Tetrahedron Letters 50 (2009) 1435–1437

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 3-aryl substituted benzo[1,2,5]triazepin-4-ones via intramolecular imine formation

Mirosław J. Tomaszewski, Luc Boisvert, Shujuan Jin *

Department of Medicinal Chemistry, AstraZeneca R&D Montréal, 7171 Frédérick-Banting, Saint-Laurent, Québec, Canada H4S 1Z9

ARTICLE INFO

Article history:
Received 22 December 2008
Revised 11 January 2009
Accepted 12 January 2009
Available online 19 January 2009

Keywords:
Heterocycles
α-Ketoamides
Pyrido[1,2,5]triazepin-4-ones
Trifluoroacetyl hydrazines

ABSTRACT

3-Aryl substituted benzo[1,2,5]triazepin-4-ones and their pyrido counterparts have been synthesized in five steps from commercially available starting materials. The key step involves base-induced cleavage of trifluoroacetyl-protected hydrazine intermediates and in situ intramolecular imine formation.

The benzodiazepinone scaffold (**A**, Fig. 1) has emerged over the years as an extremely rewarding template for drug discovery.[1,2] Besides the widely used sedative diazepam, benzodiazepinones have shown promise for treating a variety of conditions, including ventricular arrhythmia,[3] rheumatoid arthritis,[4] obesity,[5] migrane,[6] and Alzheimer's disease (AD).[7] Compounds possessing a benzo[1,2,5]triazepine core (**B**) also display significant activities against an array of molecular targets,[8] such as the dopamine D-1 and serotonin (5HT) receptors[9,10] and the reverse transcriptase of HIV-1.[11]

Although several methods for constructing benzotriazepines can be found in the literature,[12] the related benzotriazepinones (**C**) have only received scant attention.[13,14] Members of the latter class were first prepared by Rossi and co-workers using cyclization of diazonium salts derived from acyl-*o*-phenylenediamines.[13] While the yields of benzotriazepinones are generally high, the preparation of diazonium salts is an obvious inconvenience, especially on a large scale. An alternative, more recent approach relies on the dehydrative cyclization of *N*-(*o*-aminoaryl) succinate or malonate hydrazones.[14a,b] However, this approach is limited with regard to the nature of the C3-substituent due to competing 1,2,4-triazine formation.[14b,c] Hence there is a need for new methodology that would allow access to a range of custom-designed benzotriazepinones from readily available precursors.

Of particular interest to us were the hitherto unknown 3-aryl-substituted benzo and pyrido[1,2,5]triazepin-4-ones (**1**). Earlier attempts to prepare such compounds by Kodato and co-workers have failed due to competing *6-endo-trig* cyclization of the hydrazone intermediates.[15] Here we report a successful strategy for constructing **1** based on the retrosynthetic analysis outlined in Scheme 1. Assemblage of the triazepinone ring was envisioned by intramolecular imine formation of hydrazine α-ketoamides **2** which would arise from halonitroaromatics **4** by S_NAr substitution (cf. **4**→**3**), reduction of the nitro group, α-ketoamide formation, and removal of the *N*-protecting group (PG).

Initial efforts to probe the feasibility of this pathway established that the trifluoroacetyl group was a good choice for hydrazine protection (vide infra). The preparation of the requisite trifluoroacetylhydrazines (cf. **3a–d**) was readily achieved from commercially available chloro or fluoro nitroaromatics (**4a–d**), by conversion to the corresponding methylhydrazines (**5a–d**)[16] and ensuing reaction with trifluoroacetic anhydride in the presence of Hünig's base (Table 1).

