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Synthesis of Unsymmetrical 3,4-Diaryl-3-pyrrolin-2-ones Utilizing Pyrrole Weinreb Amides

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Abstract

A regiocontrolled synthesis of unsymmetrical 3,4-diaryl-3-pyrrolin-2-ones has been achieved in three steps from 1,2-diaryl-1-nitroethenes with pyrrole-2-carboxamides (pyrrole Weinreb amides) serving as the key linchpin intermediates. Two different methods for the preparation of the requisite nitroalkenes were investigated: (1) modified Henry reaction between aryl nitromethanes and arylimines; and (2) Suzuki-Miyaura cross-coupling reaction of 2-aryl-1-bromo-1-nitroethenes with arylboronic acids. Some difficulty was encountered in the preparation of aryl nitromethanes, thus leading to the exploration of a cross-coupling strategy that proved more useful. A Barton-Zard pyrrole cyclocondensation reaction between 1,2-diaryl-1-nitroethenes and *N*-methoxy-*N*-methyl-2-isocyanoacetamide gave the corresponding pyrrole Weinreb amides, which were then converted into the desired 3-pyrrolin-2-ones in two steps. Overall, this method allowed for the construction of 3,4-diaryl-3-pyrrolin-2-ones with complete regiocontrol of the substituents with respect to the lactam carbonyl. The utility of this synthetic methodology was demonstrated by the preparation of eight unsymmetrical and symmetrical 3,4-diaryl-3-pyrrolin-2-ones including the *N*-H lactam analog of the selective COX-II inhibitor, rofecoxib.

INTRODUCTION

3-Pyrrolin-2-ones (1*H*-pyrrol-2(5*H*)-ones) are an important class of nitrogen heterocycles that are the central components of natural products (*e.g.*, plant pigments¹ and heme metabolites²), biologically active drug candidates, and molecular probes. 3-Pyrrolin-2-ones also serve as building blocks for the preparation of 5-arylidene-3-pyrrolin-2-ones,³ pyrroles,⁴ azacarbohydrates,⁵ and γ -amino acid derivatives.⁶ We are particularly interested in 3,4-diaryl-3-pyrrolin-2-ones due to their diverse biological activity. Examples of biologically active 3,4-diaryl-3-pyrrolin-2-ones include (Figure 1): imrecoxib (**1**)⁷ and structurally related sulfone **2**,⁸ selective cyclooxygenase-II (COX-II) inhibitors; **3**,⁹ a vascular endothelial growth factor receptor (VEGF-R) inhibitor; staurosporinone (**4**),¹⁰ a potent inhibitor of protein kinase C (PKC); and Gö6976 (**5**),¹¹ an isozyme selective inhibitor of PKC. The latter two compounds are examples of indolocarbazoles, a class of molecules that has demonstrated a wide range of biological activity¹² and has drawn a significant level of synthetic interest.¹³ Winterfeldt¹⁴ and others¹⁵ have developed syntheses of differentially protected 3,4-bis(indol-2'-yl)-3-pyrrolin-2-ones as precursors to indolocarbazoles. Additional examples of biologically active 3,4-diaryl-3-pyrrolin-2-ones have recently appeared in the patent literature including corticoid receptor antagonists (*e.g.*, **6**),¹⁶ phosphodiesterase inhibitors (*e.g.*, **7**),¹⁷ and cytokine inhibitors.¹⁸ Due to the wide array of

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Supporting Information. Experimental procedures and spectral data for all other compounds mentioned in the manuscript and copies of ¹H NMR spectra and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

biological activity demonstrated by 3,4-diaryl-3-pyrrolin-2-ones, these molecules make attractive synthetic targets.

Prior to our work in this field,^{19,20} all of the reported²¹ synthetic approaches to 3,4-diaryl-3-pyrrolin-2-ones **I** employed intramolecular aldol-like condensation reactions of completely functionalized amidoketones **II** (Scheme 1). Given their significant biological activity and the lack of different synthetic approaches available for their preparation, we aimed to develop a common synthetic strategy that could target a diverse array of 3,4-diaryl-3-pyrrolin-2-ones **I** (e.g., **1-7**) employing simple starting materials. Thus, we developed a novel synthetic approach to pyrrole-2-carboxamides **8** and found these compounds to be competent precursors to 3,4-diaryl-3-pyrrolin-2-ones through a two-step sequence (Scheme 1):¹⁹ (1) reduction of *N*-methoxy-*N*-methylamide (Weinreb amide)²² **8** to aldehyde **9** utilizing lithium aluminum hydride; and (2) conversion of **9** to 3,4-diaryl-3-pyrrolin-2-ones **10** by oxidation with hydrogen peroxide.²³ One advantage of the present method compared to previous methods to 3,4-diaryl-3-pyrrolin-2-ones is the wide range of aryl groups that are possible due to the large pool of commercially available benzaldehydes and arylboronic acids.

Our synthesis of 3,4-diaryl-3-pyrrolin-2-ones **10** is predicated on the ease of synthesizing pyrrole-2-carboxamides **8**. A versatile approach to 2,3,4-trisubstituted pyrroles involves a reaction first reported by Schöllkopf and his students²⁴ and later by Barton and Zard.²⁵ The transformation, often referred to as the Barton-Zard pyrrole reaction,²⁶ involves a cyclocondensation between nitroalkenes (e.g., **11**) and activated isocyanides (e.g., **12**) (Scheme 2). This strategy and close variants have been utilized to prepare a number of 2,3,4-trisubstituted pyrroles including 3,4-diarylpyrroles.²⁷ We previously adapted the Barton-Zard reaction to prepare pyrrole-2-carboxamides **8** including one example of a 3,4-diarylpyrrole.¹⁹ We synthesized **8a** (Ar³ = Ph; Ar⁴ = Ph) by the cyclocondensation of the corresponding nitroalkene **11a** with 2-isocyano-*N*-methoxy-*N*-methylacetamide (**12**).¹⁹ We herein report a significant extension of our methodology to the synthesis of unsymmetrical 3,4-diarylpyrrole-2-carboxamides **8** and to their subsequent conversion to the corresponding 3,4-diaryl-3-pyrrolin-2-ones **10** (Ar³ ≠ Ar⁴). This work describes an entirely new approach that varies greatly from previously reported methods to this class of molecules. The key to the utility of our strategy is the simplicity of the starting materials: arylboronic acids (source of Ar⁴), arylaldehydes (source of Ar³), and Boc-protected glycine (precursor to isocyanide **12**).

RESULTS AND DISCUSSION²⁸

Our initial approach to 1,2-diaryl-1-nitroethenes **11** utilized the method first reported by Robertson²⁹ that involved a modified Henry reaction between arylnitromethanes **14-18**³⁰ and benzylideneimines **19**³¹ (Table 1, **Method #1**). The latter were prepared by condensation of the corresponding aldehydes with *n*-butylamine in benzene utilizing a Dean-Stark apparatus. Phenylnitromethane (**14**)^{30,32} was prepared in up to 53% yield by treatment of benzyl bromide **13** (R¹ = H) with sodium nitrite and urea in DMF at -10 °C. Condensation of **14** with different benzylideneimines **19** in acetic acid gave nitroethenes **11a-11c** in moderate yields. This strategy worked well for preparing **11** with different “B” rings. In order to prepare **11** with different “A” rings, we explored the synthesis of functionalized arylnitromethanes **15-18**.

Unfortunately, the synthesis of arylnitromethanes **15** and **16** from the corresponding *para*-substituted benzyl bromides **13** proved to be problematic. Utilizing the conditions that were successful for the synthesis of unsubstituted **14**, thioether **15** was only obtained in low yields while sulfone **16** was seemingly never obtained. Different reaction conditions including

silver nitrite/ether³³ or silver nitrite/H₂O³⁴ did not improve matters for preparing these substrates. These low yields are likely due to the ambident nature³⁵ of nitrite as a nucleophile and/or the relative instability of the nitroalkane products (*e.g.*, Nef reactions³⁶). By-products observed in these reactions include the corresponding benzyl alcohols, benzyl nitrites, and benzaldehydes. The compounds are distinguishable by ¹H NMR analysis of the benzylic protons (see Supporting Information). We briefly explored other options for the synthesis of arylnitromethanes **15** and **16**³² such as converting benzaldoximes into the corresponding arylnitromethanes *via* oxidation, but this transformation also proved to be elusive.^{32c} Interestingly, the preparation of nitro-substituted arylnitromethanes **17** and **18** using silver nitrite in ether did not present the same problem as sulfone **16** as moderate yields were obtained.^{33,37}

Given the difficulties encountered in preparing arylnitromethanes **15** and **16**, we decided to investigate alternate methods for obtaining nitroethenes **11**. We were inspired to explore a cross-coupling strategy (Table 1, **Method #2**) after reading the work of Namboothiri and Ganesh.³⁸ They prepared **11** by employing a Suzuki-Miyaura cross-coupling reaction between 2-aryl-1-bromo-1-nitroethenes **22** and arylboronic acids. Thus, our synthesis began with β -nitrostyrenes **21** which were prepared by a Henry reaction of the corresponding benzaldehyde **20** with nitromethane.^{39,40} Following the procedure utilized by Namboothiri³⁸ (and Parham⁴¹), bromination of **21** was accomplished by treatment with bromine in the presence of pyridine, which gave **22** in relatively good yields. The cross-coupling of **22** with commercially available arylboronic acids and palladium tetrakis(triphenylphosphine) in the presence of sodium carbonate afforded **11** in moderate yields. This method proved to be highly versatile, allowing for the easy integration of different aryl substituents, including different “A” rings containing electron-donating groups, electron-withdrawing groups, and halogens. Overall, we found **Method #2** to be the superior approach to making nitroethenes **11** due to the availability of arylboronic acids compared to the corresponding arylnitromethanes.⁴²

We prepared sulfone-substituted nitroethene **11k** by treatment of thioether-substituted nitroethene **11c** with two equivalents of *m*-CPBA (supporting information: **Method #3**).⁴³ This also served as an alternative synthesis of nitroethene **11j** (from **11e**).

