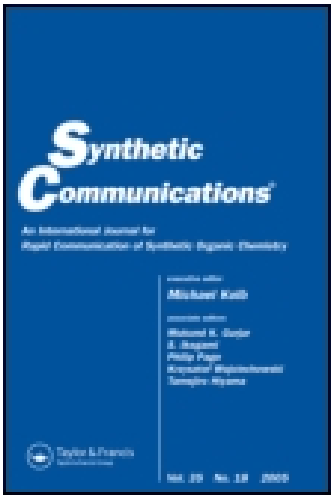


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Palladium-Catalyzed N-Arylation of 3-Functionalized 2-Amino-4,5-dimethylpyrroles

Carlos P. Griswold [a], Nisaraporn Suthiwangcharoen [a], Steven M. Pochini [a] & Chad E. Stephens [a]

[a] Department of Chemistry and Physics, Augusta State University, Augusta, Georgia, USA

Published online: 20 Apr 2011.

To cite this article: Carlos P. Griswold, Nisaraporn Suthiwangcharoen, Steven M. Pochini & Chad E. Stephens (2011) Palladium-Catalyzed N-Arylation of 3-Functionalized 2-Amino-4,5-dimethylpyrroles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:11, 1672-1681, DOI: 10.1080/00397911.2010.492073

To link to this article: http://dx.doi.org/10.1080/00397911.2010.492073

Synthetic Communications®, 41: 1672–1681, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.492073

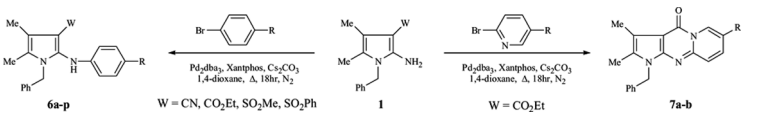
Taylor & Francis
Taylor & Francis Group

PALLADIUM-CATALYZED N-ARYLATION OF 3-FUNCTIONALIZED 2-AMINO-4,5-DIMETHYLPYRROLES

Carlos P. Griswold, Nisaraporn Suthiwangcharoen, Steven M. Pochini, and Chad E. Stephens

Department of Chemistry and Physics, Augusta State University, Augusta, Georgia, USA

GRAPHICAL ABSTRACT



Abstract *A versatile class of 2-aminopyrroles containing various electron-withdrawing substituents at the 3-position have been N-arylated on the amine using a palladium-catalyzed cross-coupling reaction. Using this methodology, a pyrimidone-based tricyclic system has been prepared in just one step from a starting 2-aminopyrrole.*

Keywords 2-Aminopyrrole; DPEphos; N-arylation; palladium-catalyzed; pyrrolo[2,3-*d*]pyrido[1,2-*a*]pyrimidine; xantphos

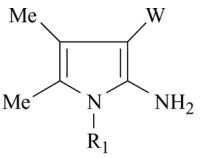
INTRODUCTION

2-Amino-4,5-dimethylpyrroles (**1**) containing various functional groups at the 3-position are readily prepared by a one-pot reaction that involves condensation of acetoin with a primary amine, followed by reaction of the intermediate α-aminoketone with a functionalized acetonitrile.[1–3] Possible substituents at the 3-position of these pyrroles include CN, CO_2R, SO_2R, and others. Because a substituted amine must be used in the synthesis or else a pyrazine is obtained, the 1-position of the pyrrole is typically substituted with either an alkyl or aryl group (Fig. 1).

These 2-aminopyrroles have served as building blocks to various bicyclic ring systems. Examples include pyrrolo[1,2-a]pyrimidines,[4] pyrrolo[2,3-d]pyrimidines,[5] pyrrolo[2,3-b]pyridines,[6] pyrrolo[2,3-d][1,3]oxazines,[7] pyrrolo[3,2-b][1,4]thiazines,[8] pyrrolo[2,3-e][1,3,4]thiadiazines,[9] and others.[10] These pyrroles have also served as precursors to 5-hydroxy-2-aminoindoles.[11] Some of these fused-ring derivatives possess interesting biological activity.[5,11]

Received December 8, 2009.

Address correspondence to Chad E. Stephens, Department of Chemistry and Physics, Augusta State University, Augusta, GA 30904, USA. E-mail: cstephe7@aug.edu



W = CN, CO_2R, SO_2R, etc
R_1 = alkyl or aryl

1

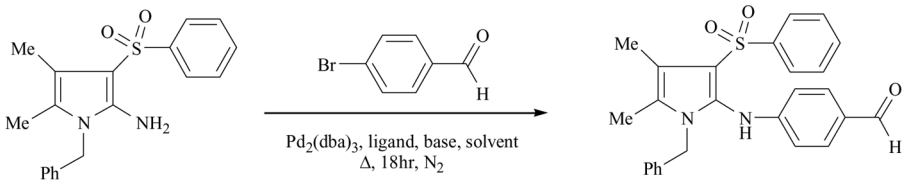
Figure 1. Structure of 2-amino-4,5-dimethypyrroles **1**.

