Suzuki–Miyaura Cross-Coupling Approach to 3,4-Diaryl-3-pyrrolin-2-ones from Tetramic Acid Triflates

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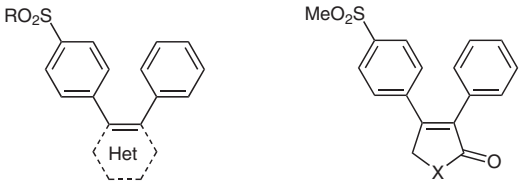
This article is dedicated to Professor Paul Wender in honor of his 60th birthday.

Abstract: A three-step approach to 4-aryl-3-phenyl-3-pyrrolin-2-ones from a readily available tetramic acid is described. The introduction of different aryl groups to the 4-position of the ring system was accomplished utilizing Suzuki–Miyaura cross-coupling reactions of the corresponding tetramic acid triflate. This strategy was successfully employed in the first synthesis of the NH lactam analogue of rofecoxib.

Key words: lactams, Suzuki–Miyaura cross-couplings, arylations, 3-pyrrolin-2-ones, tetramic acids

3-Pyrrolin-2-ones [or 1*H*-pyrrol-2(5*H*)-ones] are an important class of nitrogen heterocycles found in a variety of natural product classes including oligopyrrole plant pigments,[1] indolocarbazoles,[2] steroidal alkaloids,[3] and the pukeleimides.[4] Small molecule examples of 3-pyrrolin-2-ones have demonstrated interesting biological activity as inhibitors of platelet aggregation,[5] tyrosine phosphatase,[6] and cyclooxygenase-2 (COX-2).[7,8] With regard to the latter, a large number of diaryl heterocyclic compounds of general structure **1** have been investigated as selective inhibitors of COX-2 (Figure 1). The most notable example is furan-2-one **2a**[9] also known as rofecoxib (Vioxx®). Structurally related 3-pyrrolin-2-ones analogues of **2a** have also been investigated including *N*-alkyl lactam derivatives **2b**[7] and *N*-aryl lactam derivatives **2c**.[8] To our knowledge, the corresponding NH lactam analogue **7f** has not been previously reported. Due to their wide range of possible applications as bioactive molecules and as building blocks for more complex materials, we have on-going interest in developing novel, efficient syntheses of highly functionalized 3-pyrrolin-2-ones including N-unsubstituted derivatives.[10] Herein, we report our progress directed at developing a flexible synthesis of 3,4-diaryl-3-pyrrolin-2-ones **7**.

We envisioned that 3-phenyltetramic acid **4a** would provide convenient access to 4-aryl-3-phenyl-3-pyrrolin-2-ones **5** through palladium-catalyzed cross-coupling reactions at the 4-position. Similar chemistry has been investigated with maleimides,[11] furan-2-ones,[12] and coumarins.[13] We chose to incorporate the dimethoxybenzyl (DMB) protecting group due to its relative ease of removal late in the synthesis under acidic conditions. Wood



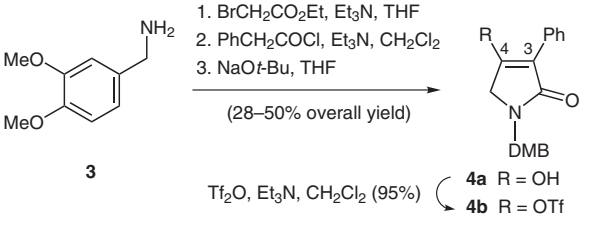
1 R = Me or NH_2

2a X = O (rofecoxib)
2b X = N-alkyl
2c X = N-aryl
7f X = N-H

Figure 1 General structures of diaryl heterocyclics **1**, **2**, and **7f**

and co-workers had utilized DMB as a lactam protecting group in their total synthesis of the indolocarbazole natural product K-252a.[14]