From **11**, we finished our synthesis of 3-pyrrolin-2-ones in three subsequent steps (Table 2):¹⁹ (1) treatment of **11** with 1.5 equivalents of isocyanide **12**^{44,45} in the presence of DBU and inhibitor-free THF⁴⁶ gave pyrrole-2-carboxamides **8** (Barton-Zard reaction²⁶); (2) reduction of Weinreb amide functional group by treatment of **8** with LiAlH₄ gave pyrrole-2-carboxaldehydes **9**;⁴⁷ and (3) Baeyer-Villiger type oxidation²³ *via* treatment of **9** with excess hydrogen peroxide in the presence of sodium bicarbonate gave 3-pyrrolin-2-ones **10**.⁴⁸ In most cases, this strategy worked well for the synthesis of pyrrole-2-carboxamides **8**,⁴⁹ pyrrole-2-carboxaldehydes **9**,⁵⁰ and 3-pyrrolin-2-ones **10**.^{51,52} These results demonstrate the flexibility of our methodology for preparing 3,4-diaryl-3-pyrrolin-2-ones including regioisomers (*e.g.*, **10b** and **10d**) and halogen-substituted analogs (**10f** and **10g**). It is important to note that the oxidation of **9** operates with complete regioselectivity; we have never observed the presence of regioisomers in ¹H NMR analyses of the crude reaction mixtures.

A few substrates proved to be problematic. This strategy did not work for the synthesis of thioether-substituted 3-pyrrolin-2-ones **10c** and **10e**. Oxidation of neither **9c** or **9e** gave known 3-pyrrolin-2-one **10c**^{20a} or the unknown **10e**, respectively. Instead, it appears that the H₂O₂ partially oxidized the thioether and left the aldehyde unchanged. Another shortfall was the pyrrole cyclocondensation of sulfone-substituted nitroethene **11j**. Utilizing the general reaction conditions (excess **12**), none of the expected product **8j** or the starting nitroethene

11j was detected during analysis of the crude reaction mixture by ^1H NMR. We then revisited this reaction by using excess nitroalkene **11j** and obtained a 40% yield of **8j**. We speculated that the electron-withdrawing sulfone might be responsible for the low yield. To test this idea, we prepared both *para*- and *meta*- nitro-substituted nitroethenes **11m** and **11n** and submitted them to the Barton-Zard pyrrole cyclocondensation conditions. Interestingly, the yields were fairly consistent with our previous results (with **12** in excess); thus, **11j** appears to be an exceptional case.

Due to the lower yield obtained for **8j**, we explored an alternate synthesis; **8j** is the precursor to **10j**, the lactam analog of the selective COX-II inhibitor rofecoxib. We found that **8j** could alternately be obtained by oxidation of thioether **8e** with *m*-CPBA⁴³ in 95% yield. With a reliable route to **8j**, the synthesis of the rofecoxib analog **10j** was achieved by reduction with LiAlH_4 followed by oxidation with H_2O_2 in the same manner previously used (Scheme 3). Newly synthesized compound **10j** was identical with an authentic sample that was prepared in our lab using a different method.^{20a} Interestingly, the synthesis of isomeric 3-pyrrolin-2-one **10k** was not as successful. Although **9k** could be obtained in two reasonable yielding steps from nitroethene **11k** (or three steps from **11c**), subsequent oxidation with H_2O_2 gave **10k** in only trace amounts. The low yield, in part, could possibly be due to the low solubility of **9k** in methanol; in one run, 80% of the starting material was recovered unchanged. Heating the reaction did not improve matters. A brief exploration of this reaction in acetone gave a slightly better result (5% yield) and allowed for the preparation of the analytical sample.

CONCLUSION

A new method for the regiocontrolled construction of both symmetrical and unsymmetrical 3,4-diaryl-3-pyrrolin-2-ones **10** has been achieved starting from β -nitrostyrenes **21** with pyrrole-2-carboxamides (pyrrole Weinreb amides) **8** serving as the key intermediates. Suzuki-Miyaura cross-coupling reactions of 2-aryl-1-bromo-1-nitroethenes **22** with arylboronic acids provided a superior route to 1,2-diaryl-1-nitroethenes **11** compared to our initial approach, which used a modified Henry reaction involving aryl nitromethanes (*e.g.*, **15**) that proved to be difficult to prepare. Pyrrole-2-carboxamides **8** were synthesized using a Barton-Zard pyrrole cyclocondensation; these were then converted into the corresponding 3,4-diaryl-3-pyrrolin-2-ones **10** in two steps. This methodology was then used to prepare eight 3,4-diaryl-3-pyrrolin-2-ones **10** including the *N*-H lactam analog of rofecoxib **10j**. We will continue to explore the use of this methodology for the synthesis of biologically active 3,4-diaryl-3-pyrrolin-2-ones, such as those depicted in Figure 1.

EXPERIMENTAL SECTION

2-Isocyano-*N*-methoxy-*N*-methylacetamide (**12**)^{19,45}

Our previously reported procedure¹⁹ was followed with a slight modification.⁴⁴ To a 0 °C stirred solution of 2-formamido-*N*-methoxy-*N*-methylacetamide¹⁹ (2.4 g, 16 mmol) in CH_2Cl_2 (50 mL) and diisopropylamine (4.5 g, 44 mmol), neat phosphorus oxychloride (2.8 g, 18 mmol) was added dropwise *via* syringe over the course of 5 min. This was stirred at 0 °C for 2 h, and then a saturated solution of Na_2CO_3 (15 mL) was added dropwise *via* addition funnel. The resulting mixture was stirred at rt for 1.5 h and then was transferred to a separatory funnel with the aid of deionized water and CH_2Cl_2 . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 $\times$ 50 mL). The combined organic layers were washed with deionized water (4 $\times$ 100 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave the desired product as a tan amorphous solid (1.9 g, 92% yield) which could be used directly without further purification: mp 81-82 °C (lit.¹⁹ mp 85-86 °C); R_f (1:1 ethyl acetate/petroleum ether) = 0.20 (visualized with I_2); IR

(ATR, neat) 2982, 2954, 2160, 1670, 1467, 1435, 1400, 1326, 1200, 1183, 1158, 1112, 1011, 960, 915, 798 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 4.41 (s, 2H), 3.72 (s, 3H), 3.23 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.1, 161.1, 61.9, 44.0, 33.0 ppm.

4-(Methylsulfonyl)benzyl alcohol⁵³

A modification of the procedure reported by Wayner and Arnold was followed.⁵⁴ To a 0 °C stirred solution of 4-(thiomethyl)benzyl alcohol (7.0 g, 45 mmol) in CH_2Cl_2 (100 mL), *m*-CPBA (77% purity, 10.4 g, 136 mmol) was added. The solution was then stirred at rt for 6 h. The reaction mixture was treated with a saturated solution of NaHCO_3 (200 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with saturated solutions of NaHCO_3 (2×100 mL) and dried over sodium sulfate. Removal of the solvent gave the title product as a white powder (5.0 g, 27 mmol, 60% yield) which could be used without further purification: mp 81–82 °C (lit.⁵³ mp 83.5–84 °C); R_f (1:1 ethyl acetate/petroleum ether) = 0.10; IR (ATR, neat) 3483, 3006, 2923, 1597, 1449, 1411, 1328, 1277, 1196, 1141, 1089, 1049, 1015, 965, 947, 817, 758 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.88 (d, 2H, J = 8.5 Hz), 7.55 (d, 2H, J = 8.5 Hz), 4.80 (s, 2H), 3.04 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz), δ 147.6, 139.5, 127.8, 127.5, 64.4, 44.8 ppm.

General Method. Synthesis of Benzyl Bromides 13

A modification of the procedure reported by Bjørnholm *et al.* was followed.⁵⁵ To a 0 °C stirred solution of benzyl alcohol (20 mmol) in CH_2Cl_2 (40 mL), neat PBr_3 (1.9 mL, 5.4 g, 20 mmol) was added dropwise over the course of 5 min. The reaction mixture was stirred at rt for 1 h (monitored by TLC) and then poured into a mixture of ice and deionized water (50 mL). After warming to rt, the organic layer was separated and washed with deionized water (50 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave the benzyl bromides as amorphous solids which could be used directly without further purification.

4-(Thiomethyl)benzyl bromide (13i)⁵⁵

Off-white amorphous solid: 92% yield; mp 41–42 °C (lit.⁵⁵ mp 43–44 °C); R_f (1:2 CH_2Cl_2 /petroleum ether) = 0.50; IR (ATR, neat) 3021, 2979, 2917, 1598, 1562, 1489, 1432, 1402, 1326, 1226, 1204, 1185, 1128, 1090, 1012, 970, 954, 873, 826, 810, 717 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.31 (d, 2H, J = 8.6 Hz), 7.21 (d, 2H, J = 8.6 Hz), 4.48 (s, 2H), 2.48 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 139.5, 134.6, 129.8, 126.7, 33.7, 15.8 ppm.

4-(Methylsulfonyl)benzyl bromide (13ii)⁵⁴

White powder: 51% yield; mp 95–97 °C (lit.⁵⁴ mp 94–96 °C); R_f (1:3 ethyl acetate/petroleum ether) = 0.43; IR (ATR, neat) 3006, 2925, 1598, 1445, 1325, 1289, 1228, 1146, 1089, 1020, 963, 848, 816, 766, 719 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.92 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 4.51 (s, 2H), 3.06 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 144.0, 140.6, 130.2, 128.2, 44.8, 31.6 ppm.

General Method. Synthesis of Arylnitromethanes 14 and 15

A modification of the procedure reported by Kornblum *et al.* was followed.³⁰ To a rt stirred solution of DMF (100 mL) and NaNO_2 (10.4 g, 150 mmol), urea (12.0 g, 200 mmol) was added. The urea was allowed to dissolve completely and the solution was cooled to –10 °C. A solution of benzyl bromide **13** (100 mmol) dissolved in DMF (100 mL) was then added dropwise *via* addition funnel. The reaction mixture was stirred at –10 °C for 2–6 h (monitored by TLC). The reaction solution was poured onto ice cooled H_2O (500 mL). The aqueous layer was extracted with cold ether (3×200 mL). The combined organic layers were then washed with ice cooled brine (500 mL) and dried over Na_2SO_4 . The solvent was

removed in vacuo to give the crude product. Crude oils were purified by vacuum distillation and crude solids were purified by flash column chromatography (ethyl acetate/petroleum ether gradient).

Phenylnitromethane (14)

Light yellow oil: 53% yield; bp 50-60 °C (15 mm Hg); lit.³⁰ bp 76-78 °C (2 mm Hg); R_f (1:10 CH₂Cl₂/petroleum ether) = 0.23; ¹H NMR (CDCl₃, 400 MHz) δ 7.46-7.40 (m, 5H), 5.42 (s, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 130.3, 130.2, 130.0, 129.4, 80.3 ppm.

