An Intramolecular N-Arylation Approach to 3-Functionalized 4,9-Dihydropyrrolo[2,1-*b*]quinazolines

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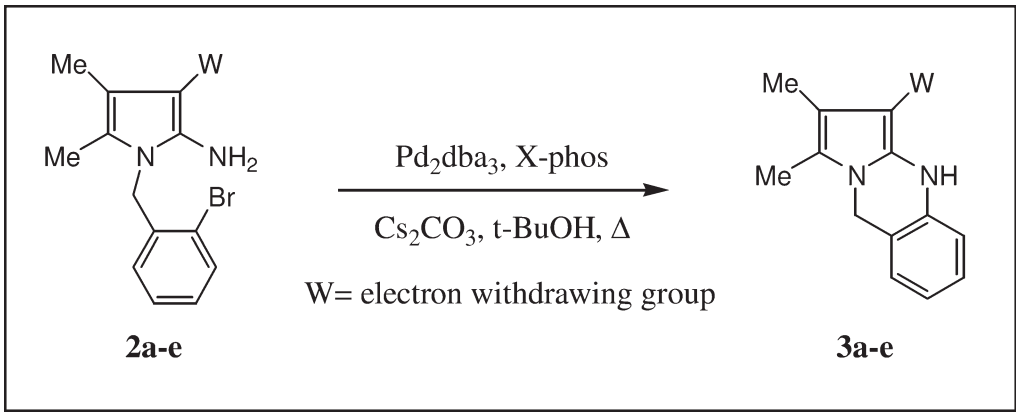

A series of 4,9-dihydropyrrolo[2,1-*b*]quinazolines containing electron withdrawing groups at the 3-position have been prepared by the palladium-catalyzed intramolecular *N*-arylation of some 2-aminopyrroles having a 2-bromobenzyl group at the *N*-1 position. Important for success of the reaction is the use of X-phos, a biphenyl mono-phosphine ligand, instead of xantphos, a more standard diphosphine ligand, and the use of *t*-BuOH as reaction solvent.

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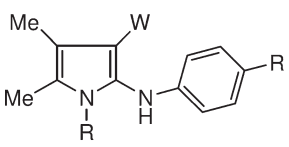
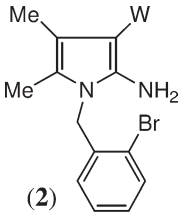
INTRODUCTION

Recently, we have described the palladium-catalyzed *N*-arylation (Buchwald-Hartwig amination) of 3-functionalized 2-aminopyrroles whereby the amino group is coupled with various aryl bromides to give *N*-arylated 2-aminopyrrole analogues (**1**) [1]. All couplings in that study were intermolecular. Considering recent reports of various intramolecular *N*-arylations to yield nitrogen-containing heterocycles [2], we have become interested in exploring such cyclization approaches to certain pyrrolo-fused ring systems. As a result of our efforts, we now wish to describe the palladium-catalyzed intramolecular *N*-arylation of some 2-aminopyrroles having a 2-bromobenzyl group at the *N*-1 position (**2**) to yield 3-functionalized 4,9-dihydropyrrolo[2,1-*b*]quinazolines (**3**). These tricyclic compounds are structurally related to a number of partially reduced quinazoline-based alkaloids, such as vasicine, (**4**) which possess interesting biological properties, including anti-inflammatory, antimicrobial, antidepressant, and antitumor activities [3]. As there is continued interest in these alkaloids, our work here may complement recent efforts [4] to develop new synthetic approaches to the pyrrolo[2,1-*b*]quinazoline ring system.



(**1**)



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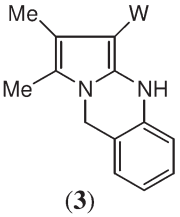
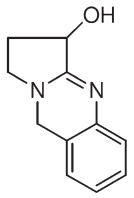


(**3**)



