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Phenyl α-bromovinyl sulfone in cycloadditions with azomethine ylides: an unexpected facile aromatization of the cycloadducts into pyrroles

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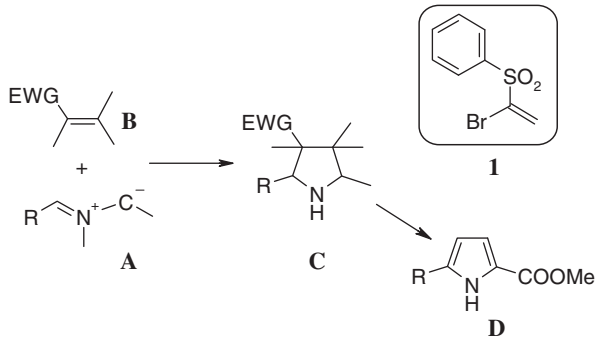
ABSTRACT

Phenyl α-bromovinyl sulfone reacts with glycine ester Schiff bases regioselectively in the presence of catalytic amounts of AgOAc and DBU yielding polysubstituted pyrrolidine cycloadducts. Utilization of excess DBU induces subsequent facile aromatization of the cycloadducts and affords 5-arylpyrrole-2-carboxylic acid esters in 39–85% yields in a single step.

Pyrroles and their hydrogenated analogs, pyrrolidines, occupy a sizeable part of the drug-like chemical space represented by numerous biologically[1] and pharmaceutically[2] active small molecules derived from these five-membered nitrogen heterocyclic scaffolds. Some recent developments of pyrrolidine and pyrrole compounds include ionotropic glutamate receptor antagonists,[3] a clinical anticoagulant candidate based on a factor Xa inhibitor,[4] avian influenza neuraminidase inhibitors,[5] a potential agent for treatment of liver cirrhosis,[6] antimycobacterials with high protection indices,[7] and nanomolar selective β-secretase inhibitors.[8]

An efficient synthetic strategy for the construction of polysubstituted pyrrolidines **C** is 1,3-dipolar cycloaddition between azomethine ylides **A** and activated olefins **B** (Scheme 1).[9] Modified 5-arylpyrrolidine-2-carboxylic acid derivatives generated by this chemistry have been used for creating *Staphylococcus aureus* sortase A inhibitors,[10] antiplatelet agents[11], and thrombin inhibitors.[12] Obviously, the structural variations of pyrrolidines **C** depend on both the nature of the azomethine and dipolarophile.[13] Aiming to increase the available diversity of pyrrolidines prepared via 1,3-dipolar cycloadditions, we have studied for the first time the application of phenyl α-bromovinyl sulfone (**1**) as a dipolarophile in reactions with azomethine ylides (Scheme 1). We also discovered a convenient transformation of the corresponding



Scheme 1. Formation of a pyrrolidine ring by azomethine ylide cycloaddition. Phenyl α-bromovinyl sulfone (**1**) as a dipolarophile and conversion of **C** into **D**.

cycloadducts into pyrroles **D** (R = Ar) which are suitable intermediates for the synthesis of biologically active compounds.[14]

Initial experiments were conducted with iminoesters **2a,b** and vinyl sulfone **1** using an equimolar ratio of the reagents (Table 1). Despite typical application of equimolar amounts of silver(I) acetate and triethylamine as a system for the generation of azomethine ylides,[9] we found that 20 mol % of both AgOAc and DBU were appropriate for efficient cycloaddition.[15] ^{1}H NMR spectroscopy of the reaction mixture, in all cases, indicated two sets of signals corresponding to the products **3** and **4**. The regioselectivity of the