4'-(Thiomethyl)phenylnitromethane (15)

Orange amorphous solid: 20% yield; mp 41-42 °C; R_f (1:1 CH₂Cl₂/petroleum ether) = 0.57; IR (ATR, neat) 2961, 2926, 1602, 1543, 1494, 1424, 1405, 1368, 1307, 1221, 1191, 1122, 1089, 1018, 966, 950, 890, 861, 838, 810, 737 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.34 (d, 2H, J = 8.5 Hz), 7.25 (d, 2H, J = 8.5 Hz), 5.36 (s, 2H), 2.47 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 141.8, 130.7, 126.6, 126.2, 79.9, 15.5 ppm; HRMS (EI) calcd for C₈H₉NO₂S: 183.0354, found 183.0343.

General Method. Synthesis of Nitrophenylnitromethanes

A modification of the procedure reported by Kornblum *et al.* was followed.³³ To a 0 °C stirred mixture of silver nitrite (33 mmol) in ether (50 mL), a solution of nitrobenzyl bromide dissolved in ether (80 mL) was added dropwise *via* addition funnel over a period of 1 h. The reaction mixture was stirred at 4 °C for 24-48 h (cold room) monitored by TLC. The reaction mixture was filtered through celite with the aid of ether. The organic layer was dried over sodium sulfate and solvent was concentrated on a rotary evaporator until crystallization was observed. The crystals were then isolated by filtration (multiple crops) giving the desired products which could be used directly without further purification.

4'-Nitrophenylnitromethane (17)^{37,56}

Yellow crystals (ether); 57% yield; mp 84-85 °C (lit.^{37,56} mp 90-91 °C); R_f (1:1 CH₂Cl₂/petroleum ether) = 0.33; IR (ATR, neat) 1613, 1553, 1538, 1373, 1347, 1314, 1299, 1196, 1106, 1015, 904, 858, 826, 767, 721 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (d, 2H, J = 8.8 Hz), 7.67 (d, 2H, J = 8.8 Hz), 5.56 (s, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 149.2, 136.0, 131.4, 124.6, 79.0 ppm.

3'-Nitrophenylnitromethane (18)³⁷

Yellow crystals (ether); 62% yield; mp 92.5-94 °C (lit.³⁷ 91-93 °C); R_f (1:1 CH₂Cl₂/petroleum ether) = 0.22; IR (ATR, neat) 3080, 1543, 1518, 1430, 1348, 1315, 1216, 1100, 1081, 931, 886, 832, 815, 713 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.33-8.36 (m, 2H), 7.81-7.83 (m, 1H), 7.67 (t, 1H, J = 8.0 Hz), 5.56 (s, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.8, 136.3, 131.4, 130.6, 125.5, 125.3, 78.9 ppm.

General Method. Synthesis of Benzylidenimines 19

To a rt stirred solution of an aldehyde (10.0 mmol) in benzene (100 mL), *n*-butylamine (10.0 mmol) was added. A Dean-Stark apparatus was attached, and the reaction mixture was heated to reflux and allowed to stir for 12-24 h. The solvent was removed in vacuo to give a crude oil that was purified by fractional vacuum distillation.

N-(benzylidene)butan-1-amine (19i)^{31,57}

Light yellow oil; 91% yield; bp 130-134 °C (15 mm Hg); lit.⁵⁷ bp 74 °C (0.7 mm Hg); ¹H NMR (CDCl₃, 400 MHz) δ 8.27 (s, 1H), 7.71-7.73 (m, 2H), 7.39-7.42 (m, 3H), 3.61 (t, 2H,

$J = 7.2$ Hz), 1.69 (quint, 2H, $J = 7.2$ Hz), 1.40 (sext, 2H, $J = 7.2$ Hz), 0.95 (t, 3H, $J = 7.2$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.0, 136.7, 130.7, 128.8, 128.3, 61.7, 33.3, 20.7, 14.2 ppm.

***N*-(4'-Methoxybenzylidene)butan-1-amine (19ii)^{31,58}**

Clear oil; 90% yield; bp 155-160 °C (15 mm Hg); lit.⁵⁸ bp 126-127 °C (3.5 mm Hg); ^1H NMR (CDCl_3 , 400 MHz) δ 8.18 (s, 1H), 7.64 (d, 2H, $J = 8.8$ Hz), 6.90 (d, 2H, $J = 8.8$ Hz), 3.82 (s, 3H), 3.55 (t, 2H, $J = 7.0$ Hz), 1.64 (tt, 2H), 1.36 (tq, 2H), 0.92 (t, 3H, $J = 7.6$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.7, 160.3, 129.8, 129.6, 114.2, 61.7, 55.6, 33.4, 20.7, 14.2 ppm.

***N*-[4'-(Methylthio)benzylidene]butan-1-amine (19iii)⁵⁹**

Clear oil; 95% yield; bp 170-178 °C (3 mm Hg); ^1H NMR (CDCl_3 , 400 MHz) δ 8.21 (s, 1H), 7.62 (d, 2H, $J = 8.6$ Hz), 7.24 (d, 2H, $J = 8.6$ Hz), 3.6 (t, 2H, $J = 7.2$ Hz), 2.49 (s, 3H), 1.65 (tt, 2H), 1.39 (tq, 2H), 0.94 (t, 3H, $J = 7.6$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.4, 142.0, 133.4, 128.6, 126.1, 61.8, 33.3, 20.7, 15.6, 14.2 ppm.

General Method. General Procedure to β -Nitrostyrenes 21

A modification of the procedure reported by Namboothiri *et al.* was followed.^{39a} To a 5 °C solution of aldehyde **20** (50 mmol) in MeOH (10 mL), a solution of nitromethane (50 mmol) in MeOH (10 mL) was added. Ice cooled 4 M NaOH (10 mL) was then added dropwise *via* addition funnel while maintaining an internal temperature of 5 °C. The cloudy yellow/white reaction mixture stirred at 5 °C for 1 h. It was then diluted with ice cooled H_2O (20 mL), and the resulting mixture was then added dropwise to ice cooled 4 M HCl (25 mL). The resulting yellow mixture stirred at 5 °C until TLC showed the absence of starting material. The yellow mixture was filtered through sintered glass and washed with water giving a crude yellow, amorphous solid that was purified by flash column chromatography (CH_2Cl_2 /petroleum ether gradient). Recrystallization then gave analytically pure samples.

(*E*)-1-(4'-Methoxyphenyl)-2-nitroethene (21ii)⁶⁰

Yellow crystals (EtOH): 62% yield; mp 87-88 °C (lit.⁶⁰ mp 86-88 °C); R_f (1:2 CH_2Cl_2 /petroleum ether) = 0.41; IR (ATR, neat) 3108, 2906, 2839, 1623, 1600, 1570, 1515, 1493, 1424, 1323, 1307, 1274, 1247, 1172, 1122, 1029, 964, 940, 865, 843, 832, 818, 806, 779 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.97 (d, 2H, $J = 13.6$ Hz), 7.48-7.54 (m, 3H), 6.96 (d, 2H, $J = 8.8$ Hz), 3.87 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 136.2, 139.2, 135.3, 131.4, 122.8, 115.2, 55.8 ppm.

(*E*)-1-[4'-(Methylthio)phenyl]-2-nitroethene (21iii)⁶¹

Yellow crystals: 53% yield; mp 84-86 °C (lit.⁶¹ mp 84-86 °C); R_f (1:2 CH_2Cl_2 /petroleum ether) = 0.33; IR (ATR, neat) 3106, 1619, 1588, 1546, 1489, 1406, 1325, 1262, 1186, 1124, 1088, 963, 811, 747, 730 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.97 (d, 1H, $J = 13.6$ Hz), 7.58 (d, 1H, $J = 13.6$ Hz), 7.46 (d, 2H, $J = 8.4$ Hz), 7.27 (d, 2H, $J = 8.4$ Hz), 2.51 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 145.4, 139.0, 136.4, 129.7, 129.5, 126.2, 15.1 ppm.

General Method. Synthesis of 2-Aryl-1-bromo-1-nitroethenes 22

A modification of the procedure reported by Namboothiri *et al.* was followed.³⁸ To a rt stirred solution of β -nitrostyrene **21** (5.0 mmol) in pyridine (6.5 mmol) and cyclohexane (20 mL), neat Br_2 (6.0 mmol) was added dropwise over 5 min. The cloudy yellow reaction was then heated to reflux and allowed to stir for 4-12 h (monitored by TLC). The reaction mixture was then transferred to a single-neck round-bottom flask with the aid of ethyl acetate. The solvent was removed and the resulting residue was taken up in ethyl acetate (50

mL). The organic layer was washed with aqueous Na₂S₂O₃ (1.0 M, 2 × 20 mL), H₂O (20 mL), and brine (20 mL) and then dried over Na₂SO₄. The solvent was removed in vacuo to give a crude solid that was purified by flash chromatography (CH₂Cl₂/petroleum ether gradient).

(Z)-1-Bromo-1-nitro-2-phenylethene (22i)³⁸

Yellow needles (EtOH); 78% yield; mp 62-64 °C (lit.³⁸ mp 63-64 °C); R_f (1:10 CH₂Cl₂/petroleum ether) = 0.16; IR (ATR, neat) 3032, 1596, 1572, 1526, 1446, 1305, 1284, 1209, 1161, 1056, 1033, 955, 930, 904, 859, 763, 753, 688 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.65 (s, 1H), 7.88-7.90 (m, 2H), 7.50-7.53 (m, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 137.0, 132.1, 131.2, 130.4, 129.2, 128.4 ppm.

(Z)-1-Bromo-2-(4'-methoxyphenyl)-1-nitroethene (22ii)³⁸

Yellow crystals (EtOH); 88% yield; mp 64-65 °C (lit.³⁸ mp 67-68 °C); R_f (1:2 CH₂Cl₂/petroleum ether) = 0.42; IR (ATR, neat) 2942, 1591, 1564, 1519, 1426, 1307, 1293, 1261, 1180, 1055, 1033, 1021, 957, 912, 866, 825, 793, 713 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.64 (br s, 1H), 7.93 (d, 2H, *J* = 8.8 Hz), 7.01 (d, 2H, *J* = 8.8 Hz), 3.89 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 163.1, 136.6, 133.7, 125.7, 122.7, 114.8, 55.8 ppm.

(Z)-1-Bromo-2-[4'-(methylthio)phenyl]-1-nitroethene (22iii)

Yellow needles (EtOH); 81% yield; mp 86-88 °C; R_f (1:5 CH₂Cl₂/petroleum ether) = 0.20; IR (ATR, neat) 2919, 1601, 1586, 1549, 1518, 1492, 1406, 1291, 1213, 1197, 1134, 1088, 1010, 947, 906, 862, 827, 810, 763, 727, 703, 674 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.61 (s, 1H), 7.84 (d, 2H, *J* = 8.8 Hz), 7.30 (d, 2H, *J* = 8.8 Hz), 2.54 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 145.5, 136.3, 131.7, 127.0, 126.3, 125.7, 15.0 ppm; Anal. calcd for C₉H₈BrNO₂S: C, 39.43; H, 2.94; N, 5.11; S, 11.70. Found: C, 39.16; H, 2.86; N, 5.13; S, 11.72.