Chemoselective reduction of the nitro group in **3** was achieved with over 90% efficiency by reaction with hydrogen in the presence of Adam's catalyst in toluene (Table 2). Keeping reaction times short, by monitoring amine formation with LC–MS, proved essential due to the instability of the resulting amine products, attributed to their propensity of undergoing cyclization to triazines.[16b,17] The crude

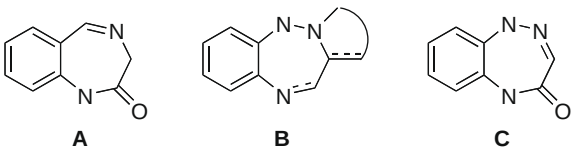
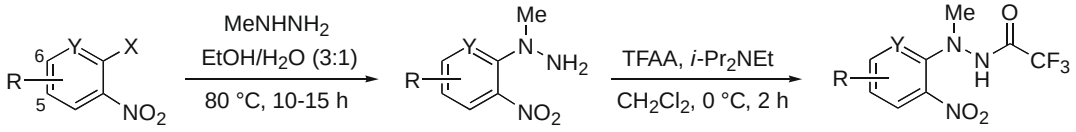


Figure 1. Scaffolds **A**–**C**.

* Corresponding author. Tel.: +1 514 832 3200; fax: +1 514 832 3232.
E-mail address: shujuan.jin@astrazeneca.com (S. Jin).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.064

Table 1
Synthesis of aromatic trifluoroacetylhydrazines



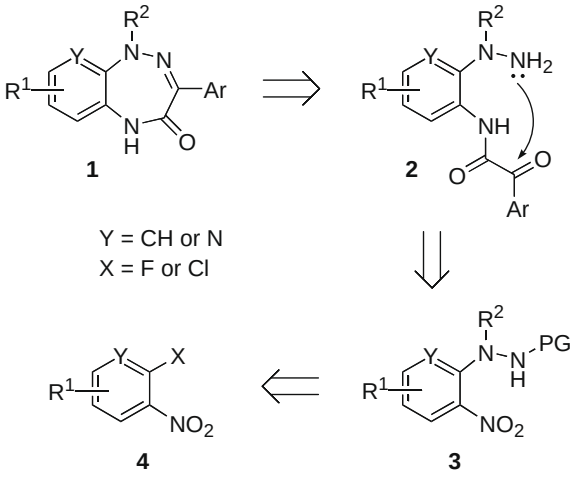
4a-d **5a-d** **3a-d**

Entry	Substrate	R	X	Y	% Yield[a] of **5**	% Yield[a] of **3**
1	**4a**	H	Cl	CH	94 (**5a**)	77 (**3a**)
2	**4b**	5-CF_3	F	CH	93 (**5b**)	95 (**3b**)
3	**4c**	6-Me	F	CH	82 (**5c**)	93 (**3c**)
4	**4d**	H	Cl	N	75 (**5d**)	92 (**3d**)

[a] Yields refer to chromatographically isolated products.

amines were immediately transformed to the desired α-ketoamides by reaction with the appropriate α-ketoacid chloride, prepared in situ from the corresponding α-ketoacid and thionyl chloride. Using this simple procedure,[18] a range of α-ketoamides (**6a**–**h**) were obtained in good to excellent yields (Table 2).

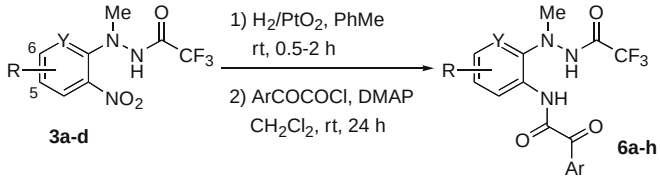
Exposure of the α-ketoamides to potassium carbonate in MeOH/H_2O at room temperature accomplished both removal of the trifluoroacetyl group and intramolecular imine formation to



1 **2** **3** **4**

Scheme 1. Retrosynthetic analysis of **1**.