The preparation of the tetramic acid **4a** was accomplished in three steps starting from veratrylamine (**3**) (Scheme 1)[14b,15] as follows: (1) an N-alkylation with ethyl bromoacetate gave a crude secondary amine intermediate; (2) an N-acylation of this with phenylacetyl chloride gave a crude tertiary amide intermediate; and (3) finally an intramolecular Dieckmann-type cyclocondensation gave **4a** after an acidic work-up. Compound **4a** was obtained in analytically pure form by crystallization from ethyl acetate. We initially attempted to transform the enol moiety into the corresponding vinyl halide. All of our attempts to convert **4a** into the vinyl bromide (PBr_3 or CBr_4/PPh_3) or vinyl chloride ($POCl_3$) failed. Eventually, we obtained the cross-coupling substrate enol triflate **4b** upon treatment of **4a** with triflic anhydride in the presence of triethylamine. Triflate **4b** proved to be a very stable entity as it remained unchanged (by ^1H NMR) even after storage at room temperature for one year. In a separate study,[10b] we found that a structurally similar 3-unsubstituted tetramic acid triflate proved to be quite unstable.



3

(DMB = 3,4-dimethoxybenzyl)

Scheme 1

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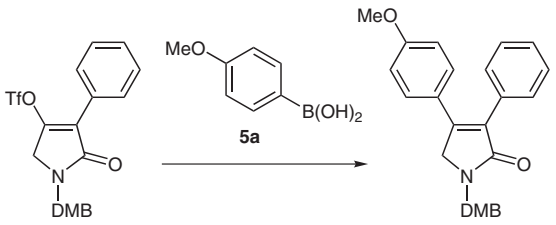
With triflate **4b** in hand, we investigated the Suzuki–Miyaura cross-coupling reaction with arylboronic acids **5** (Table 1). Our initial conditions included 1.1 equivalents of the boronic acid **5**, 10 mol% of tetrakis(triphenylphosphine)palladium(0), Na_2CO_3 as the base, and THF as the solvent. Initially with boronic acid **5a**, these conditions proved to be fairly successful (Table 1, entry 1). A brief survey of different bases including Cs_2CO_3,[16] K_3PO_4,[13] KOAc[17] showed sodium carbonate to be superior. We also explored a different palladium catalyst, $PdCl_2(dppf)$,[16] and observed no change in yield (Table 1, entries 2 and 3). We then switched to using 1.5 equivalents of the boronic acid substrates **5** in order to obtain more consistent results. A survey of different solvents found our initial choice of THF to give the best yields (Table 1, entry 6). Importantly, we were able to maintain the high yield after dropping the catalyst to 5 mol% (Table 1, entry 10). Notably, a cross-coupling reaction with a structurally related tetronic acid tosylate substrate containing a phenyl group at the 3-position proved to be very low yielding.[18] It seems that the higher reactivity offered by the triflate might be required for cross-coupling reactions involving sterically congested (*vicinal*-aryl) substrates.

Table 1 Survey of Suzuki–Miyaura Reaction Conditions with **4b**[a]

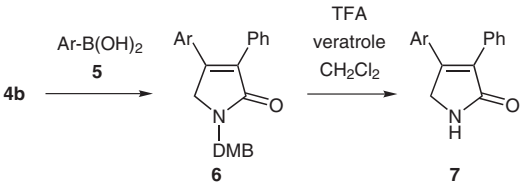


Entry	**5a** (equiv)	Pd cat. (mol%)	Base	Solvent	Yield (%)[b]
1	1.1	10	Na_2CO_3	THF	85
2	1.1	10	Cs_2CO_3	THF	72
3	1.1	10[c]	Cs_2CO_3	THF	71
4	1.1	10	K_3PO_4	THF	23
5	1.1	10	KOAc	dioxane	56
6	1.5	10	Na_2CO_3	THF	94
7	1.5	10	Na_2CO_3	dioxane	88
8	1.5	10	Na_2CO_3	toluene	66
9	1.5	10	Na_2CO_3	DMF	22
10	1.5	5	Na_2CO_3	THF	95

[a] Conditions: 1.1 or 1.5 equiv **5a**, 5 or 10 mol% $Pd(PPh_3)_4$ catalyst, 2.2 equiv base, solvent/H_2O, 40 min at r.t., then 1–6 h at reflux.
[b] Isolated yields of **6a** after column chromatography.
[c] 10 mol% $PdCl_2(dppf)$; dppf = bis(diphenylphosphino)ferrocene.