General Method #1. Synthesis of Nitroethenes 11 via Modified Henry Reaction

A modification of the procedure reported by Robertson was followed.²⁹ To a rt stirred solution of an aryl nitromethane (1.00 mmol) in AcOH (5 mL), an imine **17** (1.00 mmol) was added. The light yellow solution was stirred at rt for 1 h, MeOH (50 mL) was added, and the reaction solution was stirred at rt for an additional 1.5 h. The solvent was removed in vacuo to give an oil or amorphous solid. MeOH (50 mL) was added and then partially removed on a rotary evaporator until crystal formation was observed (in some cases, this process was repeated several times). Filtration then gave nitroalkenes **11** as yellow crystals.

General Method #2. Synthesis of Nitroethenes 11 via Suzuki-Miyaura Cross-Coupling

A modification of the procedure reported by Ganesh and Namboothiri was followed.³⁸ To a rt stirred solution of 2-aryl-1-bromo-1-nitroethene **20** (1.00 mmol) and arylboronic acid (1.50 mmol) in THF (10 mL), Pd(PPh₃)₄ (0.05 mmol) was added. To the resulting mixture, a solution of Na₂CO₃ (2.50 mmol) in H₂O (1 mL) was added. The light yellow solution was stirred at rt for 40 min and then heated to reflux for 5-30 h until TLC analysis showed complete conversion of **20**. The reaction solution was filtered through celite with the aid of ethyl acetate. The solvent was removed in vacuo to give crude solids. Purification by flash column chromatography (CH₂Cl₂/petroleum ether gradient) gave nitroethenes **11** as yellow amorphous solids. Recrystallization then gave analytically pure samples.

General Method #3. Oxidation of thioethers to sulfones

To a rt stirred solution of thioether compound (1.00 mmol) in CH₂Cl₂ (15 mL), *m*-CPBA (2.00 mmol) was added. The yellow reaction solution stirred at rt for 4 h then was diluted

with CH₂Cl₂ (15 mL). The organic layer was washed with 5% Na₂SO₃ (15 mL) and 5% NaHCO₃ (15 mL), dried over Na₂SO₄, and then filtered through a sintered glass funnel with the aid of CH₂Cl₂ (10 mL). Removal of the solvent in vacuo gave the desired sulfones as amorphous solids which could be utilized directly without further purification. Recrystallization provided analytically pure samples.

(E)-1-Nitro-1,2-diphenylethene (11a)³⁸

Yellow needles (EtOH): General Method #1 (42% yield); General Method #2 (77% yield); mp 74-76 °C (lit.³⁸ mp 72-74 °C); R_f (1:5 CH₂Cl₂/petroleum ether) = 0.33; IR (ATR, neat) 3059, 2973, 1652, 1574, 1508, 1491, 1445, 1370, 1317, 1291, 1214, 1159, 1055, 1033, 1001, 967, 936, 915, 860, 793, 776, 759, 738, 709 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (s, 1H), 7.49-7.51 (m, 3H), 7.30-7.38 (m, 3H), 7.20-7.26 (m, 2H), 7.10 (d, 2H, *J* = 8.8 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 149.9, 135.1, 131.5, 131.4, 131.0, 130.85, 130.83, 130.3, 129.5, 129.0 ppm.

(E)-2-(4'-Methoxyphenyl)-1-nitro-1-phenylethene (11b)³⁸

Yellow crystals (EtOH): General Method #1 (62% yield); General Method #2 (77% yield); mp 152-154 °C (lit.³⁸ mp 152-153 °C); R_f (1:2 CH₂Cl₂/petroleum ether) = 0.21; IR (ATR, neat) 3057, 2939, 2844, 1642, 1601, 1567, 1517, 1493, 1455, 1442, 1424, 1381, 1308, 1256, 1177, 1119, 1073, 1021, 972, 942, 931, 920, 869, 831, 804, 783, 740, 725, 709 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.23 (s, 1H), 7.50-7.52 (m, 3H), 7.33-7.35 (m, 2H), 7.04 (d, 2H, *J* = 9.0 Hz), 6.74 (d, 2H, *J* = 9.0 Hz), 3.78 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 162.0, 147.7, 135.3, 133.5, 131.3, 130.9, 130.2, 129.6, 123.9, 114.6, 55.7 ppm.

(E)-2-[4'-(Methylthio)phenyl]-1-nitro-1-phenylethene (11c)

Yellow crystals (EtOH): General Method #1 (70% yield); General Method #2 (83% yield); mp 119-120 °C; R_f (1:1 CH₂Cl₂/petroleum ether) = 0.42; IR (ATR, neat) 3057, 1638, 157, 1506 1488, 1443, 1430, 1407, 1378, 1303, 1223, 1191, 1164, 1090, 1031, 1012, 1001, 969, 942, 918, 865, 813, 775, 721, 703 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (s, 1H), 7.49-7.51 (m, 3H), 7.32-7.34 (m, 2H), 7.05 (d, 2H, *J* = 8.6 Hz), 6.99 (d, 2H, *J* = 8.6 Hz), 2.44 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.9, 143.7, 134.9, 131.7, 131.1, 130.8, 130.3, 129.6, 127.6, 125.6, 15.0 ppm; Anal. calcd for C₁₅H₁₃NO₂S: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.22; H, 4.63; N, 5.29; S, 11.56.

(E)-1-(4'-Methoxyphenyl)-1-nitro-2-phenylethene (11d)³⁸

Yellow needles (EtOH): General Method #2 (84% yield); mp 100-102 °C (lit.³⁸ mp 95-96 °C); R_f (1:2 CH₂Cl₂/petroleum ether) = 0.24; IR (ATR, neat) 2937, 1648, 1606, 1509, 1447, 1370, 1315, 1292, 1245, 1210, 1168, 1113, 1056, 1027, 968, 932, 912, 860, 832, 811, 765, 742 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.18 (s, 1H), 7.22-7.32 (m, 5H), 7.14 (d, 2H, *J* = 8.8 Hz), 6.99 (d, 2H, *J* = 8.8 Hz), 3.88 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 161.1, 150.0, 134.7, 132.3, 131.8, 131.4, 130.9, 129.0, 122.8, 115.0, 55.6 ppm.

(E)-1-[4'-(Methylthio)phenyl]-1-nitro-2-phenylethene (11e)

Yellow crystals (EtOH): General Method #1 (25% yield); General Method #2 (81% yield); mp 103-105 °C; R_f (1:1 CH₂Cl₂/petroleum ether) = 0.30; IR (ATR, neat) 3071, 2916, 1645, 1593, 1518, 1489, 1450, 1431, 1398, 1369, 1313, 1210, 1187, 1167, 1120, 1090, 1032, 1017, 965, 933, 916, 861, 819, 785, 772, 747 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (s, 1H), 7.23-7.33 (m, 7H), 7.15 (d, 2H, *J* = 7.6 Hz), 2.54 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 149.5, 141.9, 135.0, 131.5, 131.3, 131.2, 131.0, 129.0, 126.8, 126.5, 15.3 ppm; Anal. calcd for C₁₅H₁₃NO₂S: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.53; H, 4.84; N, 5.15; S, 11.79.

(E)-1-(4'-Fluorophenyl)-1-nitro-2-phenylethene (11f)⁶²

Light yellow crystals (EtOH): General Method #2 (76% yield); mp 88-90 °C; R_f (1:2 CH₂Cl₂/petroleum ether) = 0.33; IR (ATR, neat) 3070, 1647, 1600, 1508, 1490, 1146, 1363, 1322, 1300, 1214, 1161, 1104, 1074, 1029, 977, 941, 926, 907, 863, 841, 822, 773, 763, 732 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (s, 1H), 7.30-7.36 (m, 3H), 7.23-7.27 (m, 2H), 7.16-7.21 (m, 2H), 7.09-7.11 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 163.4 (d, J_{C-F} = 250.6 Hz), 148.9, 135.6, 133.1 (d, J_{C-F} = 8.2 Hz), 131.4, 131.3, 131.2, 129.1, 126.8 (d, J_{C-F} = 3.7 Hz), 116.8 (d, J_{C-F} = 22.5 Hz) ppm; Anal. calcd for C₁₄H₁₀FN₂O₂: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.27; H, 4.10; N, 5.82.

(E)-1-(4'-Chlorophenyl)-1-nitro-2-phenylethene (11g)⁶³

Yellow crystals (EtOH): General Method #2 (75% yield); mp 105-107 °C; R_f (1:5 ethyl acetate/petroleum ether) = 0.33; IR (ATR, neat) 3060, 1915, 1648, 1594, 1519, 1489, 1445, 1399, 1365, 1319, 1211, 1183, 1168, 1087, 1030, 1018, 973, 946, 928, 908, 861, 834, 786, 768, 748, 732, 689 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.22 (s, 1H), 7.44 (d, 2H, J = 8.8 Hz), 7.22-7.32 (m, 5H), 7.09 (d, 2H, J = 8.8 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.7, 136.6, 135.7, 132.4, 131.4, 131.3, 131.2, 129.9, 129.22, 129.17 ppm; Anal. calcd for C₁₄H₁₀ClNO₂: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.63; H, 3.94; N, 5.38.

(E)-1,2-bis(4'-Methoxyphenyl)-1-nitroethene (11h)⁶⁴

Fine yellow crystals (EtOH): General Method #2 (70% yield); mp 142-144 °C (lit.⁶⁴ mp 140-141 °C); R_f (1:1 CH₂Cl₂/petroleum ether) = 0.30; IR (ATR, neat) 2936, 2840, 1642, 1599, 1569, 1502, 1451, 1440, 1425, 1378, 1303, 1249, 1177, 1118, 1033, 1021, 965, 952, 932, 919, 869, 847, 813, 789, 756, 746, 722, 690 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (s, 1H), 7.26 (d, 2H, J = 8.8 Hz), 7.09 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.77 (d, 2H, J = 8.8 Hz), 3.89 (s, 3H), 3.80 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 161.9, 160.9, 147.7, 135.0, 133.4, 132.3, 124.2, 123.3, 115.1, 114.6, 55.64, 55.63; Anal. calcd for C₁₆H₁₅NO₄: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.15; H, 5.27; N, 4.95.