Table 2
Synthesis of α-ketoamides

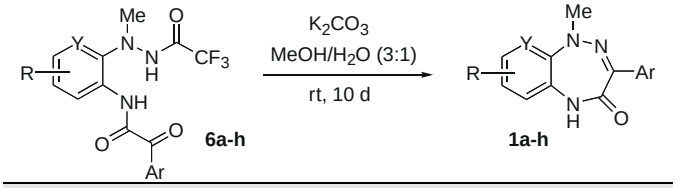


3a-d **6a-h**

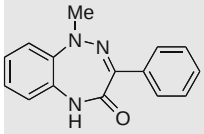
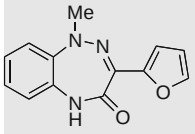
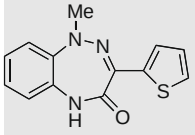
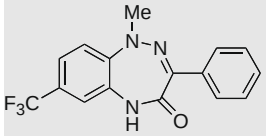
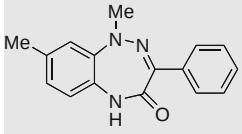
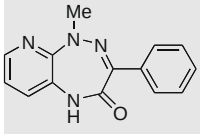
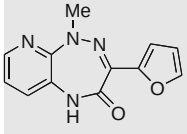
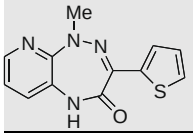
Entry	Substrate	R	Y	Ar	% Yield[a] of **6**
1	**3a**	H	CH	Ph	84 (**6a**)
2	**3a**	H	CH	2-Furyl	75 (**6b**)
3	**3a**	H	CH	2-Thienyl	78 (**6c**)
4	**3b**	5-CF_3	CH	Ph	99 (**6d**)
5	**3c**	6-Me	CH	Ph	90 (**6e**)
6	**3d**	H	N	Ph	95 (**6f**)
7	**3d**	H	N	2-Furyl	91 (**6g**)
8	**3d**	H	N	2-Thienyl	96 (**6h**)

[a] Overall yields of chromatographically isolated products after two steps.

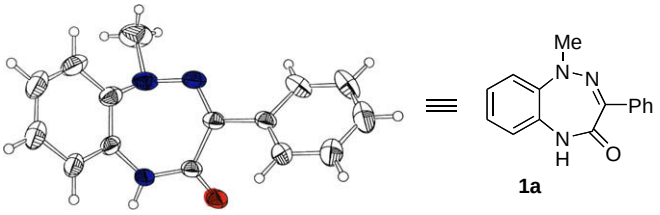
Table 3
Synthesis of benzo and pyridotriazepinones



6a-h **1a-h**

Product	% Yield[a]
	73 (**1a**)
	55 (**1b**)
	46 (**1c**)
	57 (**1d**)
	52 (**1e**)
	76 (**1f**)
	33 (**1g**)
	38 (**1h**)

[a] Yields refer to chromatographically isolated products of over 98% purity (HPLC).



1a

Figure 2. X-ray structure of benzotriazepinone **1a**.

furnish the desired benzotriazepinones in yields of 33–76% after purification by preparative HPLC (Table 3).[19] The products (**1a**–**h**) were readily identified by the characteristic ^{13}C NMR signal of the carbonyl carbon at ca. 163–166 ppm.[20] As all of these compounds were crystalline, we were able to secure irrefutable proof for the proposed structures by performing X-ray diffraction analysis of benzotriazepinone **1a** (Fig. 2).[21]

Finally, it is worth mentioning that the choice of trifluoroacetyl group for protecting the hydrazine moiety proved crucial for success of the final step in the synthesis (cf. **6**→**1**). Attempts to transform either the Boc or Fmoc-protected analogues of **6a** to triazepinone **1a** under acidic or basic conditions, respectively, led to complex mixtures in which none of the desired product could be detected by LC–MS.

In summary, a convenient synthesis of the previously unknown 3-aryl-substituted benzo and pyrido[1,2,5]triazepin-4-ones has been developed. The key step involves one-pot deprotection-intramolecular imine formation of trifluoroacetylhydrazines **6**, which are prepared in four straightforward steps from commercial starting materials. Efforts aimed at establishing shorter versions of this pathway are currently underway.

Acknowledgments

We thank Dr. Christopher Walpole for his support and encouragement during this work and Ms. May-Britt Kary for the HRMS data.