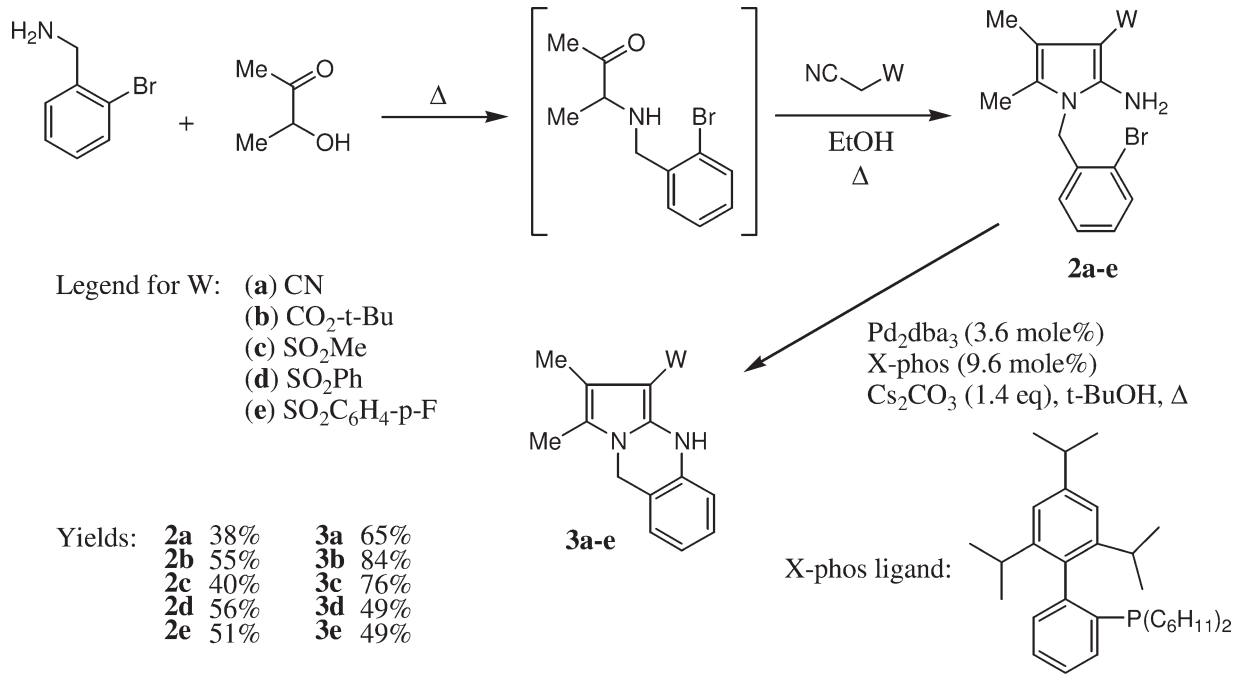
(**4**) Vasicine

W = electron withdrawing functional group

RESULTS AND DISCUSSION

The 2-bromobenzyl-substituted pyrroles (**2a-e**) were prepared in a similar manner to other such 2-

Scheme 1



aminopyrroles [5] by reaction of 2-bromobenzylamine with acetoin (3-hydroxy-2-butanone), followed by reaction of the intermediate α-aminoketone with a functionalized acetonitrile, such as malononitrile (Scheme 1). As a modification to the standard method, we simply heated the amine and acetoin together for a short time without solvent to form the intermediate. This approach is more convenient, compared with azeotropic removal of water with a Dean-Stark trap and eliminates the use of benzene or toluene as reaction solvent. Subsequent reaction of the intermediate with the functionalized acetonitrile was conducted in the usual manner by refluxing in EtOH for 2 h. Functional groups at the 3-position of pyrroles **2** include cyano, *t*-butyl ester, and three different sulfonyls (methyl, phenyl, and 4-fluorophenyl). Benzylamine is often used in this pyrrole synthesis to give *N*-benzyl pyrroles, [5] but this appears to be the first use of 2-bromobenzylamine. Purified yields for these new 2-aminopyrroles ranged from 38 to 56%.