(E)-1,2-bis[4'-(Methylthio)phenyl]-1-nitroethene (11i)

Yellow crystals (EtOH): General Method #2 (68% yield); mp 108-110 °C; R_f (1:2 CH₂Cl₂/petroleum ether) = 0.23; IR (ATR, neat) 3065, 2916, 2166, 1641, 1587, 1485, 1421, 1404, 1375, 1302, 1218, 1189, 1168, 1126, 1085, 1012, 968, 957, 939, 926, 865, 843, 826, 818, 788, 757, 713, 702 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.17 (s, 1H), 7.32 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.06 (d, 2H, J = 9.2 Hz), 7.02 (d, 2H, J = 9.2 Hz), 2.54 (s, 3H), 2.45 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.5, 143.8, 141.8, 134.9, 131.7, 131.2, 127.6, 127.1, 126.6, 125.7, 15.3, 15.0 ppm; Anal. calcd for C₁₆H₁₅NO₂S₂: C, 60.54; H, 4.76; N, 4.41; S, 20.20. Found: C, 60.73; H, 4.80; N, 4.39; S, 20.02.

(E)-1-[4'-(Methylsulfonyl)phenyl]-1-nitro-2-phenylethene (11j)

Yellow crystals (ethyl acetate): General Method #2 (48% yield); General Method #3 (84% yield); mp 165-167 °C; R_f (4:1 CH₂Cl₂/petroleum ether) = 0.16; IR (ATR, neat) 3066, 3006, 2925, 1657, 1518, 1449, 1415, 1400, 1376, 1326, 1311, 1293, 1278, 1215, 1180, 1170, 1144, 1105, 1088, 1029, 1019, 983, 957, 932, 907, 868, 847, 790, 777, 765, 745, 731, 714 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.34 (s, 1H), 8.07 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz), 7.25-7.37 (m, 3H), 7.07 (d, 2H, J = 8.4 Hz), 3.14 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 147.6, 142.1, 136.9, 136.5, 132.2, 131.8, 131.4, 130.5, 129.4, 128.6, 44.7 ppm; Anal. calcd for C₁₅H₁₃NO₄S: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.48; H, 4.22; N, 4.71; S, 10.41.

(E)-2-[4'-(Methylsulfonyl)phenyl]-1-nitro-1-phenylethene (11k)

Yellow crystals (EtOH): General Method #3 (95% yield); mp 152-153 °C; R_f (1:1 CH₂Cl₂/petroleum ether) = 0.09; IR (ATR, neat) 2929, 1658, 1596, 1520, 1409, 1322, 1300, 1213, 1189, 1145, 1088, 950, 917, 867, 832, 760, 729, 706 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.19 (s, 1H), 7.79 (d, 2H, J = 8.6 Hz), 7.50-7.55 (m, 3H), 7.27-7.33 (m, 4H), 3.02 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 152.6, 141.9, 137.0, 132.3, 131.7, 131.0, 130.7, 129.73, 129.65, 127.9, 44.5 ppm; Anal. calcd for C₁₅H₁₃NO₄S: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.32; H, 4.24; N, 4.72; S, 10.58.

(E)-1-(4'-Nitrophenyl)-1-nitro-2-phenylethene (11m)⁶⁵

Light yellow crystals (EtOH): General Method #1 (36% yield); General Method #2 (0% yield); mp 116-118 °C (lit.⁶⁵ mp 117.5-118 °C); R_f (1:1 CH₂Cl₂/petroleum ether) = 0.38; IR (ATR, neat) 1648, 1601, 1519, 1446, 1349, 1313, 1287, 1212, 979, 958, 934, 832, 776, 754, 720, 689 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.35 (s, 1H), 8.33 (d, 2H, J = 8.8 Hz), 7.54 (d, 2H, J = 8.8 Hz), 7.35-7.37 (m, 1H), 7.24-7.28 (m, 2H), 7.07 (d, 2H, J = 8.8 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.9, 147.3, 137.3, 137.0, 132.3, 131.8, 131.3, 130.5, 129.3, 124.6 ppm.

(E)-1-(3'-Nitrophenyl)-1-nitro-2-phenylethene (11n)⁶⁵

Light yellow crystals (EtOH): General Method #1 (12% yield); General Method #2 (52% yield); mp 106-107 °C (lit.⁶⁵ mp 107-108 °C); R_f (1:1 CH₂Cl₂/petroleum ether) = 0.50; IR (ATR, neat) 1650, 1614, 1527, 1515, 1489, 1446, 1347, 1321, 1288, 1182, 985, 943, 882, 815, 789, 775, 758, 720 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.38-8.40 (m, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.68-7.70 (m, 2H), 7.35-7.39 (m, 1H), 7.25-7.29 (m, 2H), 7.09 (d, 2H, J = 7.6 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 148.9, 147.1, 137.2, 137.1, 132.5, 131.8, 131.4, 130.6, 130.5, 129.4, 126.3, 125.2 ppm; Anal. calcd for C₁₄H₁₀N₂O₄: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.00; H, 3.64; N, 10.33.

General Method. Synthesis of Pyrrole-2-carboxamides 8

A modification of our previously reported literature procedure was followed.¹⁹ To a 0 °C stirred solution of **12** (1.5 mmol) and DBU (1.5 mmol) and *i*-PrOH (1.5 mmol) in inhibitor-free THF⁴⁶ (15 mL), a solution of **11** (1.0 mmol) in THF (15 mL) was added dropwise *via* addition funnel. The yellow solution stirred at 0 °C for 30 min then at rt until analysis by TLC showed complete conversion of the starting material **11** (usually 6-24 h). The solvent was removed in vacuo giving a crude oil or solid. Purification by flash column chromatography (ethyl acetate/petroleum ether gradient) then gave pyrrole-2-carboxamides **8**. The TLC plates used in the analysis were visualized with UV and then by staining with I₂ (the latter is necessary to observe unreacted **12**). Recrystallization then gave analytically pure samples.

N-Methoxy-N-methyl-3,4-diphenyl-1H-pyrrole-2-carboxamide (8a)¹⁹

White crystals (EtOH): 87% yield; mp 163-164 °C (lit.¹⁹ mp 137-140 °C); R_f (2:1 ethyl acetate/petroleum ether) = 0.36; IR (ATR, neat) 3240, 1612, 1599, 1526, 1481, 1427, 1393, 1228, 1186, 1080, 1018, 971, 941, 912, 866, 784, 747 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 9.62 (br s, 1H), 7.14-7.30 (m, 8H), 7.04 (d, 1H, J = 3.2 Hz), 7.01 (d, 2H, J = 8.4 Hz), 3.58 (s, 3H), 3.03 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 162.1, 135.5, 135.0, 130.6, 128.8, 128.4, 128.2, 128.1, 127.0, 126.2, 126.0, 121.7, 119.5, 61.2, 35.0 ppm.

N-Methoxy-3-(4'-methoxyphenyl)-N-methyl-4-phenyl-1H-pyrrole-2-carboxamide (8b)

White crystals (EtOH): 89% yield; mp 141-142 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.22; IR (ATR, neat) 3331, 1649, 1600, 1529, 1476, 1462, 1421, 1387, 1288, 1239, 1180,

1125, 1035, 1018, 970, 936, 867, 845, 769, 749, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.43 (br s, 1H), 7.10-7.22 (m, 7H), 7.04 (d, 1H, $J = 3.1$ Hz), 6.84 (d, 2H, $J = 9.0$ Hz), 3.81 (s, 3H), 3.63 (s, 3H), 3.05 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.2, 158.7, 135.1, 131.6, 128.7, 128.4, 128.0, 127.6, 126.2, 125.9, 121.5, 119.5, 113.7, 61.3, 55.4, 35.1 ppm; Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.15; H, 6.06; N, 8.26.

***N*-Methoxy-*N*-methyl-3-(4'-(methylthio)phenyl)-4-phenyl-1*H*-pyrrole-2-carboxamide (8c)**

Tan crystals (ethyl acetate): 79% yield; mp 137-139 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.19; IR (ATR, neat) 3200, 1638, 1605, 1490, 1472, 1436, 1377, 1226, 1100, 1069, 1027, 958, 932, 861, 821, 768, 741, 695 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.48 (br s, 1H), 7.08-7.23 (m, 9H), 7.04 (d, 1H, $J = 3.1$ Hz), 3.63 (s, 3H), 3.09 (s, 3H), 2.48 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.9, 136.8, 134.9, 132.1, 131.0, 128.8, 128.5, 128.0, 126.3, 126.2, 126.0, 121.5, 119.5, 61.4, 34.8, 16.0 ppm; Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.37; H, 5.62; N, 8.08; S, 8.87.

***N*-Methoxy-4-(4'-methoxyphenyl)-*N*-methyl-3-phenyl-1*H*-pyrrole-2-carboxamide (8d)**

White crystals (EtOH): 89% yield; mp 142-144 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.18; IR (ATR, neat) 3183, 2966, 1605, 1577, 1559, 1534, 1488, 1457, 1436, 1426, 1391, 1281, 1242, 1173, 1139, 1101, 1079, 1025, 1005, 993, 963, 941, 918, 871, 830, 776, 754, 718, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.54 (br s, 1H), 7.20-7.27 (m, 5H), 7.01 (d, 2H, $J = 8.8$ Hz), 7.00 (d, 1H, $J = 2.9$ Hz), 6.72 (d, 2H, $J = 9.0$ Hz), 3.74 (s, 3H), 3.58 (s, 3H), 3.00 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.1, 158.2, 136.0, 130.6, 129.8, 128.2, 128.0, 127.4, 126.9, 125.6, 121.5, 119.1, 113.8, 61.2, 55.4, 34.9 ppm; Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.52; H, 5.89; N, 8.48.

***N*-Methoxy-*N*-methyl-4-(4'-(methylthio)phenyl)-3-phenyl-1*H*-pyrrole-2-carboxamide (8e)**

White crystals (ethyl acetate): 78% yield; mp 153-154 °C; R_f = 0.19 (1:1 ethyl acetate/petroleum ether); IR (ATR, neat) 3233, 2923, 1623, 1600, 1557, 1541, 1522, 1473, 1424, 1381, 1264, 1176, 1145, 1087, 1075, 1023, 972, 937, 863, 839, 817, 757, 739, 695 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.60 (br s, 1H), 7.20-7.31 (m, 5H), 7.00-7.09 (m, 4H), 7.03 (d, 1H, $J = 2.8$ Hz), 3.58 (s, 3H), 3.02 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 162.1, 135.9, 135.4, 132.0, 130.5, 129.1, 128.3, 127.9, 127.0, 126.7, 125.3, 121.7, 119.5, 61.2, 35.0, 16.2 ppm; Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.25; H, 5.76; N, 7.97; S, 9.03.