With the optimized reaction conditions, we explored the generality of the cross-coupling reaction with additional arylboronic acid substrates **5** (Table 2). In each case, the expected 4-aryl-3-pyrrolin-2-ones **6** were obtained in good yields with electron-rich (**5a** and **5e**), electron-neutral (**5b**), electron-poor (**5c**), and heterocyclic (**5d**) boronic acids. Removal of the DMB protecting group was then realized upon treatment of **6** with trifluoroacetic acid in the presence of the cation scavenger, veratrole.[14b] This reaction proved to be somewhat sluggish and often required long reaction times (in some runs, heating to reflux as well) in order to push the reactions to completion. Nevertheless, the 'free' lactams **7** were obtained in good yields in all cases with the exception of the furan analogue **7d** (Table 2, entry 4). We steered away from pursuing the DMB removal under oxidative conditions[19] due to the possibility of oxidizing the 3-pyrrolin-2-ones to the corresponding maleimides[20] although we did not investigate this directly.

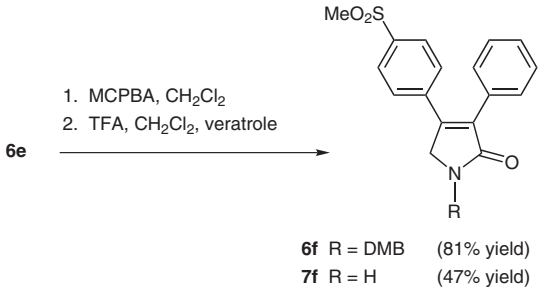
Table 2 Preparation of 3,4-Diaryl-3-pyrrolin-2-ones **7**[a]



Entry	Ar	Substrate	Yield **6** (%)[b]	Yield **7** (%)[b]
1	4-$OMeC_6H_4$	**a**	95	84
2	Ph	**b**	91	72
3	4-FC_6H_4	**c**	90	64
4	2-furyl	**d**	80	30
5	4-$SMeC_6H_4$	**e**	89	62

[a] Conditions: 1.5 equiv **5**, 5 mol% Pd catalyst, 2.2 equiv Na_2CO_3, THF–H_2O, 40 min at r.t., then 1–6 h at reflux.
[b] Isolated yields of **6** and **7** after column chromatography.

We next turned our attention to the preparation of the rofecoxib analogue **7f** (Scheme 2). Oxidation of thioether **6e** to the corresponding the methyl sulfone **6f** was achieved in 81% yield by treatment with *m*-chloroperoxybenzoic acid (MCPBA). Removal of the DMB group then gave the desired rofecoxib analogue **7f** in 47% yield. Interestingly, using our initial DMB deprotection procedure (concentration of the volatiles followed by chromatography), **7f** was apparently obtained as the corresponding TFA salt (**7f**·TFA) based on CHN analysis. We did not observe TFA salts in our previous synthesis of 3-unsubstituted 4-aryl-3-pyrrolin-2-ones,[10a] nor did we observe it with other substrates here. Nevertheless, this was subsequently avoided by doing a basic work-up (aq $NaHCO_3$) of the crude material obtained after removal of TFA.



Scheme 2

In summary, we have developed a short synthetic sequence to 4-aryl-3-phenyl-3-pyrrolin-2ones **7** starting from tetramic acid **4a**. The utility of the methodology was demonstrated through the preparation of the lactam analogue **7f** of rofecoxib (**2a**). We next plan to explore the use of 3-pyrrolin-2-ones **6** as building blocks to 3,4-diarylpyrroles by reduction[21] of the lactam and to 2,3,4-triarylpyrroles by conversion of the lactam to the triflate[22] and subsequent cross-coupling. The latter would allow for a controlled, step-wise introduction of aryl groups onto the pyrrole nucleus[23] which could prove useful to the preparation of complex pyrrole natural products (i.e., lamellarins[24]).

All reactions were performed under a positive argon atmosphere with magnetic stirring unless otherwise noted. Anhyd THF, CH_2Cl_2, and toluene were obtained by passage through a column of alumina utilizing a PureSolv 400 solvent purification system. Anhyd dioxane and DMF were purchased from commercial sources. Et_3N was distilled fresh from CaH_2 immediately prior to use. Petroleum ether used refers to the fraction boiling in the range 35–60 °C. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. ^1H NMR and ^{13}C NMR were run at 300 MHz and 75 MHz, respectively, utilizing an Oxford multinuclear Fourier transform instrument. Chemical shifts are reported in parts per million (δ) using the solvent's residual proton or carbon signal ($CDCl_3$: $\delta_H = 7.24$, $\delta_C = 77.3$; DMSO-d_6: $\delta_H = 2.50$, $\delta_C = 39.5$) as an internal reference. Flash chromatography was performed with silica gel (230–400 mesh) and TLC was performed utilizing glass-backed silica gel plates and visualized utilizing UV (254 nm). IR spectra were measured utilizing a PerkinElmer Spectrum 100 with ATR sampler (attenuated total reflectance). All yields are for chromatographed or crystallized, isolated materials.