Attempted cyclization of pyrroles **2** using our originally reported conditions for intermolecular *N*-arylation of similar 2-aminopyrroles (Pd_2dba_3, xantphos, Cs_2CO_3, 1,4-dioxane, 100°C, 18 h) was surprisingly unsuccessful in giving tricyclics **3**, with starting pyrrole primarily being recovered. A change in reaction solvent to DMF (100°C) or to refluxing xylenes led to no noticeable improvement. These results are consistent with observations that catalyst systems, which are useful for intermolecular *N*-arylations may fail with cyclizations. [6] Preliminary experiments using $Pd(PPh_3)_4$ as a palladium and ligand combination [2a] (with K_2CO_3 as base in DMF at 100°C for 18 h) afforded cyclized product in modest yield (~10%, W = SO_2Ph). However, much improved yields were obtained upon returning to our original conditions (Pd_2dba_3 as palladium source and Cs_2CO_3 as base), but using X-phos, a sterically-hindered mono-phosphine ligand, [7] in place of xantphos, a bidentate ligand. A further improvement in yield, and in purity of crude product, was realized upon changing the reaction solvent from 1,4-dioxane to *tert*-butyl alcohol [7c]. Under these optimized conditions, the reaction was complete in just 4 h, with tricyclics **3a-e** (Scheme 1) being readily isolated as solids upon addition of water to the reaction mixture. Recrystallization from MeOH or DMF/MeOH gave pure crystalline samples in 49–84% yield, with all products being characterized by NMR (^1H, ^{13}C, and ^{19}F when applicable), IR, combustion analysis, and melting point.

CONCLUSIONS

In conclusion, a palladium-catalyzed intramolecular *N*-arylation approach to a series of 4,9-dihydropyrrolo[2,1-*b*]quinazolines containing electron withdrawing groups at the 3-position has been described. Precursors for the cyclization reaction are 2-aminopyrroles containing a 2-bromobenzyl substituent at the *N*-1 position. These pyrroles were prepared by a modified procedure that eliminates the use of benzene or toluene as initial

solvent. For the cyclization reaction, X-phos, a sterically hindered mono-phosphine ligand, proved to be a much better ligand compared to xantphos, a more standard bidentate ligand. Also, *tert*-butyl alcohol was found to be an excellent reaction solvent for the cyclization reaction.

EXPERIMENTAL

General. Melting points were obtained using a Mel-Temp apparatus and are uncorrected. IR spectra were obtained using a Perkin–Elmer Spectrum 100 instrument using attenuated total reflection. NMR were recorded on a Bruker 300 Avance instrument, with signals referenced to residual DMSO-d_6 solvent (2.49 ppm for ^{1}H NMR, 39.5 ppm for ^{13}C NMR) or to hexafluorobenzene (set to 0 ppm for ^{19}F NMR). Elemental analyses were performed by Atlantic Microlab in Norcross, GA. 2-Bromobenzylamine, cesium carbonate (fine powder) and Pd_2dba_3 [tris(dibenzylideneacetone)dipalladium(0)] were obtained from Alfa Aesar. X-Phos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) was obtained from Aldrich. (Methylsulfonyl)acetonitrile, (phenylsulfonyl)acetonitrile, and (4-fluorophenylsulfonyl)-acetonitrile are commercially available. All reagents were weighed in open air.

Representative procedure for synthesis of 2-aminopyrroles 2a-e. ***2-Amino-1-(2-bromobenzyl)-3-cyano-4,5-dimethylpyrrole (2a).*** Acetoin (3-hydroxy-2-butanone, finely ground) (3.52 g, 40 mmol) and 2-bromobenzylamine (7.44 g, 40 mmol) were combined in a 50 mL round-bottom flask and heated with a heat gun or on a hotplate until the acetoin dissolved and a homogenous yellow liquid was obtained (~2–3 min of heating). The water vapor that condensed in the neck of the flask was removed using a chemwipe. EtOH (5–10 mL) was then added followed by malononitrile (2.64 g, 40 mmol) and the solution was heated at reflux for 2 h. The solution was then transferred to a beaker with addition of a small amount of water to produce a crystalline yellow solid. After chilling, this solid was filtered by suction and recrystallized from MeOH (50 mL) to give course powdery crystals (4.60 g, 38%). An analytical sample was obtained by recrystallization of a small amount (1.0 g) from MeOH (15–20 mL) to give course yellow crystals (0.69 g), mp 148–150°C (MeOH). IR (cm^{-1}): 3452, 3405, 3336, 3300, 3223, 3185, 2915, 2858, 2187, 1637, 1558, 1440, 1219, 1105, 1025, 751, 658. ^{1}H NMR (DMSO-d_6): 1.78 (s, 3H), 1.90 (s, 3H), 4.93 (s, 2H), 5.78 (s, NH_2), 6.29 (d, J = 7.6 Hz, 1H), 7.20–7.23 (m, 1H), 7.29–7.32 (m, 1H), 7.63 (dd, J = 7.8 and 1.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): 9.0, 9.8, 45.5, 71.3, 112.0, 116.9, 118.3, 121.1, 126.5, 128.1, 129.0, 132.5, 136.4, 146.8. *Anal*. *Calcd* for $C_{14}H_{14}BrN_3$ (304.19): C, 55.28; H, 4.64; N, 13.81. Found: C, 55.30; H, 4.51; N, 13.71.