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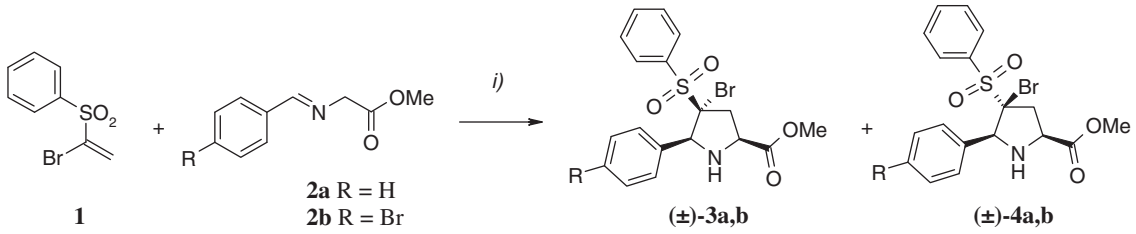
Table 1
Phenylsulfonyl bromopyrrolidines **3** and **4** produced via cycloaddition[a]



Entry	R	Solvent	Base (equiv)	AgOAc (equiv)	Conversion of **1** (%)	Ratio **3**:**4**[b]	Yield[c] (**3** + **4**) (%)
1	H	Toluene	Et_3N (1.0)	1.0	100	3:1	72
2	H	Toluene	DBU (0.2)	0.2	100	2:1	90
3	H	CH_2Cl_2	DBU (0.2)	0.2	72	1:1	70
4	H	THF	DBU (0.2)	0.2	96	1:1	95
5	H	CH_3CN	DBU (0.2)	0.2	95	1:1.1	91
6	Br	Toluene	Et_3N (1.0)	1.0	100	4:1	90
7	Br	Toluene	DBU (0.2)	0.2	100	1:1	96

[a] Reagents and conditions: (i) Vinyl sulfone **1** (5.9 mmol), iminoester **2** (5.9 mmol), AgOAc, base, solvent (25 ml), rt, 24 h under argon.
[b] Determined from ^1H NMR spectroscopy of the reaction mixture.
[c] Isolated yield.

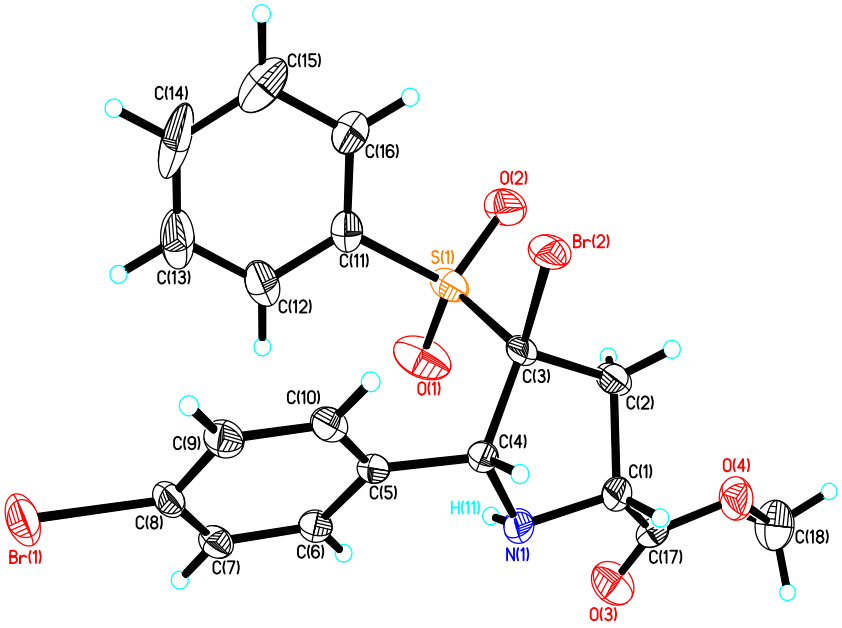
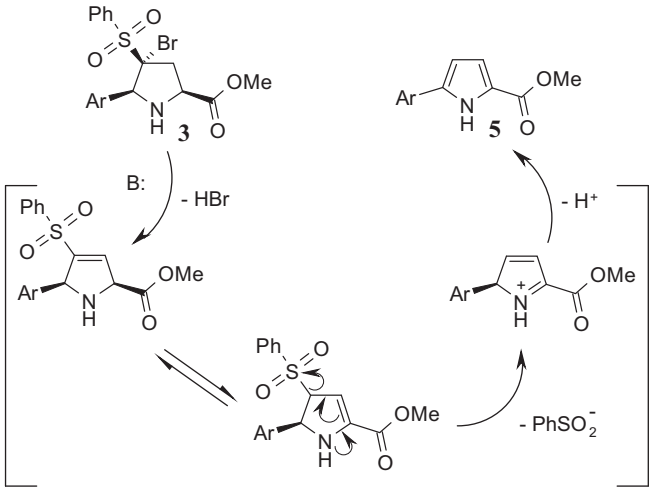