The transition metal–catalyzed N-arylation of amines has been a highly active area of research in the past decade, with palladium-catalyzed reactions receiving a large focus.[12,13] To date, however, there has been no report of N-arylation chemistry with the title 2-aminopyrroles. The development of a transition metal–catalyzed N-arylation method would thus expand the scope of chemistry that is possible with these compounds and would also allow for construction of novel types of fused-ring systems. Herein, we present the first N-arylations of pyrroles **1**. We also illustrate the use of this N-arylation chemistry for the construction of a pyrimidine-based tricyclic system in just one step from a starting 2-aminopyrrole.

RESULTS AND DISCUSSION

As a model reaction, we first explored the N-arylation of 3-(phenylsulfonyl)-pyrrole **1a** with 4-bromobenzaldehyde to give product **6a** (Table 1). We initially chose to use Pd_2dba_3 as a palladium(0) catalyst and xantphos as a bidentate ligand. This catalyst–ligand system has been used previously for the N-arylation of amines,[14,15] as well as for other nitrogen-containing functional groups.[16–18] As

Table 1. Yield data for model N-arylation reaction



1a **6a**

Entry	Ligand	Base	Solvent	Yield[a] (%)
1	Xantphos	Cs_2CO_3	1,4-Dioxane	37
2	DPEphos	Cs_2CO_3	1,4-Dioxane	37
3	X-phos	Cs_2CO_3	1,4-Dioxane	33
4	Xantphos	K_3PO_4	1,4-Dioxane	11
5	Xantphos	CsOAc	1,4-Dioxane	Trace[b]
6	Xantphos	Cs_2CO_3	DME	Trace[b]
7	Xantphos	Cs_2CO_3	Toluene	Trace[b]

[a]Isolated yield of pure product after column chromatography.
[b]Based on TLC comparison to an authentic sample.

shown in Table 1, use of this catalyst system (1.5 mol% Pd_2dba_3, 3 mol% xantphos), along with Cs_2CO_3 (1.4 eq.) as base and 1,4-dioxane as solvent (entry 1), gave N-arylated product **6a** in 37% purified yield after heating at 100 °C overnight (18 h). The use of DPEphos, another bidentate ligand,[19] or X-phos, a sterically hindered monodentate ligand,[20] afforded no improvement in yield compared to xantphos (entries 2 and 3). The use of K_3PO_4 as base (entry 4) gave a much lesser yield compared to Cs_2CO_3, whereas the use of the weaker base CsOAc (entry 5) gave only a trace of product. Similarly, only a trace of product was formed when either DME (dimethoxyethane) or toluene were used as solvent in place of 1,4-dioxane (entries 6 and 7). Ultimately, our best yield of 37% (entry 1) was considered reasonable given that the starting pyrrole was consumed in the reaction and that a significant amount of darkening typically occurred in all reactions (an indication of decomposition). The yield is also reasonable considering that these amines are known to have much reduced nucleophilicity, likely due to their substantial enamine character[3] and the steric hindrance of the two substituents at the 1- and 3-positions of the pyrrole.

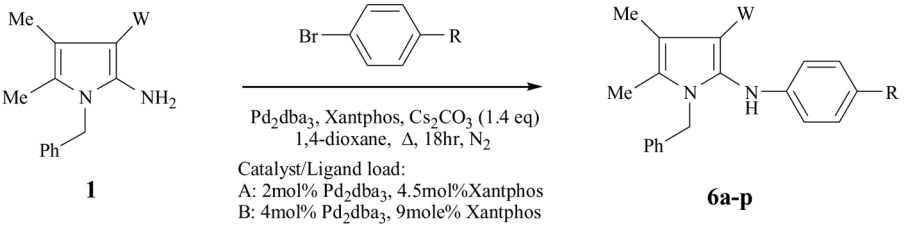
With a working procedure in hand [Pd_2dba_3 (2 mol%), xantphos (4.5 mol%), Cs_2CO_3, 1,4-dioxane: conditions A], we further explored the scope of this chemistry by reacting a variety of 2-aminopyrroles with different aryl bromides (Table 2). The starting pyrroles were substituted at the 3-position with either a sulfone (phenyl or methyl), ethyl ester, or a cyano group. In each case, the alkyl group on the nitrogen of the pyrrole was benzyl. The benzyl group can be subsequently removed from the pyrrole in some cases (see Ref. 5). Substituents on the aryl bromides employed were electron withdrawing, electron donating, or simply hydrogen.

As shown in Table 2, we were able to readily N-arylate the various 2-aminopyrroles with aryl bromides containing different electron-withdrawing groups. Yields when using such activated aryl bromides ranged from 37 to 86% yield (entries 1–11), with the yield for our model reaction (entry 1) ultimately being the lowest. In contrast to-these good results, when using bromobenzene or aryl bromides containing electron-donating groups such as 4-bromotoluene or 4-bromoanisole, the coupling reaction was more sluggish and generally gave only trace amounts of product when using conditions A. A single exception was the coupling of the 3-cyano pyrrole with bromobenzene, which gave a reasonable yield of 37% when using our original conditions (entry 12). This favorable result may be due to the low steric demand of the cyano group at the 3-position compared to the other functional groups, such as the ester or sulfonyl.