2-Amino-1-(2-bromobenzyl)-3-(tert-butoxycarbonyl)-4,5-dimethylpyrrole (2b). Using *tert*-butyl cyanoacetate in place of malononitrile, this compound was obtained in 55% yield as yellow/tan crystals, mp 134–135°C (MeOH). IR (cm^{-1}): 3443, 3335, 2974, 2927, 1649, 1607, 1504, 1439, 1364, 1302, 1245, 1104, 1026, 753, 743. ^{1}H NMR (DMSO–d_6): 1.47 (s, 9H), 1.78 (s, 3H), 2.00 (s, 3H), 4.93 (s, 2H), 5.95 (s, NH_2), 6.31 (dd, J = 7.7 and 1.5 Hz, 1H), 7.20–7.23 (m, 1H), 7.28–7.31 (m, 1H), 7.63 (dd, J = 7.8 and 1.3 Hz, 1H). ^{13}C NMR (DMSO-d_6): 8.6, 11.6, 28.5, 45.1, 77.6, 92.3, 111.2, 116.6, 121.1, 126.6, 128.1, 129.0, 132.4, 136.6, 146.9, 165.8. Analysis for calcd for $C_{18}H_{23}BrN_2O_2$ (379.29): C, 57.00; H, 6.11; N, 7.39. Found: C, 56.89; H, 6.21; N, 7.30.

2-Amino-1-(2-bromobenzyl)-4,5-dimethyl-3-(methylsulfonyl)-pyrrole (2c). Using (methylsufonyl)acetonitrile in place of malononitrile, this compound was obtained in 40% yield as course tan crystals, mp 155–157°C (MeOH). IR (cm^{-1}): 3400, 3315, 2921, 1618, 1540, 1481, 1276, 1099, 1025, 943, 762. ^{1}H NMR (DMSO-d_6): 1.81 (s, 3H), 2.01 (s, 3H), 2.97 (s, 3H), 4.96 (s, 2H), 5.60 (s, NH_2), 6.34 (dd, J = 7.7 and 1.5 Hz, 1H), 7.21–7.24 (m, 1H), 7.31–7.34 (m, 1H), 7.64 (dd, J = 7.9 and 1.2 Hz, 1H). ^{13}C NMR (DMSO-d_6): 8.6, 9.6, 45.4, 45.5, 96.3, 109.9, 117.8, 121.1, 126.5, 128.2, 129.1, 132.5, 136.2, 142.8. *Anal*. *Calcd* for $C_{14}H_{17}BrN_2O_2S$ (357.27): C, 47.07; H, 4.80; N, 7.84. Found: C, 46.95; H, 4.67; N, 7.76.

2-Amino-1-(2-bromobenzyl)-4,5-dimethyl-3-(phenylsulfonyl)-pyrrole (2d). Using (phenylsulfonyl)acetonitrile in place of malononitrile, this compound was obtained in 56% yield as light tan/colorless crystals, mp 186–187°C (MeOH). IR (cm^{-1}): 3458, 3360, 2911, 1616, 1541, 1482, 1440, 1275, 1126, 1077, 751, 726, 689. ^{1}H NMR (DMSO-d_6): 1.74 (s, 3H), 1.89 (s, 3H), 4.96 (s, 2H), 5.90 (s, NH_2), 6.25 (d, J = 7.4 Hz, 1H), 7.21–7.30 (m, 2H), 7.55–7.69 (m, 4H), 7.78–7.82 (m, 2H). ^{13}C NMR (DMSO-d_6): 8.6, 9.8, 45.5, 95.4, 109.9, 118.4, 121.2, 125.1, 126.3, 128.1, 129.1, 129.2, 132.0, 132.6, 136.1, 143.8, 145.5. *Anal*. *Calcd* for $C_{19}H_{19}BrN_2O_2S$ (419.34): C, 54.42; H, 4.57; N, 6.68. Found: C, 54.26; H, 4.69; N, 6.64.