1-(3′,4′-Dimethoxybenzyl)-4-hydroxy-3-phenyl-1*H*-pyrrol-2(5*H*)-one (4a)

A three-step reaction sequence was utilized to prepare the title product with intermediates taken on directly without purification. To a 0 °C stirred solution of veratrylamine (**3**; 10.0 g, 59.8 mmol) and Et_3N (6.35 g, 62.8 mmol) in THF (50 mL), was added a solution of ethyl bromoacetate (9.99 g, 59.8 mmol) in THF (50 mL) dropwise via addition funnel. The mixture was stirred at 0 °C for 2 h and then at r.t. for 16 h. The mixture was filtered through sintered glass and the solid was washed with Et_2O (2 × 20 mL). The combined organic layers were concentrated in vacuo giving known ethyl 2-(3′,4′-dimethoxybenzylamino)acetate[25] as an impure yellow oil (11.3 g).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.77–6.95 (m, 3 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.71 (s, 2 H), 3.50 (s, 2 H), 3.36 (s, 1 H), 1.20–1.26 (m, 3 H).

The crude yellow oil was taken up in CH_2Cl_2 (100 mL) and the solution was cooled to 0 °C and charged with Et_3N (5.53 g, 54.7 mmol) followed by the dropwise addition of phenylacetyl chloride (7.58 g, 49.0 mmol). The mixture was stirred at 0 °C for 2 h and then at r.t. for 15 h. The mixture was washed with an aq solutions of HCl (1.0 M, 100 mL), $NaHCO_3$ (saturated, 100 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4) and then the solvent was removed in vacuo to give crude intermediate ethyl 2-[*N*-(3′,4′-dimethoxybenzyl)-2″-phenylacetamido]acetate as an impure yellow oil (16.1 g). The last step involved a base-induced cyclization leading to the title tetramic acid.[14b,15b] The crude oil was taken up in THF (200 mL) and cooled to 0 °C. The resulting mixture was charged with *t*-BuONa (4.99 g, 52.0 mmol) and the mixture was stirred at 0 °C for 4 h then at r.t. for 2 h. The solvent was then removed in vacuo giving a yellow oil. The crude oil was taken up in enough EtOAc (~80 mL) to dissolve all of the material and aq HCl was added (50 mL). The aqueous layer was separated and further extracted with EtOAc (4 × 50 mL). The combined organic layers were dried (Na_2SO_4) and then partially concentrated by rotary evaporation until crystallization was observed. Repeated cycles of filtration and concentration gave the title compound **4a** as an analytically pure white powder [5.36 g, 28% yield from veratrylamine (**3**)]; mp 187–189.5 °C. In nine other runs through this sequence where the material was not all taken forward, yields ranging from 31–50% were obtained based on **3**.

IR (ATR, neat): 3011, 2836, 2428 (br), 1660, 1587, 1512, 1497, 1455, 1442, 1421, 1382, 1332, 1315, 1299, 1283, 1240, 1215, 1159, 1132, 1021, 973, 959, 887, 856, 805, 781, 763, 743, 734, 695, 672, 657 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.66 (br s, 1 H), 8.01 (d, *J* = 7.5 Hz, 2 H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 6.86 (d, *J* = 1.8 Hz, 1 H), 6.75 (dd, *J* = 1.8, 8.1 Hz, 1 H), 4.47 (s, 2 H), 3.82 (s, 2 H), 3.73 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.0, 167.0, 148.8, 148.0, 132.4, 130.4, 127.7, 126.7, 125.6, 119.8, 111.9, 111.6, 102.9, 55.5, 55.4, 48.6, 44.3.

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.03; H, 5.88; N, 4.29.