Ultimately, we were able to obtain reasonable yields for couplings with bromobenzene simply by doubling the amount of palladium catalyst and ligand (conditions B, entries 13–16). The use of additional catalyst led to an increase in yield for the coupling of the 3-cyano pyrrole with bromobenzene from 37% to 60% (compare entries 12 and 13). It also allowed for coupling of the 3-methylsulfonyl pyrrole with 4-bromotoluene in reasonable yield (22%, entry 17). However, other attempted couplings with substrates containing electron-donating groups, such as with 4-bromoanisole (entry 18), were still generally unsuccessful.

Next, in an effort to construct a tricyclic system using this chemistry, we performed the coupling reaction between ester-substituted pyrrole **1b** and 2-bromopyridine. In this case, annulation can occur via intramolecular addition of

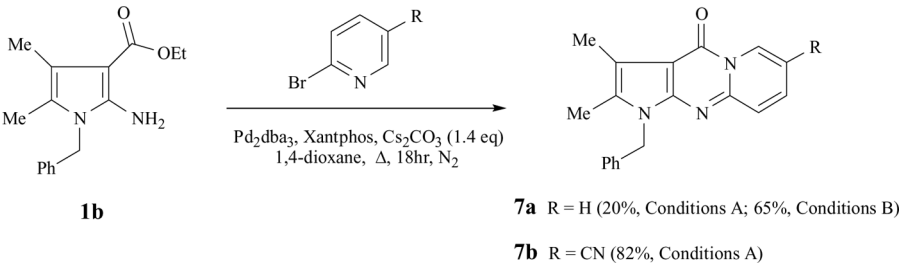
Table 2. Yield data for various N-arylations of pyrroles **1**



Entry	W	R	Conditions	Product	Yield[a] %
1	SO_2Ph	CHO	A	**6a**	37
2	SO_2Ph	COMe	A	**6b**	55
3	SO_2Ph	CN	A	**6c**	59
4	SO_2Ph	NO_2	A	**6d**	76
5	SO_2Me	CHO	A	**6e**	68
6	SO_2Me	NO_2	A	**6f**	86
7	SO_2Me	Cl	A	**6g**	60
8	CO_2Et	CN	A	**6h**	86
9	CN	COMe	A	**6i**	72
10	CN	CO_2Me	A	**6j**	43
11	CN	Cl	A	**6k**	72
12	CN	H	A	**6l**	37
13	CN	H	B	**6l**	60
14	SO_2Ph	H	B	**6m**	15
15	SO_2Me	H	B	**6n**	71
16	CO_2Et	H	B	**6o**	55
17	SO_2Me	Me	B	**6p**	22
18	CN	OMe	B	**6q**	Trace[b]

[a]Isolated yield of pure product after column chromatography.
[b]Based on ^{1}H NMR of the partially purified product.

the pyridine nitrogen to the ester group after the N-arylation.[21] As shown in Scheme 1, this reaction gave pyrimidone-based tricyclic **7a** in modest yield (20%) when using conditions A. However, this was improved to 65% when using conditions B. An analogous coupling with 5-cyano-2-bromopyridine proceeding readily using conditions A, giving **7b** in 82% yield. In this latter case, no reaction took place when



Scheme 1. Synthesis of pyrimidone-based tricyclics **7a** and **7b**.

the catalyst and ligand were omitted, indicating that the reaction is indeed catalytic. It is noteworthy that this tricyclic ring system has been studied as a potential scaffold for antibacterial agents[22] and has recently been prepared by others using an alternative approach that involves formation of the pyrrole ring as the last step.[23]

CONCLUSION

In conclusion, we have described the first N-arylations of a versatile class of 3-functionalized 2-aminopyrroles. This palladium-catalyzed coupling proceeds most readily when using aryl bromides that are activated by an electron-withdrawing substituent, although good yields have also been obtained when using bromobenzene through use of additional catalyst and ligand. Consistent with other N-arylations with the palladium/xantphos system, the reaction does not proceed well when using deactivated aryl bromides, although one coupling with 4-bromotoluene has been achieved. Finally, using this N-arylation chemistry, a pyrimidone-based tricyclic system has been prepared in just one step from an ester-substituted 2-aminopyrrole.

EXPERIMENTAL

NMR spectra were recorded on a Bruker 300 Avance spectrometer. The residual solvent peak (dimethyl sulfoxide, DMSO) was used as internal standard (2.49 ppm for proton, and 39.5 ppm for carbon). Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 Fourier transform (FT)–IR spectrometer using attenuated total reflectance (ATR). Melting points were recorded in open capillaries using a Mel-Temp 1201D apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. Starting 2-aminopyrroles were prepared according to the literature.[1–3] All other reagents were commercial and used as received.