Figure 1. ORTEP drawing of molecule **3b**. Displacement ellipsoids are shown at 50% probability level.

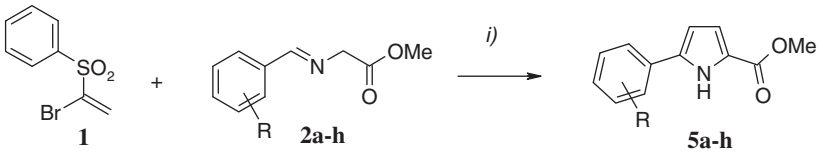
cycloaddition was determined based on the singlet resonances at 5.00 and 5.20 ppm consistent with the H-5 protons of **3** and **4**, respectively. This fact indicates that the phenylsulfonyl and bromine substituents are located at C-4 of the pyrrolidine based on the absence of H-5 spin interactions. Both isomers behave similarly under different chromatographic conditions and were isolated as mixtures (Table 1). Fractional crystallization of the 4-bromophenyl cycloadducts led to isolation of the individual isomer **3b**, which was characterized by X-ray analysis (Fig. 1).[16]

With the aim to introduce an endocyclic double bond in cycloadducts **3** and **4** we studied the reaction of these pyrrolidines with bases. Treatment of compounds **3** and **4** with Et_3N or DBU at elevated temperatures in different solvents converted the starting sulfonyl bromopyrrolidines into a certain extent (data not shown), and in all cases pyrroles 5 were isolated from the reactions (Scheme 2). A plausible mechanism for this transformation would include E2-type elimination of HBr, double bond migration, and phenylsulfinic acid elimination (Scheme 2). An analogous reaction pathway can be proposed for the aromatization of the isomeric



Scheme 2. Aromatization of cycloadduct **3** under the influence of a base.

Table 2
5-Arylpyrrole-2-carboxylic acid derivatives **5** produced via the one-pot cycloaddition-aromatization cascade[a]



Pyrrole	R	Yield (%)[b]	Mp (°C)	Mp (°C) (Lit.)
5a	H	70	145–147	145–146[19]
5b	Br	62	182–183	182–183[19]
5c	3,4,5-$(MeO)_3$	75	110–112	—
5d	2-F	52	105–107	—
5e	3,5-$(Cl)_2$	39	189–191	—
5f	Thienyl	85	106–107	105–106[19]
5g	4-CF_3	60	197–198	196–197[19]
5h	4-Cl	65	177–179	177–179[20]

[a] Reagents and conditions: (i) Vinyl sulfone **1** (0.81 mmol), iminoester **2** (0.81 mmol), THF (15 ml), AgOAc (0.16 mmol), DBU (2.03 mmol), rt, 24 h under argon, then 10 h at reflux under argon.
[b] Isolated yield.