1-(3′,4′-Dimethoxybenzyl)-3-phenyl-4-trifluoromethanesulfonyl-1*H*-pyrrol-2(5*H*)-one (4b)

To a stirred solution of tetramic acid **4a** (3.16 g, 9.73 mmol) and Et_3N (1.31 g, 12.9 mmol) in CH_2Cl_2 (20 mL) at –15 °C was added neat trifluoromethanesulfonic anhydride dropwise via syringe. The mixture was stirred at –15 °C for 1 h and then poured into an aq solution of HCl (1.0 M, 50 mL), and H_2O (50 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were washed with aq $NaHCO_3$ (1% w/v, 100 mL), brine (100 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo gave a crude orange-brown oil. Trituration with PE (10 mL) gave the desired product **4b** as a tan powder (4.20 g, 95%); mp 85–86.5 °C; R_f = 0.20 (EtOAc–PE, 1:4).

IR (ATR, neat): 3007, 2909, 2837, 1694, 1593, 1516, 1498, 1449, 1420, 1334, 1314, 1252, 1239, 1222, 1192, 1168, 1131, 1103, 1027, 985, 959, 941, 918, 900, 842, 804, 782, 762, 753, 701, 663 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.76 (m, 2 H), 7.36–7.47 (m, 3 H), 6.82 (s, 1 H), 6.79–6.82 (m, 2 H), 4.63 (s, 2 H), 4.12 (s, 2 H), 3.86 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 153.2, 149.7, 149.2, 129.9, 129.0, 128.8, 127.3, 124.1, 120.9 (2C), 118.5 (q, *J* = 319 Hz), 111.55, 111.48, 56.3, 56.2, 48.7, 46.3.

Anal. Calcd for $C_{20}H_{18}F_3NO_6S$: C, 52.51; H, 3.97; N, 3.06; S, 7.01. Found: C, 52.37; H, 3.93; N, 3.05; S, 6.86.

Suzuki Cross-Coupling Reaction Leading to 3,4-Diaryl-3-pyrrolin-2-ones 6; General Procedure A

To a stirred solution of triflate **4b** (0.328 mmol) and an arylboronic acid **5** (0.492 mmol) in THF (15 mL) at r.t., was added $Pd(PPh_3)_4$ (0.0164 mmol) followed by an aq solution of Na_2CO_3 (0.076 g, 0.72 mmol, 2 mL of H_2O). The mixture was stirred at r.t. for 40 min and then heated to reflux for 1–6 h until TLC showed complete conversion of the starting material **4b**. The mixture was filtered through a short plug of Celite with the aid of CH_2Cl_2 and the bulk of the solvent was removed in vacuo. The crude material was taken up in CH_2Cl_2 (30 mL) and washed with H_2O (30 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4). Removal of the solvent gave a crude solid. The desired products **6** were obtained after purification by flash chromatography [gradient: EtOAc–PE, 1:4 to 1:2).

1-(3′,4′-Dimethoxybenzyl)-4-(4″-methoxyphenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (6a)

The title product **6a** was obtained utilizing general procedure A; yield: 95%; yellow solid; mp 163–164.5 °C; R_f = 0.36 (EtOAc–PE, 1:1).

IR (ATR, neat): 2961, 2915, 1676, 1635, 1604, 1590, 1573, 1510, 1471, 1452, 1422, 1393, 1364, 1312, 1299, 1250, 1231, 1194, 1175, 1142, 1106, 1042, 1016, 950, 936, 919, 845, 828, 809, 789, 765, 754, 741, 730, 714, 701, 669, 655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.44 (m, 2 H), 7.28–7.37 (m, 3 H), 7.16 (d, *J* = 6.9 Hz, 2 H), 6.87 (s, 1 H), 6.81–6.90 (m, 2 H), 6.73 (d, *J* = 6.9 Hz, 2 H), 4.67 (s, 2 H), 4.13 (s, 2 H), 3.86 (s, 6 H), 3.75 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 160.5, 149.5, 148.8, 147.5, 132.7, 131.0, 130.3, 129.8, 129.2, 128.7, 128.2, 125.7, 120.9, 114.2, 111.8, 111.3, 56.3, 56.2, 55.5, 52.1, 46.5.

Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 74.91; H, 6.04; N, 3.33.