Conditions A: Representative Procedures for 4-(1-Benzyl-4,5-dimethyl-3-phenylsulfonylpyrrol-2-ylamino)benzaldehyde (6a)

A mixture of 2-amino-1-benzyl-4,5-dimethyl-3-phenylsulfonylpyrrole (**1a**) (0.204 g, 0.6 mmol), 4-bromobenzaldehyde (0.122 g, 0.66 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 2 mol%), xantphos (15.6 mg, 0.027 mmol, 4.5 mol%), cesium carbonate (0.274 g, 0.84 mmol), and anhydrous 1,4-dioxane (1–2 mL) was heated at 100–105 °C (oil bath) under nitrogen atmosphere for 18 h. The resulting dark suspension was then diluted with water and extracted with EtOAc. Purification of the extract by column chromatography (silica gel) using a gradient of hexanes–ethyl acetate (5:1 to 2:1) as eluent gave, following concentration of pure fractions, a yellow powdery solid (0.088 g, 37%). Recrystallization from EtOH, followed by drying in vacuo, gave fine yellow/orange crystals, mp 177–179 °C. IR (cm^{-1}): 3310, 3058, 3033, 2929, 2805, 2731, 1682, 1599, 1583, 1297, 1159, 828, 744, 689, 586, 553, 507. ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H), 2.07 (s, 3H), 4.89 (s, 2H), 6.50 (br d, $J = 7.5$ Hz, 2H), 6.97 (d, $J = 7.5$ Hz, 2H), 7.22–7.29 (m, 3H), 7.38 (m, 2H), 7.51 (m, 1H), 7.57 (d, $J = 8.8$ Hz, 2H), 7.63 (d, $J = 7.9$ Hz, 2H), 8.73 (s, NH), 9.68 (s, CHO). ^{13}C NMR (DMSO-d_6): 9.6, 9.8, 45.8, 112.9, 113.0, 114.3, 124.7, 126.2, 126.4, 127.3, 127.4, 128.6,

128.9, 129.8, 131.5, 132.5, 136.8, 143.3, 152.8, 190.4. Analysis for $C_{26}H_{24}N_2O_3S$ (444.55): calcd. C, 70.25; H, 5.45; N, 6.31; found C, 70.41; H, 5.35; N, 6.37.

Analytical Data for Other Compounds Prepared Using Conditions A

1-[(1-Benzyl-4,5-dimethyl-3-phenylsulfonylpyrrol-2-ylamino)phenyl]-ethanone (6b). Tan/orange crystals (toluene/hexanes), mp 152–154 °C. IR (cm^{-1}): 3354, 3060, 2952, 2936, 1668, 1600, 1585, 1357, 1284, 1260, 1132, 833, 737, 722, 695. ^{1}HNMR (DMSO-d_6): 1.95 (s, 3H), 2.06 (s, 3H), 2.43 (s, 3H), 4.88 (s, 2H), 6.44 (broad d, $J = 7.8$ Hz, 2H), 6.97 (d, $J = 7.2$ Hz, 2H), 7.20–7.31 (m, 3H), 7.38 (t, 2H), 7.52 (t, 1H), 7.62–7.68 (m, 4H), 8.53 (s, NH). ^{13}C NMR (DMSO-d_6): 9.6, 9.8, 26.1, 45.7, 112.6, 112.8, 114.1, 124.5, 126.2, 126.4, 127.3, 127.5, 128.6, 128.9, 130.1, 130.3, 132.4, 136.9, 143.4, 151.5, 195.6.

4-(1-Benzyl-4,5-dimethyl-3-phenylsulfonylpyrrol-2-ylamino)benzonitrile (6c). Tan crystals (MeOH), mp 149–150 °C. IR (cm^{-1}): 3321, 3053, 3033, 2927, 2220, 1607, 1511, 1404, 1310, 1301, 1164, 1134, 1083, 831, 745, 719, 689. ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H), 2.07 (s, 3H), 4.87 (s, 2H), 6.44 (broad d, $J = 7.0$ Hz, 2H), 6.96 (d, $J = 7.2$ Hz, 2H), 7.22–7.31 (m, 3H), 7.40–7.43 (m, 4H), 7.50–7.54 (m, 1H), 7.63 (d, $J = 8.2$ Hz, 2H), 8.66 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 9.8, 45.7, 99.1, 112.9, 113.5, 114.9, 119.9, 124.7, 126.2, 126.3, 127.3, 128.6, 128.9, 129.6, 132.5, 133.3, 136.8, 143.3, 151.2.

1-Benzyl-4,5-dimethyl-2-(4-nitrophenyl)amino-3-phenylsulfonylpyrrole (6d). Amber crystals (EtOH), mp 206–208 °C. IR (cm^{-1}): 3306, 3065, 3032, 2926, 1594, 1497, 1321, 1298, 1272, 1164, 1134, 1109, 1082, 842, 743, 721, 688. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.08 (s, 3H), 4.89 (s, 2H), 6.45 (broad s, 2H), 6.95 (d, $J = 7.2$ Hz, 2H), 7.20–7.30 (m, 3H), 7.38–7.43 (m, 2H), 7.52 (t, 1H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.91 (d, $J = 9.0$ Hz, 2H), 9.04 (s, NH). ^{13}C NMR (DMSO-d_6): 9.6, 9.8, 45.8, 112.7, 113.1, 114.7, 125.0, 125.7, 126.2, 126.4, 127.3, 128.7, 129.0, 129.0, 132.6, 136.7, 138.3, 143.2, 153.5.