2-Amino-1-(2-bromobenzyl)-3-(4-fluorophenylsulfonyl)-4,5-dimethylpyrrole (2e). Using (4-fluorophenylsulfonyl)acetonitrile in place of malononitrile, this compound was obtained in 51% yield as light tan/colorless crystals, mp 148–149°C (EtOH). IR (cm^{-1}): 3452, 3358, 3099, 3071, 2926, 2856, 1615, 1587, 1536, 1486, 1271, 1226, 1125, 1077, 844, 821, 752, 713, 663. ^{1}H NMR (DMSO-d_6): 1.75 (s, 3H), 1.89 (s, 3H), 4.97 (s, 2H), 5.92 (s, NH_2), 6.25 (dd, J = 7.6 and 1.5 Hz, 1H), 7.30–7.42 (m, 4H), 7.64 (dd, J = 7.8 and 1.4Hz, 1H), 7.83–7.88 (m, 2H). ^{13}C NMR (DMSO-d_6): 8.6, 9.8, 45.5, 95.2, 109.8, 116.3 (d, J = 22 Hz), 118.5, 121.1, 126.3, 128.0, 128.1, 129.1, 132.6, 136.0, 141.9 (d, J = 3 Hz), 143.9, 163.9 (d, J = 249 Hz). ^{19}F NMR (DMSO-d_6): 54.9 (m). *Anal*. *Calcd* for $C_{19}H_{18}BrFN_2O_2S$ (437.32): C, 52.18; H, 4.15; N, 6.41. Found: C, 52.19; H, 4.04; N, 6.36.

Representative procedure for synthesis of pyrrole[2,1-*b*]quinazolines 3a-e. ***3-Cyano-1,2-dimethyl-4,9-dihydropyrrolo[2,1-b]quinazoline (3a).*** A mixture of pyrrole **2a** (3.65 g, 12.0 mmol), Pd_2dba_3 (0.197 g, 0.215 mmol, 3.6 mol% Pd), X-phos (0.547 g, 1.15 mmol, 9.6 mol%) and Cs_2CO_3 (5.47 g, 16.8 mmol, 1.4 eq) in *tert*-butyl alcohol (75 mL) was heated at gentle reflux under nitrogen for 4 h. The resulting burgundy suspension was then diluted with excess water (~100 mL) to give a tan solid which was filtered by suction and washed with water. Recrystallization of the dried product from EtOH (~400 mL), with hot filtration to remove traces of Pd metal, gave pinkish colored microneedles (1.75 g, 65%), mp 230–233°C. IR (cm^{-1}): 3281, 3226, 2913, 2851, 2197, 1622, 1581, 1531, 1493, 1417, 1307, 1256, 1037, 859, 750. ^{1}H NMR (DMSO-d_6): 1.93 (s, 3H), 2.10 (s, 3H), 4.99 (s, 2H), 6.82–6.86 (m, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.09–7.15 (m, 2H), 9.73 (s, NH). ^{13}C NMR (DMSO-d_6): 8.7, 9.5, 42.7, 69.6, 112.6, 114.0, 114.2, 117.4, 117.7, 120.4, 127.0, 128.1, 135.7, 138.1. *Anal*. *Calcd* for $C_{14}H_{13}N_3$ (223.27): C, 75.31; H, 5.87; N, 18.82. Found: C, 75.10; H, 5.91; N, 18.75.

3*-tert-*Butoxycarbonyl-1,2-dimethyl-4,9-dihydropyrrolo[2,1-b]quinazoline (3b). This compound was obtained in 84% yield as gray microneedles, mp 142–143°C (MeOH). IR (cm^{-1}): 3374, 3059, 3005, 2969, 2935, 2856, 1640, 1612, 1579, 1419, 1277, 1268, 1179, 1127, 1107, 1067, 779, 740, 706. ^1H NMR (DMSO-d_6): 1.49 (s, 9H), 2.01 (s, 3H), 2.09 (s, 3H), 4.99 (s, 2H), 6.82–6.87 (m, 1H), 7.10–7.15 (m, 3H), 8.60 (s, NH). ^{13}C NMR (DMSO-d_6): 8.4, 11.0, 28.4, 42.5, 78.1, 92.2, 111.5, 114.4, 114.9, 117.7, 120.5, 127.0, 128.0, 135.5, 137.9, 165.2. *Anal*. *Calcd* for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.20; H, 7.35; N, 9.28.