1-(3′,4′-Dimethoxybenzyl)-3,4-diphenyl-1*H*-pyrrol-2(5*H*)-one (6b)

The title product **6b** was obtained utilizing general procedure A; yield: 91%; yellow solid; mp 55–58 °C; R_f = 0.39 (EtOAc–PE, 1:1).

IR (ATR, neat): 2932, 1674, 1591, 1512, 1446, 1403, 1359, 1258, 1232, 1138, 1072, 1025, 959, 916, 845, 810, 786, 763, 694, 672 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.44 (m, 2 H), 7.28–7.36 (m, 3 H), 7.20–7.26 (m, 5 H), 6.80–6.90 (m, 3 H), 4.68 (s, 2 H), 4.16 (s, 2 H), 3.86 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 149.6, 148.9, 147.9, 133.4, 132.6, 132.2, 130.2, 129.8, 129.4, 128.9, 128.7, 128.4, 127.8, 121.0, 111.8, 111.4, 56.3, 56.2, 52.2, 46.6.

1-(3′,4′-Dimethoxybenzyl)-4-(4″-fluorophenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (6c)

The title product **6c** was obtained utilizing general procedure A; yield: 90%; white solid; mp 145–147 °C; R_f = 0.43 (EtOAc–PE, 1:1).

IR (ATR, neat): 3062, 2921, 1673, 1603, 1509, 1456, 1418, 1402, 1363, 1283, 1265, 1236, 1215, 1180, 1152, 1123, 1097, 1074, 1033, 1003, 966, 928, 866, 841, 827, 798, 787, 766, 748, 717, 701, 676, 654 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.41 (m, 5 H), 7.16–7.22 (m, 2 H), 6.81–6.95 (m, 5 H), 4.67 (s, 2 H), 4.13 (s, 2 H), 3.86 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 163.2 (d, *J* = 250 Hz), 149.6, 148.9, 146.7, 132.6, 132.1, 130.1, 129.79, 129.77 (d, *J* = 8 Hz), 129.5 (d, *J* = 3 Hz), 128.8, 128.5, 121.0, 116.0 (d, *J* = 21 Hz), 111.9, 111.4, 56.3, 56.2, 52.2, 46.6.

Anal. Calcd for $C_{25}H_{22}FNO_3$: C, 74.43; H, 5.50; N, 3.47. Found: C, 74.39; H, 5.49; N, 3.46.

1-(3′,4′-Dimethoxybenzyl)-4-(furan-2″-yl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (6d)

The title product **6d** was obtained utilizing general procedure A; yield: 80%; yellow solid; mp 101–104 °C; R_f = 0.41 (EtOAc–PE, 1:1).

IR (ATR, neat): 3107, 2933, 2835, 1669, 1592, 1514, 1482, 1451, 1405, 1352, 1307, 1259, 1232, 1136, 1077, 1026, 963, 938, 883, 848, 807, 781, 765, 734, 696, 658 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.54 (m, 6 H), 6.80–6.89 (m, 3 H), 6.47 (d, *J* = 3.5 Hz, 1 H), 6.33 (dd, *J* = 1.7, 3.5 Hz, 1 H), 4.65 (s, 2 H), 4.21 (s, 2 H), 3.86 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 149.6, 148.9, 148.5, 143.6, 137.3, 132.2, 130.1, 129.7, 128.7, 128.6, 120.9, 112.2, 111.7, 111.4, 111.3, 56.3, 56.2, 50.1, 46.6 (missing one aromatic).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.5, 148.8, 148.1, 147.7, 144.7, 136.9, 132.1, 129.9, 129.5, 128.2, 128.1, 128.0, 120.0, 112.2, 111.9, 111.8, 111.7, 55.5, 55.4, 49.6, 45.3.

1-(3′,4′-Dimethoxybenzyl)-4-[4″-(methylthio)phenyl]-3-phenyl-4-1*H*-pyrrol-2(5*H*)-one (6e)

The title product **6e** was obtained utilizing general procedure A; yield: 89%; yellow solid; mp 63–67 °C; R_f = 0.51 (EtOAc–PE, 1:1).