4-(1-Benzyl-4,5-dimethyl-3-methylsulfonylpyrrol-2-ylamino)benzaldehyde (6e). Yellow amorphous solid. IR (cm^{-1}): 3309, 3023, 2925, 2816, 2740, 1680, 1600, 1582, 1525, 1403, 1292, 1221, 1159, 1113, 950, 827, 762, 733, 697. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.14 (s, 3H), 2.93 (s, 3H), 4.93 (s, 2H), 6.59 (d, $J = 8.1$ Hz, 2H), 7.00 (d, $J = 7.0$ Hz, 2H), 7.20–7.32 (m, 3H), 7.64 (d, $J = 8.5$ Hz, 2H), 8.62 (s, NH), 9.68 (s, CHO). ^{13}C NMR (DMSO-d_6): 9.6, 9.7, 44.9, 45.6, 112.9, 113.0, 114.6, 124.2, 126.4, 127.3, 127.3, 128.6, 129.1, 131.7, 137.0, 153.3, 190.4.

1-Benzyl-4,5-dimethyl-3-methylsulfonyl-2-(4-nitrophenyl)aminopyrrole (6f). Light orange needles (Et_2O/hexanes), mp 125–127 °C. IR (cm^{-1}): 3290, 3003, 2926, 1599, 1509, 1498, 1324, 1302, 1289, 1270, 1109, 951, 838, 771, 736, 690. ^{1}H NMR (DMSO-d_6): 2.03 (s, 3H), 2.14 (s, 3H), 2.95 (s, 3H), 4.94 (s, 2H), 6.57 (broad d, $J = 7.4$ Hz, 2H), 6.99 (d, $J = 7.2$ Hz, 2H), 7.20–7.31 (m, 3H), 7.99 (d, $J = 8.8$ Hz, 2H), 8.92 (s, NH). ^{13}C NMR (DMSO-d_6): 9.6, 9.6, 44.8, 45.7, 112.7, 113.1, 114.9, 124.6, 125.9, 126.4, 127.3, 128.4, 128.6, 136.9, 138.3, 153.9.

1-Benzyl-2-(4-chlorophenyl)amino-4,5-dimethyl-3-methylsulfonylpyrrole (6g). Tan solid, mp 109–111 °C. IR (cm^{-1}): 3347, 3030, 2925, 1591, 1534, 1491, 1287, 1114, 950, 822, 761, 731, 696. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.11 (s, 3H), 2.89 (s, 3H), 4.91 (s, 2H), 6.48 (d, $J = 8.3$ Hz, 2H), 6.99 (d, $J = 7.3$ Hz, 2H), 7.11 (d, $J = 8.5$ Hz, 2H), 7.16–7.32 (m, 3H), 7.85 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 9.7, 44.9, 45.5, 112.7, 113.9, 114.8, 121.6, 123.6, 126.4, 127.2, 128.6, 128.7, 130.8, 137.2, 146.4.

Ethyl 1-Benzyl-2-(4-cyanophenyl)amino-4,5-dimethylpyrrole-3-carboxylate (6h). Amber oil. IR (cm^{-1}): 3313, 2926, 2869, 2217, 1678, 1606, 1590, 1510, 1440, 1407, 1113, 829, 729, 696. ^{1}H NMR (DMSO-d_6): 0.91 (t, 3H), 1.98 (s, 3H), 2.14 (s, 3H), 3.92 (q, 2H), 4.97 (s, 2H), 6.55 (d, $J = 8.5$ Hz, 2H), 6.95 (d, $J = 7.2$ Hz, 2H), 7.20–7.29 (m, 3H), 7.46 (d, $J = 8.4$ Hz, 2H), 8.46 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 10.8, 13.9, 45.4, 58.4, 98.4, 106.5, 113.5, 114.9, 120.1, 123.4, 126.2, 127.1, 128.6, 131.5, 133.3, 137.6, 152.1, 163.8.

2-(4-Acetylphenyl)amino-1-benzyl-4,5-dimethylpyrrole-3-carbonitrile (6i). Pale yellow/colorless crystals (MeOH), mp 150–151 °C. IR (cm^{-1}): 3239, 3071, 2942, 2922, 2212, 1660, 1589, 1580, 1269, 1171, 745, 698. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.04 (s, 3H), 2.43 (s, 3H), 4.99 (s, 2H), 6.65 (d, $J = 8.6$ Hz, 2H), 6.95 (d, $J = 7.1$ Hz, 2H), 7.18–7.30 (m, 3H), 7.77 (d, $J = 8.6$ Hz, 2H), 8.71 (s, NH). ^{13}C NMR (DMSO-d_6): 9.74, 9.74, 26.1, 45.9, 87.7, 112.6, 115.2, 115.8, 123.8, 126.2, 127.3, 127.9, 128.6, 130.4, 134.2, 137.0, 150.4, 195.6.