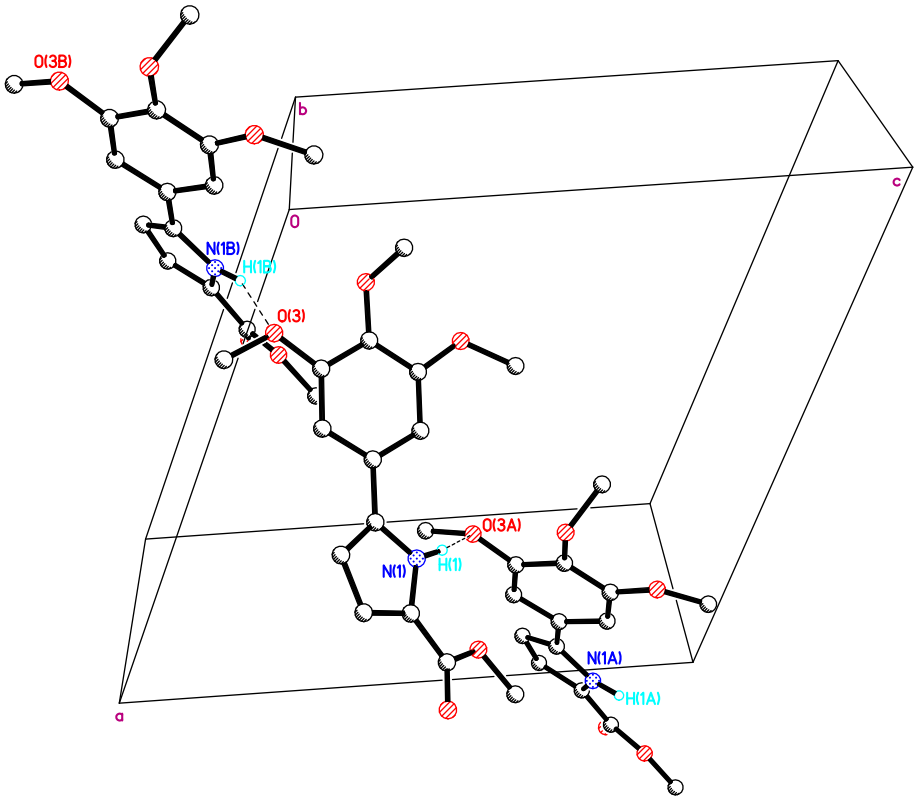


Figure 2. ORTEP drawing of the crystal packing of **5c**.

cycloadduct **4**. It is worth noting that pyrrolines, as the products of partial extrusion of HBr or $PhSO_2H$, were never detected in the reaction mixtures under various conditions.

Carretero et al. have disclosed an excellent strategy toward pyrroles via a one-pot 1,3-dipolar cycloaddition of azomethine ylides with sulfonyl dipolarophiles.[17] We decided to explore if we could achieve the same goal using phenyl α-bromovinyl sulfone (**1**) in the one-pot cycloaddition-aromatization approach. We reasoned to combine the requirements for cycloaddition and elimination steps and applied a catalytic amount of AgOAc and 2.5 equiv of DBU. At least 2 equiv of the base were needed to ensure both HBr and $PhSO_2H$ elimination. Treatment of an equimolar mixture of **1** and **2b** in THF with the chosen catalytic system over seven days at room temperature led to the formation of pyrrole **5b** in 65% isolated yield.

THF was a superior solvent for pyrrole synthesis in contrast to toluene, CH_2Cl_2, CH_3CN, and DMF. To decrease the reaction time, we also used heating of the reaction mixture. Extension of the optimized reaction conditions[18] to other glycine ester aromatic Schiff bases **2**, obtained from both electron-rich and electron-deficient benzaldehydes, provided 5-arylpyrrole-2-carboxylic acid esters **5** in moderate to good yields (Table 2).

Compounds **5a**,**b**,**f**–**h** have been synthesized previously[19,20] and demonstrate the same spectral and physico-chemical characteristics as described in the corresponding references (Table 2). Novel pyrroles **5c**–**e** were fully characterized by elemental analysis and

NMR (Supplementary data). Trimethoxy derivative **5c** was analyzed by X-ray crystallography.[16] Molecules of **5c** form H-bond stabilized chains in the crystal (Fig. 2). Each molecule of **5c** forms two H-bonds via the pyrrole *N*-hydrogen atom and ether oxygen atom.

In conclusion, the cycloaddition of the geminally-substituted dipolarophile **1** and stabilized azomethine ylides has been studied for the first time. The combination of ligand-free, 1,3-dipolar cycloaddition, and elimination stages during the reaction of glycine ester Schiff bases and phenyl α-bromovinyl sulfone (**1**) represents a simple pathway to 5-arylpyrrole-2-carboxylates.