IR (ATR, neat): 2921, 1672, 1592, 1513, 1451, 1420, 1400, 1361, 1259, 1232, 1138, 1095, 1025, 959, 817, 785, 766, 744, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.43 (m, 2 H), 7.30–7.37 (m, 3 H), 7.13 (AB system, d, *J* = 8.9 Hz, 2 H), 7.06 (AB system, d, *J* = 8.9 Hz, 2 H), 6.81–6.90 (m, 3 H), 4.67 (s, 2 H), 4.13 (s, 2 H), 3.862 (s, 3 H), 3.858 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 149.6, 148.9, 147.2, 140.7, 132.4, 132.1, 130.2, 129.8, 129.7, 128.8, 128.4, 128.1, 126.0, 121.0, 111.8, 111.3, 56.3, 56.2, 52.0, 46.6, 15.4.

Anal. Calcd for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25. Found: C, 71.65; H, 5.85; N, 3.20.

Removal of the DMB Protecting Group Leading to 3,4-Diaryl-3-pyrrolin-2-ones 7; General Procedure B

A modification of a literature procedure was utilized.[14b] A mixture of the DMB-protected 3-pyrrolin-2-one **6** (0.200 mmol) and veratrole (2.00 mmol) was charged with TFA (10 mL). The mixture was stirred for 40 min at r.t. and then heated to reflux for 6–16 h until TLC showed complete conversion of the starting material **6**. The mixture was poured into a sat. aq solution of $NaHCO_3$ (100 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were then washed with brine (100 mL) and dried (Na_2SO_4). Removal of the solvent gave a crude oil. The desired products **7** were obtained after purification by flash chromatography (gradient: EtOAc to MeOH–EtOAc, 1:19). Analytical samples were obtained by trituration with Et_2O.

4-(4′-Methoxyphenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (7a)

The title product **7a** was obtained utilizing general procedure B; yield: 84%; white solid; mp 193–196 °C; R_f = 0.18 (EtOAc–PE, 4:1).

IR (ATR, neat): 3182, 3056, 1686, 1607, 1515, 1456, 1443, 1366, 1315, 1295, 1252, 1230, 1180, 1122, 1080, 1061, 1035, 972, 892, 833, 789, 750, 708, 674 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.41 (br s, 1 H), 7.29–7.40 (m, 3 H), 7.24–7.28 (m, 4 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 4.33 (s, 2 H), 3.73 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.7, 159.8, 150.0, 132.8, 130.2, 129.4, 129.0, 128.3, 127.6, 125.5, 114.0, 55.2, 47.4.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.69; H, 5.71; N, 5.26.

3,4-Diphenyl-1*H*-pyrrol-2(5*H*)-one (7b)

The known[26] title product **7b** was obtained utilizing general procedure B; the product matched a sample (by TLC and NMR) previously prepared in our lab[10a] utilizing a different method; yield: 72%; yellow solid; mp 180–181 °C (Lit.[26b] mp 192–193 °C; Lit.[10a] mp 182–183 °C); R_f = 0.37 (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.53 (br s, 1 H), 7.25–7.36 (m, 10 H), 4.37 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.4, 150.4, 133.3, 132.4, 131.7, 129.3, 129.0, 128.6, 128.2, 127.7, 127.5, 47.5.

4-(4′-Fluorophenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (7c)

The title product **7c** was obtained utilizing general procedure B; yield: 64%; white solid; mp 204–207 °C; R_f = 0.29 (EtOAc).

IR (ATR, neat): 3184, 3060, 1682, 1603, 1512, 1493, 1442, 1408, 1363, 1343, 1226, 1162, 1105, 1059, 1015, 974, 945, 892, 837, 808, 788, 745, 715, 701, 675 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.53 (br s, 1 H), 7.15–7.39 (m, 9 H), 4.36 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.3, 162.3 (d, *J* = 246 Hz), 149.4, 132.2, 131.8, 129.83, 129.82 (d, *J* = 9 Hz), 129.3, 128.3, 127.8, 115.7 (d, *J* = 22 Hz), 47.5.

Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53. Found: C, 75.57; H, 4.87; N, 5.39.

4-(Furan-2′-yl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (7d)

The title product **7d** was obtained utilizing general procedure B; yield: 30%; white solid; mp 203–205 °C; R_f = 0.38 (EtOAc).