Methyl 4-(1-Benzyl-3-cyano-4,5-dimethylpyrrol-2ylamino)benzoate (6j). Coarse yellow crystals (MeOH), mp 156–157 °C. IR (cm^{-1}): 3266, 3171, 3068, 3035, 2956, 2211, 1692, 1606, 1539, 1435, 1282, 1271, 1170, 1116, 769, 746, 696. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.04 (s, 3H), 3.75 (s, 3H), 4.98 (s, 2H), 6.65 (d, $J = 6.9$ Hz, 2H), 6.95 (d, $J = 7.5$ Hz, 2H), 7.20–7.30 (m, 3H), 7.74 (d, $J = 8.8$ Hz, 2H), 8.46 (s, NH). ^{13}C NMR (DMSO-d_6): 9.8, 9.8, 45.9, 51.5, 87.8, 112.8, 115.2, 115.9, 119.4, 123.8, 126.2, 127.3, 128.6, 131.1, 134.3, 137.0, 150.4, 166.0.

1-Benzyl-2-(4-chlorophenyl)amino-4,5-dimethylpyrrole-3-carbonitrile (6k). Amber oil. IR (cm^{-1}): 3303, 3067, 3032, 2922, 2864, 2214, 1594, 1543, 1490, 1421, 1241, 1089, 819, 731, 697, 670. ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H), 2.00 (s, 3H), 4.97 (s, 2H), 6.60 (d, $J = 8.6$ Hz, 2H), 6.93–6.96 (m, 2H), 7.15 (d, $J = 8.6$ Hz, 2H), 7.20–7.28 (m, 3H), 8.21 (s, NH). ^{13}C NMR (DMSO-d_6): 9.8, 9.8, 45.8, 87.0, 115.0, 115.0, 116.1, 122.0, 123.3, 126.2, 127.3, 128.7, 129.0, 135.6, 137.2, 145.0.

Conditions B

The procedure was similar to the representative procedure described previously, except that 4 mol% of $Pd_2(dba)_3$ and 9 mol% of xantphos were used.

Data for Compounds Prepared Using Conditions B

1-Benzyl-4,5-dimethyl-2-phenylaminopyrrole-3-carbonitrile (6l). Amber crystals (cyclohexane), mp 133–135 °C. IR (cm^{-1}): 3308, 3105, 3060, 3026, 2917, 2861, 2203, 1603, 1593, 1546, 1495, 1442, 1406, 1304, 749, 739, 689. ^{1}H NMR

(DMSO-d_6): 1.95 (s, 3H), 2.02 (s, 3H), 4.97 (s, 2H), 6.59 (d, $J = 8.6$ Hz, 2H), 6.70 (t, 1H), 6.96 (d, $J = 8.2$ Hz, 2H), 7.12 (t, 2H), 7.16–7.28 (m, 3H), 8.04 (s, NH). ^{13}C NMR (DMSO-d_6): 9.7, 9.7, 45.7, 86.9, 113.4, 114.8, 116.2, 118.6, 123.0, 126.2, 127.2, 128.6, 129.1, 136.1, 137.2, 146.0.

1-Benzyl-4,5-dimethyl-2-phenylamino-3-phenylsulfonylpyrrole (6m). Colorless crystals (EtOAc), mp 184–186 °C. IR (cm^{-1}): 3366, 3061, 2947, 2923, 1601, 1530, 1394, 1286, 1160, 1133, 1080, 826, 750, 720, 702, 690. ^{1}H NMR (DMSO-d_6): 1.92 (s, 3H), 2.03 (s, 3H), 4.89 (s, 2H), 6.44 (d, $J = 7.7$ Hz, 2H), 6.70 (t, 1H), 6.98 (d, $J = 7.0$ Hz, 2H), 7.04 (t, 2H), 7.26–7.38 (m, 5H), 7.50 (t, 1H), 7.58 (d, $J = 7.4$ Hz, 2H), 7.76 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 9.8, 45.7, 112.4, 112.8, 113.6, 118.4, 123.8, 126.2, 126.4, 127.2, 128.6, 128.8, 128.9, 132.3, 132.5, 137.2, 143.6, 146.8.

1-Benzyl-4,5-dimethyl-3-methylsulfonyl-2-phenylaminopyrrole (6n). Light tan/colorless crystals (EtOAc/hexanes), mp 162–163 °C. IR (cm^{-1}): 3347, 3015, 2924, 1602, 1534, 1497, 1401, 1356, 1285, 1116, 961, 762, 749, 742, 728, 699. ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 2.12 (s, 3H), 2.88 (s, 3H), 4.91 (s, 2H), 6.50 (d, $J = 7.6$ Hz, 2H), 6.68 (m, 1H), 7.00 (d, $J = 7.5$ Hz, 2H), 7.10 (t, 2H), 7.22–7.30 (m, 3H), 7.65 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 9.7, 44.9, 45.5, 112.5, 113.4, 113.6, 118.3, 123.3, 126.4, 127.2, 128.6, 129.0, 131.5, 137.3, 147.2.