Acknowledgments

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Supplementary data

Supplementary data (NMR spectra of all synthesized compounds and details of X-ray experiments) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.160.

References and notes

1. Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256.
2. Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442–495.
3. Larsen, A. M.; Venskutonite, R.; Valades, E. A.; Nielsen, B.; Pickering, D. S.; Bunch, L. *ACS Chem. Neurosci.* **2011**, *2*, 107–114.
4. Anselm, L.; Banner, D. W.; Benz, J.; Zbinden, K. G.; Himber, J.; Hilpert, H.; Huber, W.; Kuhn, W.; Mary, J.-L.; Otteneder, M. B.; Panday, N.; Ricklin, F.; Stahl, M.; Thomi, S.; Haap, W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5313–5319.
5. Rungrotmongkol, T.; Udommaneethanakit, T.; Frecer, V.; Miertus, S. *Comb. Chem. High Throughput Screening* **2010**, *13*, 268–277.
6. Wang, X.; Gao, Z.; Xue, X.; Cheng, Y.; Yue, P.; Fang, X.; Qu, X. *Toxicol. In Vitro* **2011**, *25*, 897–904.
7. Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; De Logu, A.; Serra, N.; Manetti, F.; Botta, M. *Bioorg. Med. Chem.* **2010**, *18*, 8076–8084.
8. Malamas, M. S.; Barnes, K.; Hui, Y.; Johnson, M.; Lovering, F.; Condon, J.; Fobare, W.; Solvibile, W.; Turner, J.; Hu, Y.; Manas, E. S.; Fan, K.; Olland, A.; Chopra, R.; Bard, J.; Pangalos, M. N.; Reinhart, P.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2068–2073.
9. (a) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89–121; (b) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. 45, pp 231–349.
10. Kudryavtsev, K. V.; Bentley, M. L.; McCafferty, D. G. *Bioorg. Med. Chem.* **2009**, *17*, 2886–2893.
11. Kudryavtsev, K. V.; Podoplelova, N. A.; Novikova, A. F.; Panteleev, M. A.; Zabolotnev, D. V.; Zefirov, N. S. *Russ. Chem. Bull.* **2011**, *60*, 679–684.
12. Kudryavtsev, K. V.; Shulga, D. A.; Chupakhin, V. I.; Churakov, A. V.; Datsuk, N. G.; Zabolotnev, D. V.; Zefirov, N. S. *Russ. Chem. Bull.* **2011**, *60*, 685–693.
13. Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784–6794.
14. (a) Pinna, G. A.; Loriga, G.; Murineddu, G.; Grella, G.; Mura, M.; Vargiu, L.; Murgioni, C.; La Colla, P. *Chem. Pharm. Bull.* **2001**, *49*, 1406–1411; (b) Cara, L. C. L.; Camacho, M. E.; Carrion, M. D.; Tapias, V.; Gallo, M. A.; Escames, G.; Acuna-Castroviejo, D.; Espinosa, A.; Entrena, A. *Eur. J. Med. Chem.* **2009**, *44*, 2655–2666.
15. *General synthetic procedure for the cycloaddition of bromovinyl sulfone **1** and azomethines **2***: Et_3N (0.597 g, 0.822 ml, 5.9 mmol) or DBU (0.183 g, 0.179 ml, 1.2 mmol) was added dropwise to a stirred solution of **1** (1.458 g, 5.9 mmol), **2** (5.9 mmol), and AgOAc (0.985 g, 5.9 mmol or 0.200 g, 1.2 mmol) in 25 ml of solvent (Table 1) under argon. The suspension was stirred for 24 h at rt, filtered through Celite and washed with H_2O (2 × 10 ml). The organic phase was dried (Na_2SO_4), concentrated, and chromatographed on silica gel. Compound **3b**: mp 160–162 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.77 (dd, *J* 15.2, 8.2 Hz, 1H, H-3), 3.26 (br s,1H, NH), 3.38 (dd, *J* 15.2, 8.2 Hz, 1H, H-3), 3.86 (s, 3H, OCH_3), 4.21 (t, *J* 8.2 Hz, 1H, H-2), 4.93 (s, 1H, H-5), 7.38–7.44 (m, 6H, H_{Ar}), 7.57–7.64 (m, 3H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.11, 52.83, 57.98, 74.71, 80.72, 122.96, 128.51 (2C), 130.11 (2C), 131.01 (2C), 131.27 (2C), 133.60, 134.12, 136.00, 171.80. Anal. Calcd for $C_{18}H_{17}Br_2NO_4S$: C, 42.96; H, 3.41; N, 2.78. Found: C, 43.12; H, 3.45; N, 2.75.