IR (ATR, neat): 3174, 3112, 3059, 1680, 1599, 1494, 1482, 1444, 1359, 1230, 1202, 1098, 1021, 980, 931, 884, 786, 769, 760, 742, 698, 672 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.42 (br s, 1 H), 7.75 (d, *J* = 1.7 Hz, 1 H), 7.36–7.46 (m, 5 H), 6.63 (dd, *J* = 0.8, 3.5 Hz, 1 H), 6.56 (dd, *J* = 1.7, 3.5 Hz, 1 H), 4.34 (d, *J* = 1.2 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.3, 148.0, 144.5, 138.7, 132.2, 129.4, 128.9, 127.9 (2), 112.1, 111.5, 45.3.

Anal. Calcd for $C_{14}H_{11}F_3NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.36; H, 4.87; N, 6.15.

4-[4′-(Methylthio)phenyl]-1*H*-pyrrol-2(5*H*)-one (7e)

The title product **7e** was obtained utilizing general procedure B; yield: 62%; yellow solid; mp 189–192 °C; R_f = 0.27 (4:1 EtOAc–PE).

IR (ATR, neat): 3167, 3056, 2899, 1680, 1594, 1501, 1491, 1446, 1430, 1405, 1366, 1343, 1274, 1225, 1200, 1131, 1098, 1079, 1061, 1032, 975, 890, 814, 783, 767, 743, 714, 697, 667 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.48 (br s, 1 H), 7.16–7.39 (m, 9 H), 4.34 (s, 2 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.5, 149.8, 139.9, 132.5, 131.2, 129.4, 129.3, 128.3, 127.9, 127.7, 125.4, 47.3, 14.1.

Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.30; H, 5.34; N, 4.96.

1-(3′,4′-Dimethoxybenzyl)-3-phenyl-4-[4′′-(methylsulfonyl)phenyl]-1*H*-pyrrol-2(5*H*)-one (6f)

To a stirred solution of thioether **6e** (0.500 g, 1.16 mmol) in CH_2Cl_2 (17 mL) at 0 °C, was added MCPBA (0.600 g, 3.48 mmol) and the mixture was allowed to warm to r.t. After stirring at r.t. for 2 h, the mixture was washed with H_2O (30 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (80 mL) and then dried (Na_2SO_4). Removal of the solvent in vacuo gave a crude solid which was purified by flash chromatography (gradient: EtOAc–PE, 1:4 to 2:1); yield: 81%; yellow solid; mp 64–66 °C; R_f = 0.42 (EtOAc–PE, 2:1).

IR (ATR, neat): 2924, 1675, 1593, 1513, 1451, 1400, 1359, 1304, 1281, 1260, 1233, 1146, 1089, 1027, 956, 837, 770, 698, 663 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (AB system, d, *J* = 9.0 Hz, 2 H), 7.39 (AB system, d, *J* = 9.0 Hz, 2 H), 7.33–7.37 (m, 5 H), 6.82–6.90 (m, 3 H), 4.69 (s, 2 H), 4.17 (s, 2 H), 3.864 (s, 3 H), 3.861 (s, 3 H), 3.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 149.6, 149.0, 145.2, 140.8, 138.9, 135.6, 131.3, 129.74, 129.68, 129.1, 129.0, 128.8, 128.0, 121.0, 111.9, 111.4, 56.3, 56.2, 52.0, 46.7, 44.6.

4-[4′-(Methylsulfonyl)phenyl]-1*H*-pyrrol-2(5*H*)-one (7f)

The title product **7f** was obtained utilizing general procedure B; yield: 47%; white powder; mp 197–200 °C; R_f = 0.27 (EtOAc–PE, 4:1).

IR (ATR, neat): 3182, 3058, 3011, 2995, 2918, 1677, 1633, 1597, 1492, 1447, 1404, 1363, 1337, 1303, 1285, 1226, 1182, 1147, 1090, 1060, 1022, 961, 918, 890, 834, 790, 770, 737, 715, 694, 664 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.69 (br s, 1 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.35–7.38 (m, 3 H), 7.26–7.30 (m, 2 H), 4.41 (s, 2 H), 3.23 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.9, 148.8, 140.7, 138.5, 133.9, 131.6, 129.3, 128.5, 128.4, 128.1, 127.2, 47.6, 43.2.

Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 64.46; H, 4.82; N, 4.29.

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