References and notes

1. Recent reviews: (a) Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem.* **2000**, *35*, 289–298; (b) Hadjipavlou-Litina, D.; Garg, R.; Hansch, C. *Chem. Rev.* **2004**, *104*, 3751–3793.
2. (a) Dourlat, J.; Liu, W.-Q.; Gresh, N.; Garbay, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2527–2530; (b) Legerén, L.; Gómez, E.; Domínguez, D. *Tetrahedron Lett.* **2008**, *49*, 7174–7177. and references cited therein.
3. (a) Lynch, J. J., Jr.; Salata, J. J.; Wallace, A. A.; Stump, G. L.; Gilberto, D. B.; Jahansouz, H.; Liverton, N. J.; Selnick, H. G.; Claremon, D. A. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 283–289; See also: (b) Shi, Y.-J.; Wells, K. M.; Pye, P. J.; Choi, W.-B.; Churchill, H. R. O.; Lynch, J. E.; Maliakal, A.; Sager, J. W.; Rossen, K.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1999**, *55*, 909–918.
4. (a) Boitano, A.; Emal, C. D.; Leonetti, F.; Blatt, N. B.; Dineen, T. A.; Ellman, J. A.; Roush, W. R.; Opipari, A. W.; Glick, G. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3327–3330; See also: (b) Cleary, J.; Johnson, K. M.; Opipari, A. W., Jr.; Glick, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1667–1670. and references cited therein.
5. Sherrill, R. G.; Berman, J. M.; Birkemo, L.; Croom, D. K.; Dezube, M.; Ervin, G. N.; Grizzle, M. K.; James, M. K.; Johnson, M. F.; Queen, K. L.; Rimele, T. J.; Vanmiddlesworth, F.; Sugg, E. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1145–1148.
6. Williams, T. M.; Stump, G. A.; Nguyen, D. N.; Quigley, A. G.; Bell, I. M.; Gallicchio, S. N.; Zartman, C. B.; Wan, B.-L.; Penna, K. D.; Kunapuli, P.; Kane, S. A.; Koblan, K. S.; Mosser, S. D.; Rutledge, R. Z.; Salvatore, C.; Fay, J. F.; Vacca, J. P.; Graham, S. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2595–2598.
7. Owens, A. P.; Nadin, A.; Talbot, A. C.; Clarke, E. E.; Harrison, T.; Lewis, H. D.; Reilly, M.; Wrigley, J. D. J.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4143–4145.
8. For select examples of bioactive benzotriazepines see: (a) Stefancich, G.; Artico, M.; Silvestri, R.; Pantaleoni, G. C.; Giorgi, R.; Palumbo, G. *Farmaco* **1990**, *45*, 7–27; (b) Ashworth, D. M.; Pitt, G. R. W.; Hudson, P.; Yea, C. M.; Franklin, R. J. PCT Int. Appl. WO 200149682 (CA: **2001**, *135*, 77103).; (c) Ashworth, D. M.; Pitt, G. R. W.; Hudson, P.; Yea, C. M.; Franklin, R. J.; Semple, G. PCT Int. Appl. WO 200200626 (CA: **2002**, *136*, 69828).; (d) Silvestri, R.; Marfe, G.; Abruzzese, E.; Catalano, G.; Di Stefano, C.; Novellino, E.; Sinibaldi Salimei, P.; La Regina, G.; Lavecchia, A. PCT Int. Appl. WO 2007015280 (CA: **2007**, *146*, 229392).
9. Robison, R. L.; Visscher, G. E.; Roberts, S. A.; Engstrom, R. G.; Hartman, H. A.; Ballard, F. H. *Toxicol. Pathol.* **1985**, *13*, 335–348.
10. De Martino, G.; La Regina, G.; La Torre, F.; Cirilli, R.; Mereghetti, I.; Cagnotto, A.; Artico, M.; Silvestri, R. *Farmaco* **2005**, *60*, 931–937.