16. Crystallographic data (excluding structure factors) for the structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 832673 for compound **3b**, and CCDC 833574 for compound **5c**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336 033; e-mail: deposit@ccdc.cam.ac.uk].
17. (a) Lopez-Perez, A.; Robles-Machin, R.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 9261–9264; (b) Robles-Machin, R.; Lopez-Perez, A.; Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9864–9873.
18. *General procedure for the synthesis of pyrroles **5** and spectral data for novel compounds*: A solution of DBU (0.309 g, 0.304 ml, 2.03 mmol) and AgOAc (0.027 g, 0.16 mmol) in THF (1 ml) was added dropwise to a stirred solution of **1** (0.200 g, 0.81 mmol) and **2** (0.81 mmol) in 15 ml of THF under argon. The suspension was stirred for 24 h at rt and for 10 h at reflux. The mixture was diluted with 25 ml of CH_2Cl_2, washed with 5% HCl (2 × 10 ml), and H_2O (2 × 10 ml). The organic phase was dried (Na_2SO_4), concentrated, and chromatographed on silica gel. Compound **5c**: ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.91 (s, 6H, OCH_3), 6.46 (dd, *J* 3.7, 2.5 Hz, 1H, $H_{pyrrole}$), 6.75 (s, 2H, H_{Ar}), 6.94 (dd, *J* 3.7, 2.5 Hz, 1H, $H_{pyrrole}$), 9.42 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.64, 56.37 (3C), 61.05, 102.49 (2C), 108.02, 116.94, 122.90, 127.25, 137.17, 153.84 (2C), 161.86. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.98; H, 5.92; N, 4.81. Compound **5d**: ^1H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 6.67–6.69 (m, 1H, $H_{pyrrole}$), 6.99–7.01 (m, 1H, $H_{pyrrole}$), 7.14–7.23 (m, 2H, H_{Ar}), 7.25–7.30 (m, 1H, H_{Ar}), 7.67 (td, *J* 7.8, 1.7 Hz, 1H, H_{Ar}), 9.75 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.61, 109.71, 116.14, 116.51 (d, *J* 22.3 Hz), 119.02 (d, *J* 11.3 Hz), 123.37, 124.82, 127.44, 128.92 (d, *J* 8.4 Hz), 131.29, 158.86 (d, *J* 247.0 Hz), 161.42. Anal. Calcd for $C_{12}H_{10}FNO_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.68; H, 4.75; N, 6.20. Compound **5e**: ^1H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H, OCH_3), 6.48 (dd, *J* 3.8, 2.5 Hz, 1H, $H_{pyrrole}$), 6.79 (dd, *J* 3.8, 2.5 Hz, 1H, $H_{pyrrole}$), 7.12 (t, *J* 1.8 Hz, 1H, H_{Ar}), 7.69 (d, *J* 1.8 Hz, 2H, H_{Ar}), 11.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.28, 109.77, 116.57, 123.37 (2C), 124.24, 126.18 (2C), 133.82, 134.57 (2C), 160.55. Anal. Calcd for $C_{12}H_9Cl_2NO_2$: C, 53.36; H, 3.36; N, 5.19. Found: C, 53.25; H, 3.40; N, 5.02.
19. Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191–5194.
20. Barnes, K. D.; Kamhi, V. M.; Diehl, R. E. U.S. Patent 5306,827; 1994; *Chem. Abstr.* **1993**, *119*, 225812.