1,2-Dimethyl-3-(methylsulfonyl)-4,9-dihydropyrrolo[2,1-b]quinazoline (3c). This compound was obtained in 76% yield as pale orange/tan needles, mp 176–179°C (MeOH). IR (cm^{-1}): 3338, 3044, 2929, 2856, 1610, 1571, 1492, 1272, 1105, 943, 855, 754, 740, 712. ^1H NMR (DMSO-d_6): 2.02 (s, 3H), 2.18 (s, 3H), 3.02 (s, 3H), 5.03 (s, 2H), 6.84–6.91 (m, 1H), 7.10–7.16 (m, 3H), 8.26 (s, NH). ^{13}C NMR (DMSO-d_6): 8.4, 9.2, 42.6, 45.5, 96.3, 110.4, 114.2, 115.0, 118.6, 120.7, 126.9, 128.1, 134.2, 135.2. *Anal*. *Calcd* for $C_{14}H_{16}N_2O_2S$ (276.36): C, 60.85; H, 5.84; N, 10.14. Found: C, 60.87; H, 5.81; N, 10.08.

1,2-Dimethyl-3-(phenylsulfonyl)-4,9-dihydropyrrolo[2,1-b]quinazoline (3d). This compound was obtained in 49% yield as coral/orange microcrystals, mp 229–231°C (DMF/MeOH). IR (cm^{-1}): 3362, 3047, 2917, 2853, 1610, 1571, 1524, 1494, 1445, 1282, 1124, 1080, 854, 753, 723, 685. ^1H NMR (DMSO-d_6): 1.91 (s, 3H), 2.05 (s, 3H), 5.01 (s, 2H), 6.88 (t, 1H), 7.10–7.18 (m, 2H), 7.28 (d, $J = 7.6$ Hz, 1H), 7.51–7.58 (m, 3H), 7.86–7.89 (m, 2H), 8.57 (s, 1H). ^{13}C NMR (DMSO-d_6): 8.4, 9.3, 42.7, 95.9, 110.2, 114.3, 115.3, 119.3, 120.9, 125.5, 126.9, 128.1, 129.2, 132.2, 134.9, 135.2, 144.9. *Anal*. *Calcd* for $C_{19}H_{18}N_2O_2S$ (338.42): C, 67.43; H, 5.36; N, 8.28. Found: C, 67.36; H, 5.39; N, 8.26.

3-(4-Fluorophenylsulfonyl)-1,2-dimethyl-4,9-dihydropyrrolo[2,1-b]quinazoline (3e). This compound was obtained in 49% yield as coral/red microneedles, mp 222–223°C (DMF/MeOH). IR (cm^{-1}): 3379, 3103, 3069, 3043, 2918, 1609, 1571, 1491, 1281, 1222, 1128, 1079, 848, 818, 748, 710, 685, 661. ^1H NMR (DMSO-d_6): 1.91 (s, 3H), 2.05 (s, 3H), 5.01 (s, 2H), 6.88 (t, 1H), 7.10–7.15 (m, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.38 (t, 2H), 7.92–7.97 (m, 2H), 8.59 (s, NH). ^{13}C NMR (DMSO-d_6): 8.4, 9.3, 42.7, 95.7, 110.1, 114.3, 115.3, 116.2, 116.5, 119.4, 120.9, 126.9, 128.1, 128.5 (d, $J = 9$ Hz), 135.0 (d, $J = 17$ Hz), 141.3 (d, $J = 3$ Hz), 163.9 (d, $J = 250$ Hz). ^{19}F NMR (DMSO-d_6): 55.3 (m). *Anal*. *Calcd* for $C_{19}H_{17}FN_2O_2S$ (356.41): C, 64.03; H, 4.81; N, 7.86. Found: C, 63.87; H, 4.80; N, 7.80.

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