.45, 146.18, 140.85, 135.25, 129.82, 129.53, 128.51, 39.69, 22.28, 13.92. ESI-MS: *m/z* = 174.1 $[M + H]^+$. ESI-HRMS:*m/z* calcd for $C_{10}H_{12}N_3^+$ $[M + H]^+$: 174.1026; found: 174.1025.
Compound **10h**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 8.4, 0.7 Hz, 1 H), 8.35 (dd, *J* = 3.7, 1.1 Hz, 1 H), 8.02–7.97 (m, 1 H), 7.92 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1 H), 7.76 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.61 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.24 (dd, *J* = 4.9, 3.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.36, 146.00, 140.87, 140.72, 135.72, 131.31, 130.61, 129.75, 129.70, 128.65, 128.61. ESI-MS: *m/z* = 214.1 $[M + H]^+$. ESI-HRMS:*m/z* calcd for $C_{11}H_8N_3S^+$ $[M + H]^+$: 214.0433; found: 214.0432.