4-(4'-Fluorophenyl)-*N*-methoxy-*N*-methyl-3-phenyl-1*H*-pyrrole-2-carboxamide (8f)

White crystals (ethyl acetate): 69% yield; mp 152-153 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.24; IR (ATR, neat) 3221, 3007, 2936, 2160, 1625, 1602, 1552, 1529, 1504, 1480, 1602, 1552, 1529, 1504, 1480, 1443, 1473, 1386, 1302, 1274, 1220, 1179, 1165, 1144, 1100, 1090, 1079, 1019, 999, 972, 939, 920, 867, 840, 814, 778, 756, 720, 702 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.72 (br s, 1H), 7.26-7.30 (m, 3H), 7.19-7.21 (m, 2H), 7.01-7.06 (m, 3H), 6.86-6.90 (m, 2H), 3.59 (s, 3H), 3.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 162.1, 161.7 (d, $J_{\text{C-F}} = 245$ Hz), 135.3, 131.0 (d, $J_{\text{C-F}} = 3.8$ Hz), 130.5, 130.2 (d, $J_{\text{C-F}} = 7.5$ Hz), 128.3, 127.9, 127.1, 125.0, 121.7, 119.4, 115.3 (d, $J_{\text{C-F}} = 21$ Hz), 61.2, 35.0 ppm; Anal. calcd for $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_2$: C, 70.36; H, 5.28; N, 8.64. Found: C, 70.08; H, 5.42; N, 8.40.

4-(4'-Chlorophenyl)-*N*-methoxy-*N*-methyl-3-phenyl-1*H*-pyrrole-2-carboxamide (8g)

White crystals (ethyl acetate): 66% yield; mp 175-176 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.23; IR (ATR, neat) 3315, 2937, 1639, 1599, 1823, 1437, 1438, 1420, 1381, 1323, 1227, 1180, 1136, 1094, 1068, 1016, 998, 967, 940, 912, 864, 798, 776, 762, 747, 720 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.62 (br s, 1H), 7.09-7.28 (m, 9H), 7.06 (d, 2H, $J = 2.8$

Hz), 3.60 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.4, 135.5, 135.1, 130.5, 128.7, 128.3, 128.2, 127.7, 126.9, 126.1, 125.6, 121.7, 119.8, 61.1, 35.2 ppm; Anal. calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.83; H, 5.03; N, 8.26.

***N*-Methoxy-3,4-bis(4'-methoxyphenyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (8h)**

White crystals (EtOH); 82% yield; mp 167-168 °C; R_f (2:1 ethyl acetate/petroleum ether) = 0.43; IR (ATR, neat) 3223, 1608, 1534, 1512, 1436, 1380, 1284, 1244, 1177, 1140, 1025, 1000, 971, 932, 877, 829, 817, 791, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.42 (br s, 1H), 7.14 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.98 (d, 1H, J = 2.9 Hz), 6.84 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 3.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 162.2, 158.7, 158.2, 131.7, 129.8, 127.84, 127.76, 127.6, 125.6, 121.3, 119.1, 113.9, 61.3, 55.45, 55.41, 35.1 ppm; Anal. calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.64; H, 6.03; N, 7.76.

***N*-Methoxy-3,4-bis(4'-(methylthio)phenyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (8i)**

White crystals (ethyl acetate); 75% yield; mp 169-170 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.16; IR (ATR, neat) 3274, 1617, 1559, 1519, 1472, 1423, 1382, 1321, 1259, 1188, 1146, 1103, 1088, 1031, 1015, 973, 934, 861, 834, 824, 813, 759, 738, 715 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.53 (br s, 1H), 7.09-7.17 (m, 6H), 7.01-7.03 (m, 3H), 3.62 (s, 3H), 3.08 (s, 3H), 2.49 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 162.0, 136.9, 136.0, 132.1, 131.9, 131.0, 129.1, 127.6, 126.8, 126.3, 125.3, 121.6, 119.5, 61.3, 34.9, 16.2, 15.9 ppm; Anal. calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{S}_2$: C, 63.29; H, 5.56; N, 7.03; S, 16.09. Found: C, 63.06; H, 5.66; N, 6.86; S, 16.04.

***N*-Methoxy-*N*-methyl-4-(4'-(methylsulfonyl)phenyl)-3-phenyl-1*H*-pyrrole-2-carboxamide (8j)**

White crystals (ethyl acetate); General Method #3 (95% yield) from **8c**; modification of General Method #4 (40% yield) that involved 1.0 equivalents of isocyanide **12**, 1.2 equivalents of nitroalkene **11j**, and 1.5 equivalents of DBU; mp 203-205 °C; R_f (2:1 ethyl acetate/petroleum ether) = 0.29; IR (ATR, neat) 3360, 2927, 1644, 1595, 1548, 1492, 1474, 1416, 1376, 1313, 1291, 1279, 1156, 1126, 1089, 1005, 996, 957, 937, 864, 843, 799, 783, 753, 724, 703 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.80 (br s, 1H), 7.72 (d, 2H, J = 8.8 Hz), 7.19-7.32 (m, 7H), 7.14 (d, 1H, J = 3.1 Hz), 3.58 (s, 3H), 3.05 (s, 3H), 3.03 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 161.7, 141.1, 137.7, 134.8, 130.4, 129.0, 128.6, 128.3, 127.54, 127.48, 124.0, 122.4, 120.2, 61.3, 44.8, 34.7 ppm; Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 62.48; H, 5.24; N, 7.29; S, 8.34; Found: C, 62.51; H, 5.14; N, 7.31; S, 8.60.

***N*-Methoxy-*N*-methyl-3-(4'-(methylsulfonyl)phenyl)-4-phenyl-1*H*-pyrrole-2-carboxamide (8k)**

White crystals (EtOH); General Method #3 (69% yield) from **8e**; General Method #4 (65% yield); mp 202-203 °C; R_f (2:1 ethyl acetate/petroleum ether) = 0.17; IR (ATR, neat) 3275, 1603, 1548, 1471, 1435, 1383, 1302, 1147, 1088, 955, 937, 863, 835, 768, 695 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.76 (br s, 1H), 7.83 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 7.19-7.21 (m, 3H), 7.05 (d, 1H, J = 3.1 Hz), 7.01-7.03 (m, 2H), 3.69 (s, 3H), 3.23 (s, 3H), 3.07 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.9, 141.9, 138.5, 134.1, 131.6, 128.8, 128.7, 127.9, 127.1, 126.7, 126.6, 121.5, 119.7, 61.9, 44.9, 33.9 ppm; Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: C, 62.48; H, 5.24; N, 7.29; S, 8.34; Found: C, 62.58; H, 5.32; N, 7.36; S, 8.29.

***N*-Methoxy-*N*-methyl-4-(4'-nitrophenyl)-3-phenyl-1*H*-pyrrole-2-carboxamide (8m)**

Yellow crystals (EtOH); 64% yield; mp 219-220.5 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.23; IR (ATR, neat) 3213, 1592, 1499, 1430, 1393, 1330, 1148, 1079, 1013, 966, 938, 857, 758, 745, 727 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.86 (br s, 1H), 8.03 (d, 2H, J = 8.8

Hz), 7.31-7.35 (m, 3H), 7.18-7.22 (m, 4H), 7.16 (d, 1H, $J = 3.2$ Hz), 3.58 (s, 3H), 3.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 161.7, 146.0, 142.3, 134.8, 130.4, 128.7, 128.6, 128.2, 127.6, 123.8, 123.7, 122.5, 120.4, 61.3, 34.7 ppm; Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$: C, 64.95; H, 4.88; N, 11.96; Found: C, 65.04; H, 4.77; N, 12.06.

***N*-Methoxy-*N*-methyl-4-(3'-nitrophenyl)-3-phenyl-1*H*-pyrrole-2-carboxamide (8n)**

Yellow amorphous solid: 60% yield; mp 196-199 °C; R_f (2:1 ethyl acetate/petroleum ether) = 0.61; IR (ATR, neat) 3207, 1612, 1556, 1534, 1512, 1478, 1440, 1392, 1346, 1302, 1231, 1179, 1147, 1086, 1072, 1016, 1000, 974, 956, 915, 904, 864, 804, 778, 756, 734, 700 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.78 (br s, 1H), 8.03-8.04 (m, 1H), 7.97-8.00 (m, 1H), 7.28-7.32 (m, 4H), 7.19-7.22 (m, 2H), 7.16 (d, 2H, $J = 3.1$ Hz), 3.59 (s, 3H), 3.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 161.7, 148.5, 136.9, 134.7, 134.6, 130.4, 129.1, 128.6, 128.3, 127.5, 123.7, 123.1, 122.2, 121.0, 119.9, 61.3, 34.7 ppm; Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$: C, 64.95; H, 4.88; N, 11.96; Found: C, 64.67; H, 4.97; N, 11.85.

General Method. Synthesis of Pyrrole-2-carboxaldehydes 9

A modification of our previously reported literature procedure was followed.¹⁹ To a 0 °C stirred solution of LiAlH_4 (1.5 mmol) in THF (5 mL), a solution of pyrrole-2-carboxamide **8** (1.0 mmol) in THF (5 mL) was added dropwise via addition funnel. The yellow reaction solution stirred at 0 °C for 1 h. The reaction solution was diluted with ether (15 mL), then 6.0 eq. KHSO_4 (1.2 g, 8.4 mmol) in H_2O (15 mL) was added dropwise via addition funnel. The aqueous layer was extracted with ether (3×15 mL) and the combined organic layers were washed with 5% citric acid (50 mL), sat. NaHCO_3 (50 mL), brine (50 mL), and then dried over Na_2SO_4 . Removal of the solvent in vacuo gave crude amorphous solids that were purified by flash column chromatography (ethyl acetate/petroleum ether gradient). In some cases, analytical samples were obtained by recrystallization.

3,4-Diphenyl-1*H*-pyrrole-2-carboxaldehyde (9a)¹⁹

Brown-red amorphous solid: 72% yield; mp 169-170 °C (lit.¹⁹ mp 168-172 °C); R_f (ethyl acetate) = 0.43; IR (ATR, neat) 3243, 3195, 2870, 1636, 1601, 1545, 1527, 1449, 1407, 1372, 1344, 1309, 1286, 1179, 1141, 1071, 1029, 1008, 940, 911, 793, 776, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.62 (br s, 1H), 9.46 (d, 1H, $J = 1.0$ Hz), 7.15-7.37 (m, 11H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 180.7, 134.1, 133.9, 132.5, 130.9, 130.5, 128.69, 128.67, 128.63, 128.0, 126.82, 126.75, 124.1 ppm.