11. Castellano, S.; Stefancich, G.; La Colla, P.; Musiu, C. *J. Heterocycl. Chem.* **2000**, *37*, 1539–1542.
12. (a) Bouteau, B.; Imbs, J.-L.; Lancelot, J.-C.; Barthelmebs, M.; Robba, M. *Chem. Pharm. Bull.* **1991**, *39*, 81–85; (b) Lancelot, J.-C.; Robba, M. *Chem. Pharm. Bull.* **1988**, *36*, 2381–2385; (c) Korakas, D.; Kimbaris, A.; Varvounis, G. *Tetrahedron* **1996**, *52*, 10751–10760; (d) Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A. G.; Putzolu, M.; Corrias, S.; Spiga, M. G.; La Colla, P. *Bioorg. Med. Chem.* **1996**, *4*, 837–850; (e) Stefancich, G.; Artico, M.; Silvestri, R.; Pantaleoni, G. C.; Giorgi, R.; Palumbo, G. *Farmaco* **1992**, *47*, 987–999; (f) Lancelot, J.-C.; Ladurée, D.; El Kashef, H.; Robba, M. *Heterocycles* **1985**, *23*, 909–911; (g) Artico, M.; Massa, S.; Mai, A.; Silvestri, R.; Stefancich, G. *J. Heterocycl. Chem.* **1992**, *29*, 241–245.
13. (a) Rossi, S.; Pirola, O.; Selva, F. *Tetrahedron* **1968**, *24*, 6395–6409; (b) Bianchi, M.; Butti, A.; Rossi, S. *Tetrahedron* **1974**, *30*, 2765–2771.
14. (a) Schwesinger, H.; Sicker, D.; Wilde, H. *Pharmazie* **1992**, *47*, 60–61; (b) Savelli, F.; Boido, A.; Ciarallo, G. *J. Heterocycl. Chem.* **1999**, *36*, 857–862; (c) Khodja, M.; Moulay, S.; Boutoumi, H.; Wilde, H. *Heteroat. Chem.* **2006**, *17*, 166–172.
15. (a) Kodato, S.-I.; Wada, H.; Saito, S.; Takeda, M.; Nishibata, Y.; Aoe, K.; Date, T.; Onoda, Y.; Tamaki, H. *Chem. Pharm. Bull.* **1987**, *35*, 80–89; See also: (b) Andersch, J.; Sicker, D. *J. Heterocycl. Chem.* **1999**, *36*, 589–594.
16. (a) Munson, J. W.; Hodgkins, T. G. *J. Heterocycl. Chem.* **1978**, *15*, 545–550; (b) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3381–3385; (c) Waldrep, T. W.; Rieder, B. J.; Thibault, T. D.; Canada, E. J. *J. Agric. Food. Chem.* **1991**, *39*, 392–395.
17. (a) Lewis, A.; Shepherd, R. G. *J. Heterocycl. Chem.* **1971**, *8*, 41–46; (b) Reich, M. F.; Fabio, P. F.; Lee, V. J.; Kuck, N. A.; Testa, R. T. *J. Med. Chem.* **1989**, *32*, 2474–2485.
18. *Typical procedure*: Preparation of α-ketoamide **6d**. To a solution of trifluoroacetylhydrazide **3b** (1.050 g, 3.02 mmol) in toluene (20 mL), Adam's catalyst (PtO_2, 99.92 mg, 0.44 mmol) was added and the mixture was shaken under hydrogen (50 psi) for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The resulting crude aniline product was used in the next step without purification. In a separate flask, thionyl chloride (0.20 mL, 2.72 mmol) was added to a stirred solution of DMAP (0.332 g, 2.72 mmol) in CH_2Cl_2 (10 mL) at −20 °C under nitrogen. To this mixture, a solution of 2-oxo-2-phenylacetic acid (0.353 g, 2.35 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was slowly warmed to rt and stirred for a further 3 h. Then DMAP (0.332 g, 2.72 mmol) and a solution of crude aniline (0.545 g, 1.81 mmol) in CH_2Cl_2 (3 mL) were successively added and the resulting mixture was stirred at rt for 24 h. After quenching with water, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and the volatiles were removed under reduced pressure. Purification of the residue by reverse phase preparative HPLC (gradient 30–50% CH_3CN in H_2O containing 10 mM NH_4HCO_3 and 0.375% NH_4OH v/v) afforded α-ketoamide **6d** (0.783 g, 99%) as a light yellow solid (mp 168–170 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 3H), 7.39–7.55 (m, 4H), 7.64 (t, *J* = 7.42 Hz, 1H), 8.01 (s, 1H), 8.34 (d, *J* = 7.42 Hz, 2H), 8.82 (d, *J* = 1.95 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 105.0, 118.6 (q, *J* = 2 Hz), 119.5, 122.2 (q, *J* = 2 Hz), 128.8, 129.5 (q, *J* = 227 Hz), 131.5, 133.3 (q, *J* = 134 Hz), 135.0, 135.4, 139.1, 141.3, 154.6, 160.3, 186.9. HRMS (ESI, MH^+) *m/z* 434.0938 (calcd for $C_{18}H_{14}F_6N_3O_3$: 434.0934).
19. *Typical procedure*: Preparation of benzotriazepinone **1a**. A mixture of α-ketoamide **6a** (20.9 mg, 0.55 mmol) and potassium carbonate (38.0 mg, 0.275 mmol) in MeOH (1 mL) and water (0.3 mL) was stirred at rt for 10 days. The volatiles were evaporated under reduced pressure and water (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by reverse phase preparative HPLC (10–30% MeCN/water containing 0.05% TFA) giving **1a** (10.1 mg, 73%) as yellow crystals, mp 181–183 °C; ^1H NMR (400 MHz, CD_3OD) δ ppm 3.25 (s, 3H), 7.06–7.22 (m, 3H), 7.28–7.43 (m, 4H), 7.67–7.73 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ ppm 41.1, 117.8, 121.4, 125.2, 125.3, 127.6, 128.1, 130.1, 132.4, 133.4, 145.8, 157.3, 166.2; HRMS (ESI, MH^+) *m/z* 252.1130 (calcd for $C_{15}H_{14}N_3O$: 252.1131).
20. *Data for three other benzotriazepinones*: *Compound* **1d**: yellow crystals, mp 180–181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 7.16–7.47 (m, 6H), 7.71–7.92 (m, 2H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.2, 118.5, 118.8 (q, *J* = 4 Hz), 122.8 (q, *J* = 4 Hz), 126.1 (q, *J* = 270 Hz), 127.9, 128.1, 128.6, 130.8, 132.4, 132.8, 148.2, 157.1, 166.3; HRMS (ESI, MH^+) *m/z* 320.1010 (calcd for $C_{16}H_{13}F_3N_3O$ 320.1005). *Compound* **1f**: yellow crystals, mp 140–142 °C; ^1H NMR (400 MHz, CD_3OD) δ 3.33 (s, 3H), 7.11 (dd, *J* = 7.81, 1.95 Hz, 1H), 7.30–7.40 (m, 3H), 7.43 (dd, *J* = 7.81, 1.95 Hz, 1H), 7.65–7.72 (m, 2H), 8.06 (dd, *J* = 4.88, 1.95 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 40.0, 120.7, 127.2, 127.6, 128.1, 129.4, 130.1, 133.4, 143.0, 155.2, 156.4, 165.6; HRMS (ESI, MH^+) *m/z* 253.1084 (calcd for $C_{14}H_{13}N_4O$ 253.1084). *Compound* **1h**: orange crystals; ^1H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 3H), 6.95–7.05 (m, 2H), 7.26-7.35 (m, 2H), 7.57 (d, *J* = 2.73 Hz, 1H), 8.11 (dd, *J* = 4.69, 1.56 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1, 120.6, 126.0, 127.7, 129.1, 129.2, 130.1, 137.1, 143.9, 149.9, 155.1, 164.1; HRMS (ESI, MH^+) *m/z* 259.0646 (calcd for $C_{12}H_{11}N_4OS$ 259.0648).
21. CCDC 677004 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deposit.