Ethyl 1-Benzyl-4,5-dimethyl-2-phenylaminopyrrole-3-carboxylate (6o). Amber oil. IR (cm^{-1}): 3348, 3031, 2925, 2863, 1689, 1602, 1551, 1495, 1409, 1225, 1113, 1066, 748, 725, 693. ^{1}H NMR (DMSO-d_6): 0.98 (t, 3H), 1.95 (s, 3H), 2.12 (s, 3H), 3.95 (q, 2H), 4.95 (s, 2H), 6.52 (d, $J = 7.7$ Hz, 2H), 6.65 (t, 1H), 6.97 (d, $J = 7.5$ Hz, 2H), 7.07 (t, 2H), 7.20–7.30 (m, 3H), 7.54 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 10.9, 14.0, 45.4, 58.3, 105.2, 113.5, 114.4, 118.0, 122.4, 126.2, 127.0, 128.5, 128.8, 134.7, 137.9, 147.7, 164.3.

1-Benzyl-4,5-dimethyl-2-(4-methylphenyl)amino-3-methylsulfonylpyrrole (6p). Light tan/colorless crystals (EtOAc/hexanes), mp 148–150 °C. IR (cm^{-1}): 3376, 3017, 2938, 1529, 1510, 1286, 1108, 957, 944, 814, 769, 740, 700. ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H), 2.11 (s, 3H), 2.15 (s, 3H), 2.87 (s, 3H), 4.89 (s, 2H), 6.42 (d, $J = 8.3$ Hz, 2H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.99 (d, $J = 7.3$ Hz), 7.22–7.32 (m, 3H), 7.47 (s, NH). ^{13}C NMR (DMSO-d_6): 9.5, 9.7, 20.1, 45.0, 45.5, 112.4, 113.2, 113.5, 123.2, 126.4, 126.9, 127.2, 128.6, 129.5, 132.0, 137.4, 144.7.

Synthesis of Tricyclic Compounds 7a and 7b

These compounds were prepared according to the previous representative procedure using a 2-bromopyridine and either conditions A or B as noted in the text.

1-Benzyl-2,3-dimethylpyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-4-one (7a). Yellow crystals, mp 185–185.5 °C (MeOH). IR (cm^{-1}): 3099, 3036, 2917, 2851, 1683, 1637, 1485, 1430, 1129, 771, 730, 690. ^{1}H NMR (DMSO-d_6): 2.15 (s, 3H), 2.48 (s, 3H), 5.43 (s, 2H), 7.05–7.08 (m, 3H), 7.22–7.29 (m, 3H), 7.49 (d, $J = 9.0$ Hz, 1H), 7.62 (m, 1H), 8.90 (d, $J = 7.3$, 1H). ^{13}C NMR (DMSO-d_6): 9.6, 9.9, 44.4, 100.6, 108.9, 112.5, 125.0, 126.4, 126.4, 127.2, 128.7, 129.3, 133.4, 137.9, 146.3, 147.0, 153.9.

Analysis for $C_{19}H_{17}N_3O$ (303.36): calcd. C, 75.23; H, 5.65; N, 13.85; found C, 74.99; H, 5.67; N, 13.81.

1-Benzyl-7-cyano-2,3-dimethylpyrido[1,2-*a*]pyrrolo[2,3-*d*]pyrimidine-4-one (7b). Fibrous yellow needles, mp 223–224 °C (MeOH). IR (cm^{-1}): 3065, 3020, 2920, 2850, 2230, 1705, 1635, 1525, 1446, 1350, 1287, 827, 727, 688. ^{1}H NMR (DMSO-d_6): 2.17 (s, 3H), 2.36 (s, 3H), 5.45 (s, 2H), 7.06 (d, $J = 7.5$ Hz, 2H), 7.23–7.30 (m, 3H), 7.54 (d, $J = 9.4$ Hz, 1H), 7.74 (d, $J = 2.0$ and 9.4 Hz, 1H), 9.37 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (DMSO-d_6): 9.6, 9.8, 44.6, 97.3, 101.0, 110.0, 116.7, 126.1, 126.5, 127.3, 128.7, 130.3, 131.2, 135.0, 137.5, 145.1, 146.3, 153.0. Analysis for $C_{20}H_{16}N_4O$ (328.37): calcd. C, 73.15; H, 4.91; N, 17.06; found C, 73.06; H, 4.93; N, 17.03.

ACKNOWLEDGMENTS

We thank our department and the Pamplin College of Arts and Sciences for funding of this research.