3-(4'-Methoxyphenyl)-4-phenyl-1*H*-pyrrole-2-carboxaldehyde (9b)

Yellow-orange amorphous solid: 68% yield; mp 154-156 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.64; IR (ATR, neat) 3241, 1634, 1603, 1532, 1504, 1449, 1406, 1374, 1340, 1286, 1240, 1177, 1149, 1109, 1030, 1000, 913, 835, 804, 777, 760, 740 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.84 (br s, 1H), 9.45 (d, 1H, $J = 1.0$ Hz), 7.17-7.28 (m, 8H), 6.90 (d, 2H, $J = 8.8$ Hz), 3.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 180.7, 159.5, 134.2, 134.1, 132.0, 130.5, 128.7, 128.6, 126.7, 126.6, 124.5, 124.5, 114.2, 55.5 ppm; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2$: 278.1181 ($[\text{M}+\text{H}]^+$), found 278.1179 ($[\text{M}+\text{H}]^+$).

3-(4'-(Methylthio)phenyl)-4-phenyl-1*H*-pyrrole-2-carboxaldehyde (9c)

Tan crystals (CH_2Cl_2 /petroleum ether): 81% yield; mp 165-166 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.68; IR (ATR, neat) 3263, 2914, 2835, 1631, 1599, 1556, 1527, 1495, 1447, 1431, 1403, 1375, 1339, 1312, 1285, 1225, 1156, 1141, 1099, 1081, 1035, 1019, 1000, 985, 965, 953, 933, 910, 843, 815, 794, 763, 728, 711, 693 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 9.80 (br s, 1H), 9.49 (s, 1H), 7.20-7.29 (m, 10H), 2.54 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 180.6, 138.6, 134.0, 133.7, 131.3, 130.6, 129.1, 128.8, 128.7, 126.9,

126.7, 126.4, 124.5, 15.8 ppm; Anal. calcd for $C_{18}H_{15}NOS$: C, 73.69; H, 5.15; N, 4.77; S, 10.93. Found: C, 73.54; H, 5.12; N, 4.86; S, 10.84.

4-(4'-Methoxyphenyl)-3-phenyl-1H-pyrrole-2-carboxaldehyde (9d)

Off-white crystals (CH_2Cl_2 /petroleum ether); 73% yield; mp 155-157 °C; R_f (1:4 ethyl acetate/petroleum ether) = 0.17; IR (ATR, neat) 3246, 2967, 1633, 1548, 1526, 1505, 1479, 1456, 1442, 1443, 1400, 1370, 1341, 1291, 1276, 1243, 1175, 1057, 1032, 940, 833, 821, 772, 700 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 9.96 (br s, 1H), 9.45 (s, 1H), 7.30-7.37 (m, 5H), 7.22 (d, 1H, J = 2.4 Hz), 7.08 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 158.6, 134.1, 132.7, 130.9, 130.5, 129.7, 128.6, 127.9, 126.43, 126.39, 124.1, 114.1, 55.5 ppm; HRMS (ESI) calcd for $C_{18}H_{15}NO_2$: 278.1181 ($[M+H]^+$), found 278.1180 ($[M+H]^+$).

4-(4'-(Methylthio)phenyl)-3-phenyl-1H-pyrrole-2-carboxaldehyde (9e)

Brownish-red amorphous solid: 72% yield; mp 191-192 °C; R_f (1:4 ethyl acetate/petroleum ether) = 0.24; IR (ATR, neat) 3231, 2922, 2872, 1628, 1600, 1538, 1522, 1498, 1474, 1456, 1440, 1416, 1392, 1372, 1338, 1312, 1301, 1278, 1220, 1188, 1146, 1102, 1084, 1071, 1016, 1006, 963, 938, 918, 837, 815, 787, 773, 742, 702 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 9.44 (s, 1H), 7.35-7.39 (m, 3H), 7.30-7.33 (m, 2H), 7.26-7.28 (m, 1H), 7.13 (d, 2H, J = 8.8 Hz), 7.08 (d, 2H, J = 8.8 Hz), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 136.7, 134.3, 132.5, 130.9, 130.8, 130.6, 128.9, 128.7, 128.0, 126.7, 126.1, 124.6, 16.0 ppm; HRMS (ESI) calcd for $C_{18}H_{15}NOS$: 294.0953 ($[M+H]^+$), found 294.0952 ($[M+H]^+$).

4-(4'-Fluorophenyl)-3-phenyl-1H-pyrrole-2-carboxaldehyde (9f)

Orange-red amorphous solid: 70% yield; 185-186 mp °C; R_f (1:3 ethyl acetate/petroleum ether) = 0.56; IR (ATR, neat) 3269, 3062, 2925, 1678, 1627, 1604, 1577, 1547, 1526, 1504, 1478, 1455, 1442, 1420, 1393, 1366, 1338, 1301, 1275, 1220, 1162, 1139, 1095, 1069, 1007, 993, 940, 915, 849, 832, 789, 765, 734, 720, 695 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 10.26 (br s, 1H), 9.44 (d, 1H, J = 1.0 Hz), 7.34-7.38 (m, 3H), 7.27-7.30 (m, 2H), 7.25 (dd, 1H, J = 1.0, 3.0 Hz), 7.08-7.13 (m, 2H), 6.90-6.96 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 162.0 (d, J_{C-F} = 246 Hz), 134.4, 132.4, 130.9, 130.5, 130.2 (d, J_{C-F} = 8.2 Hz), 130.0 (d, J_{C-F} = 3.8 Hz), 128.7, 128.1, 125.7, 124.6, 115.6 (d, J_{C-F} = 20.9 Hz) ppm; HRMS (ESI) calcd for $C_{17}H_{12}FNO$: 266.0981 ($[M+H]^+$), found 266.0978 ($[M+H]^+$).

4-(4'-Chlorophenyl)-3-phenyl-1H-pyrrole-2-carboxaldehyde (9g)

Off-white amorphous solid: 82% yield; mp 169-170 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.71; IR (ATR, neat) 3250, 1633, 1542, 1443, 1417, 1389, 1335, 1144, 1087, 1013, 918, 840, 818, 789, 767 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H), 9.46 (d, 1H, J = 1.0 Hz), 7.27-7.39 (m, 6H), 7.21 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 8.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 134.3, 132.7, 132.5, 130.8, 130.6, 129.8, 128.9, 128.8, 128.1, 125.5, 124.4 ppm; Anal. calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; Cl, 12.58; N, 4.97. Found: C, 72.25; H, 4.37; N, 4.78.

3,4-Bis(4'-methoxyphenyl)-1H-pyrrole-2-carboxaldehyde (9h)^{47,66}

Yellow amorphous solid: 63% yield; mp 175-176 °C; R_f (1:5 ethyl acetate/petroleum ether) = 0.13; IR (ATR) 3292, 3031, 2935, 2833, 1722, 1635, 1609, 1573, 1536, 1509, 1487, 1456, 1443, 1423, 1394, 1371, 1331, 1307, 1285, 1250, 1236, 1176, 1138, 1110, 1087, 1031, 1016, 998, 960, 935, 837, 824, 814, 803, 776, 722 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 9.44 (d, 1H, J = 1.0 Hz), 7.22 (d, 2H, J = 8.8 Hz), 7.18 (dd, 1H, J = 1.0, 3.0 Hz), 7.09 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 3.84 (s,

3H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 180.6, 159.5, 158.6, 133.8, 132.0, 130.4, 129.7, 126.5, 126.3, 124.8, 123.9, 114.15, 114.11, 55.54, 55.49 ppm; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3$: 308.1286 ($[\text{M}+\text{H}]^+$), found 308.1287 ($[\text{M}+\text{H}]^+$).

4-(4'-(Methylsulfonyl)phenyl)-3-phenyl-1H-pyrrole-2-carboxaldehyde (9j)

Off-white crystals (CH_2Cl_2): 71% yield; mp 189-190 °C; R_f (1:1 ethyl acetate/petroleum ether) = 0.27; IR (ATR, neat) 3245, 2844, 1641, 1596, 1545, 1442, 1419, 1391, 1374, 1340, 1303, 1286, 1141, 1095, 1084, 966, 956, 939, 841, 774, 710 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.61 (br s, 1H), 9.47 (d, 1H, J = 1.0 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.29-7.41 (m, 8H), 3.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 180.8, 139.9, 138.3, 134.4, 131.8, 130.9, 130.8, 129.0, 128.9, 128.5, 127.8, 124.8, 124.6, 44.8 ppm; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3\text{S}$: 326.0851 ($[\text{M}+\text{H}]^+$), found 326.0848 ($[\text{M}+\text{H}]^+$).

3-(4'-(Methylsulfonyl)phenyl)-4-phenyl-1H-pyrrole-2-carboxaldehyde (9k)

White amorphous solid: 64% yield; mp 240-241 °C; R_f (1:2 ethyl acetate/petroleum ether) = 0.18; IR (ATR, neat) 3267, 3002, 2920, 2859, 1643, 1597, 1541, 1449, 1402, 1367, 1338, 1295, 1277, 1183, 1141, 1092, 1018, 999, 969, 937, 928, 842, 779, 748, 719, 707 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 12.60 (br s, 1H), 9.36 (d, 1H, J = 0.8 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.52-7.58 (m, 3H), 7.10-7.28 (m, 5H), 3.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 179.3, 139.5, 138.3, 133.5, 131.2, 130.2, 130.1, 128.5, 128.1, 126.9, 126.4, 125.5, 125.1, 43.4 ppm; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3\text{S}$: 326.0851 ($[\text{M}+\text{H}]^+$), found 326.0854 ($[\text{M}+\text{H}]^+$).

General Method #12. Synthesis of 3-Pyrrolin-2-ones 10

A modification of our previously reported literature procedure was followed.¹⁹ To a rt stirred mixture of pyrrole-2-carboxaldehyde **9** (1.0 mmol) in MeOH (20 mL), NaHCO_3 (10.0 mmol) was added followed by H_2O_2 (35% w/v, 9.7 mL, 100 mmol). The solution was allowed to stir at rt for 24-72 h until analysis by TLC showed complete conversion of the starting material **9**. In some cases, additional hydrogen peroxide was added. The reaction mixture was treated with CH_2Cl_2 (20 mL) and aqueous HCl (1.0 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 $\times$ 10 mL). The combined organic layers were dried with sodium sulfate. Removal of the solvent in vacuo gave a crude solid that was purified by flash chromatography (ethyl acetate/petroleum ether to ethyl acetate/MeOH gradient). In some cases, analytical samples were obtained by recrystallization.

3,4-Diphenyl-1H-pyrrol-2(5H)-one (10a)¹⁹

White powder: 91% yield; mp 185-187 °C (lit.¹⁹ mp 182-183 °C); R_f (ethyl acetate) = 0.43; IR (ATR, neat) 3171, 3053, 1679, 1572, 1487, 1443, 1366, 1337, 1223, 1086, 1030, 973, 889, 786, 763, 743, 688 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.54 (br s, 1H), 7.26-7.35 (m, 10H), 4.37 (d, 2H, J = 1.1 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 150.4, 133.3, 132.3, 131.7, 129.3, 129.0, 128.6, 128.2, 127.7, 127.6, 47.5 ppm.

3-(4'-Methoxyphenyl)-4-phenyl-1H-pyrrol-2(5H)-one (10b)

Opaque, white amorphous solid: 90% yield; mp 176-177 °C; R_f (4:1 ethyl acetate/petroleum ether) = 0.22; IR (ATR, neat) 3167, 3057, 2921, 2846, 1679, 1606, 1572, 1510, 1446, 1370, 1290, 1246, 1177, 1110, 1032, 974, 891, 829, 781, 763 cm^{-1} ; ^1H NMR (D_6 -DMSO, 400 MHz) δ 8.46 (s, 1H), 7.33 (s, 5H), 7.22 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 4.32 (s, 2H), 3.75 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 172.6, 158.8, 149.3, 133.7, 131.1, 130.6, 128.9, 128.6, 127.5, 124.3, 113.7, 55.0, 47.5 ppm; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: 266.1181 ($[\text{M}+\text{H}]^+$), found 266.1179 ($[\text{M}+\text{H}]^+$).

4-(4'-Methoxyphenyl)-3-phenyl-1H-pyrrol-2(5H)-one (10d)^{20a}

Opaque, white amorphous solid: 90% yield; mp 155-157 °C (lit.^{20b} mp 169-174 °C); R_f (4:1 ethyl acetate/petroleum ether) = 0.33; IR (ATR, neat) 3167, 3053, 1678, 1607, 1514, 1455, 1416, 1365, 1298, 1254, 1175, 1117, 1079, 1023, 891, 829, 786, 744, 699 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.42 (br s, 1H), 7.24-7.38 (m, 7H), 6.88 (d, 2H, J = 8.8 Hz), 4.34 (s, 2H), 3.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 172.7, 159.8, 150.0, 132.8, 130.2, 129.4, 129.0, 128.3, 127.6, 125.5, 114.1, 55.2, 47.4 ppm.

4-(4'-Fluorophenyl)-3-phenyl-1H-pyrrol-2(5H)-one (10f)

Light yellow amorphous solid: 66% yield; mp 196-198 °C (lit.^{20a} 204-207 °C); R_f (1:1 ethyl acetate/petroleum ether) = 0.24; IR (ATR, neat) 3176, 3060, 2924, 2851, 1680, 1603, 1511, 1493, 1454, 1442, 1408, 1363, 1342, 1226, 1161, 1105, 1079, 1059, 1014, 974, 835, 787, 744, 700 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.57 (br s, 1H), 7.18-7.39 (m, 9H), 4.36 (d, 2H, J = 1.0 Hz) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 172.3, 162.2 (d, $J_{\text{C-F}}$ = 247 Hz), 149.3, 132.2, 131.7, 129.81 (d, $J_{\text{C-F}}$ = 8.2 Hz), 129.80, 129.3, 128.3, 127.8, 115.6 (d, $J_{\text{C-F}}$ = 22 Hz), 47.5 ppm.

4-(4'-Chlorophenyl)-3-phenyl-1H-pyrrol-2(5H)-one (10g)^{48b}

White crystals (EtOH): 73% yield; mp 210-212 °C; R_f (4:1 ethyl acetate/petroleum ether) = 0.28; IR (ATR, neat) 3187, 3059, 2850, 1680, 1592, 1498, 1488, 1443, 1401, 1366, 1340, 1223, 1090, 1059, 1012, 974, 890, 825, 787, 742, 725 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.58 (br s, 1H), 7.26-7.42 (m, 9H), 4.36 (s, 2H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 172.2, 149.2, 133.6, 132.3, 132.2, 132.0, 129.4, 129.3, 128.7, 128.3, 127.9, 47.4 ppm; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{12}\text{ClNO}$: 270.0686 ($[\text{M}+\text{H}]^+$), found 270.0687 ($[\text{M}+\text{H}]^+$).

3,4-bis(4'-Methoxyphenyl)-1H-pyrrol-2(5H)-one (10h)

Bright yellow powder: 72% yield (based on recovered starting material); mp 213-216 °C; R_f (ethyl acetate) = 0.32; IR (ATR, neat) 3171, 3054, 2957, 2933, 2907, 2838, 1672, 1602, 1570, 1516, 1504, 1439, 1416, 1365, 1342, 1302, 1286, 1248, 1226, 1172, 1116, 1107, 1086, 1023, 975, 893, 839, 824, 799, 789, 779, 747, 720 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.38 (br s, 1H), 7.28 (d, 2H, J = 8.8 Hz), 7.22 (d, 2H, J = 8.8 Hz), 6.92 (d, 2H, J = 9.0 Hz), 6.89 (d, 2H, J = 9.0 Hz), 4.29 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 172.9, 159.7, 158.7, 149.0, 130.6, 129.7, 128.9, 125.8, 124.7, 114.1, 113.7, 55.2, 55.0, 47.3 ppm; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3$: 296.1287 ($[\text{M}+\text{H}]^+$), found 296.1284 ($[\text{M}+\text{H}]^+$).

4-(4'-(Methylsulfonyl)phenyl)-3-phenyl-1H-pyrrol-2(5H)-one (10j)^{20a}

White amorphous solid; 81% yield; mp 203-204 °C (lit.^{20a} 197-200 °C); R_f (ethyl acetate) = 0.16; IR (ATR, neat) 3452, 3178, 3056, 2994, 2917, 1677, 1633, 1596, 1564, 1490, 1446, 1403, 1362, 1336, 1302, 1284, 1225, 1181, 1147, 1089, 1060, 1032, 1021, 960, 918, 889, 838, 789, 769, 737, 715 cm^{-1} ; ^1H NMR (400 MHz, D_6 -DMSO) δ 8.70 (br s, 1H), 7.87 (d, 2H, J = 8.6 Hz), 7.56 (d, 2H, J = 8.6 Hz), 7.26-7.38 (m, 5H), 4.42 (s, 2H), 3.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, D_6 -DMSO) δ 171.9, 148.7, 140.7, 138.5, 133.9, 131.6, 129.3, 128.5, 128.4, 128.1, 127.2, 47.5, 43.2 ppm.

3-(4'-(Methylsulfonyl)phenyl)-4-phenyl-1H-pyrrol-2(5H)-one (10k)

Yellow amorphous solid; 5% yield; R_f (ethyl acetate) = 0.18; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, 2H, J = 8.8 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.30-7.40 (m, 3H), 7.24-7.26 (m, 2H), 6.40 (br s, 1H), 4.43 (d, 2H, J = 1.2 Hz), 3.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 153.4, 140.0, 137.8, 132.5, 130.8, 130.7, 130.4, 129.4, 127.88, 127.86, 48.5, 44.8 ppm; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$: 314.0851 ($[\text{M}+\text{H}]^+$), found 314.0850 ($[\text{M}+\text{H}]^+$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Selected 3,4-Diaryl-3-pyrrolin-2-ones

Scheme 2. Barton-Zard Pyrrole Cyclocondensation

Scheme 3. Synthesis of Rofecoxib Analog

Table 1
Synthesis of 1,2-Diaryl-1-nitroethenes

Substrate	Nitroalkene 11 Ar ³	Ar ⁴	Method #1 yield (%)	Method #2 yield (%)
a	Ph	Ph	42	77
b	4-MeOPh	Ph	62	77
c	4-MeSPh	Ph	70	83
d	Ph	4-MeOPh	--- ^a	84
e	Ph	4-MeSPh	25	81
f	Ph	4-FPh	--- ^a	76
g	Ph	4-ClPh	--- ^a	75
h	4-MeOPh	4-MeOPh	--- ^a	70
i	4-MeSPh	4-MeSPh	--- ^a	68
j ^b	Ph	4-MeSO ₂ Ph	--- ^a	48
k ^b	4-MeSO ₂ Ph	Ph	--- ^a	--- ^a
m	Ph	4-NO ₂ Ph	36	0
n	Ph	3-NO ₂ Ph	12	52

^a Not attempted

^b Method #3: Oxidation of corresponding thioether-substituted nitroalkene with two equivalents of *m*-CPBA (84% for **11j** from **11e**; 95% for **11k** from **11c**)

Table 2
Pyrrole-2-carboxamides, Pyrrole-2-carboxaldehydes, and 3-Pyrrolin-2-ones

Substrates	Ar ³	Ar ⁴	Amide 8 yield (%) ^a	Aldehyde 9 yield (%)	3-Pyrrolin-2-one 10 yield (%)
a	Ph	Ph	87	72	91
b	4-MeOPh	Ph	89	68	90
c	4-MeSPh	Ph	79	81	0 ^b
d	Ph	4-MeOPh	89	73	90
e	Ph	4-MeSPh	78	72	0 ^b
f	Ph	4-FPh	69	70	66
g	Ph	4-ClPh	66	82	73
h	4-MeOPh	4-MeOPh	82	63	72 ^c
i	4-MeSPh	4-MeSPh	75	---	---
j	Ph	4-MeSO ₂ Ph	40 ^e (95 ^f)	71	81
k	4-MeSO ₂ Ph	Ph	65 (69 ^f)	64	5 ^g
m	Ph	4-NO ₂ Ph	64	---	---
n	Ph	3-NO ₂ Ph	60	---	---

^a 1.0 equivalents of **11** and 1.5 equivalents of **12** used

^b Reactions were run both with 3-5 equivalents of *m*-CPBA in addition to large excess of H₂O; analysis of crude reaction mixtures by ¹H NMR revealed no 3-pyrrolin-2-one product and possible partial oxidation of the thioether moiety

^c Yield based on recovered starting material

^d Not attempted;

^e 1.2 equivalents of **11** and 1.0 equivalents of **12** used

^f Yield of reaction involving oxidation of the corresponding thioether-substituted pyrrole-2-carboxamide **8c** or **8e** with two equivalents of *m*-CPBA

^g Up to 80% of the starting material recovered unchanged