REFERENCES

1. Roth, H. J.; Eger, K. Synthese von 2-amino-3-cyano-pyrrolen. *Arch. Pharm.* **1975**, *308*, 179–185.
2. Mattson, R. J.; Wang, L.-C.; Sowell, J. W. Synthesis of substituted 2-amino-3-(alkyl or aryl)sulfonylpyrroles. *J. Heterocycl. Chem.* **1980**, *17*, 1793–1795.
3. Laks, J. S.; Ross, J. R.; Bayomi, S. M.; Sowell, J. W. Synthesis of N-1-substituted 2-amino-3-t-butoxycarbonyl-4,5-dimethylpyrroles. *Synthesis* **1985**, 291–293.
4. Vishwakarma, L. C.; Sowell, J. W. Synthesis of 4,7-dihydro-4-oxopyrrolo[2,3-b]pyridine-5-carboxylic acid derivatives as potential antimicrobial agents. *J. Heterocycl. Chem.* **1985**, *22*, 1429–1433.
5. Traxler, P. M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. 4-(Phenylamino)pyrrolopyrimidines: Potent and selective, ATP site directed inhibitors of the EGF-receptor protein tyrosine kinase. *J. Med. Chem.* **1996**, *39*, 2285–2292.
6. Bayomi, S. M.; Haddad, D. Y.; Sowell, J. W. One-step synthesis of 6,7-dimethyl-2-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a][1,3]pyrimidines. *J. Heterocycl. Chem.* **1984**, *21*, 1367–1368.
7. Ross, J. R.; Laks, J. S.; Wang, D. L.-C.; Sowell, J. W. Synthesis of 7-substituted 5,6-dimethyl-2,4-dioxo-1,2,4,7-tetrahydropyrrolo[2,3-d][1,3]oxazines. *Synthesis* **1985**, 796–798.
8. Wang, D. L.; Bayomi, S. M.; Sowell, J. W. Synthesis of substituted pyrrolo[3,2-b][1,4]-thiazine 1,1-dioxides. *Pakistan J. Sci. Ind. Res.* **1988**, *31*, 242–244.
9. Stephens, C. E.; Sowell, J. W. Synthesis of substituted pyrrolo[2,3-e][1,3,4]-thiadiazine 4,4-dioxides. *J. Heterocycl. Chem.* **1996**, *33*, 1615–1617.
10. Vorob'ev, E. V.; Kurbatov, E. S.; Krasnikov, V. V.; Mezheritskii, V. V.; Usova, E. V. Synthesis and rearrangement of 7*H*-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]- and 7*H*-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 1492–1497.
11. Player, M. R.; Sowell, J. W.; Patil, G. S.; Kam, C.-M.; Powers, J. C. 1,3-Oxazino[4,5-b]indole-2,4-(1*H*,9*H*)-diones and 5,6-dimethylpyrrolo[2,3-d]-1,3-oxazin-2,4-(1*H*,7*H*)-diones as serine protease inhibitors. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 949–954.

12. Corbet, J.-P.; Mignani, G. Selected patented cross-coupling reaction technologies. *Chem. Rev.* **2006**, *106*, 2651–2710.
13. Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. Industrial-scale palladium-catalyzed coupling of aryl halides and amines—A personal account. *Adv. Synth. Catal.* **2006**, *348*, 23–39.
14. Harris, M. C.; Geis, O.; Buchwald, S. L. Sequential N-arylation of primary amines as a route to alkyldiarylamines. *J. Org. Chem.* **1999**, *64*, 6019–6022.
15. Yin, T.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. Pd-catalyzed N-arylation of heteroarylamines. *Org. Lett.* **2002**, *4*, 3481–3484.
16. Anbazhagan, M.; Stephens, C. E.; Boykin, D. W. Palladium-catalyzed N-arylation of O-methylamidoximes. *Tetrahedron Lett.* **2002**, *43*, 4221–4224.
17. Yin, J.; Buchwald, S. L. Palladium-catalyzed intermolecular coupling of aryl halides and amides. *Org. Lett.* **2000**, *2*, 1101–1104.
18. Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. Palladium-catalyzed reaction of aryl halides with ureas. *Tetrahedron Lett.* **2001**, *42*, 4381–4384.
19. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. A highly active palladium catalyst system for the arylation of anilines. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.
20. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-catalyzed C-N bond-forming processes: The first amidation of arylsulfonates, aqueous amination, and complementarity with Cu-catalyzed reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.
21. Begouin, A.; Hesse, S.; Queiroz, M.-J. R. P.; Kirsch, G. Reactivity of substituted bromothiophenecarboxylates in palladium-catalyzed N-arylation of hetarylamines. *Synthesis* **2006**, 2794–2798.
22. Kuyper, L. F.; Garvey, J. M.; Baccanari, D. P.; Champness, J. N.; Stammers, D. K.; Beddell, C. R. Pyrrolo[2,3-d]pyrimidines and pyrido[2,3-d]pyrimidines as conformationally restricted analogues of the antibacterial agent trimethoprim. *Bioorg. Med. Chem.* **1996**, *4*, 593–602.
23. Zhang, Y.; Kawashima, K.; Noguchi, M. A convenient synthesis of 2-functionalized pyrrolo[2,3-d]pyrido[1,2-a]pyrimidines. *Heterocycles* **2006**, *70*, 181–184.