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Triethanolamine-Mediated Palladium-Catalyzed Regioselective C-2 Direct Arylation of Free NH-Pyrroles

Farnaz Jafarpour,* Soraya Rahiminejadan, and Hamideh Hazrati

School of Chemistry, University College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran

jafarpur@khayam.ut.ac.ir

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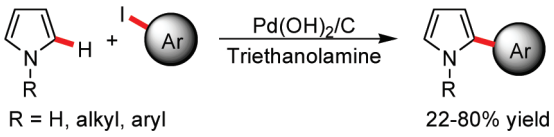

An atom-economical phosphane-free palladium-catalyzed direct C-2 arylation of unactivated free NH-pyrroles is devised. This method provides a straithforward route to a wide variety of substituted 2-aryl-1*H*-pyrroles from readily accessible starting materials. Iodoarenes bearing electron-withdrawing and electron-donating substituents are tolerated under the presented reaction conditions. The scope of the reaction is also expanded to *N*-aryl and -alkylpyrroles albeit in lower yields.

Nitrogen-containing biaryls have attracted considerable attention as they are common motifs in biologically active products.[1] 2-Arylpyrroles continue to attract the attention of synthetic organic chemists as they are integral components of natural products and pharmaceuticals. Several synthetic 2-arylpyrrole derivatives have been shown to possess interesting biological and biomedical properties.[2] For instance, atorvastatin **1**, is a member of the drug class known as statins, used for lowering blood cholesterol (Figure 1).[3] Diaryl-1*H*-pyrroles **2** and **3** have been identified as p38 mitogen-activated protein (MAP) kinases[4] and cyclooxygenase-2 (COX-2)-selective inhibitors,[5] respectively (Figure 1).

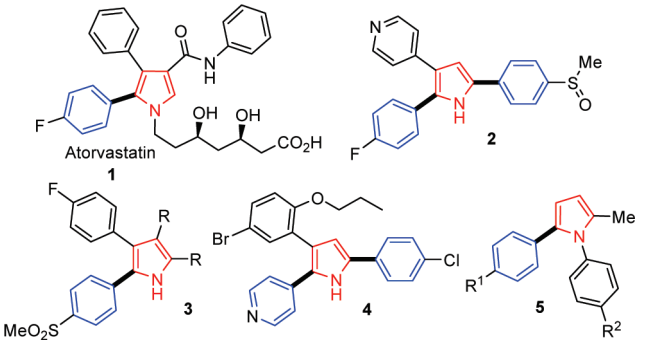

FIGURE 1. Biologically active compounds containing the 2-arylpyrrole framework.

Furthermore, the pyridyl diaryl-1*H*-pyrrole **4** has been reported to be a glucagon receptor antagonist, which is able to block glucose production (Figure 1).[6] Thus, several synthetic challenges have stimulated the development of milder and more efficient methods for the synthesis of these heterocyclic compounds. Direct functionalization of desired scaffold through regioselective C−H bond activation in the presence of a reactive N−H functionality provides an efficient cost-effective, environmentally attractive and atom-economical entry to these compounds as it eliminates the need for introducing protecting groups and reactive

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functionalities prior to C−C bond formation. Transition-metal-catalyzed cross-coupling reactions are among the most important methods published to allow for direct C−H functionalization of pyrroles.[7]

Despite significant progress in this area, *C*-arylation of unactivated free NH-pyrroles with haloarenes remains an unsolved problem. Free pyrroles are unreactive under known arylation conditions, yielding little or no C-arylated products. One approach relies on arylation of pyrrolyl salts which was first reported by Filippini and later improved by Sadighi.[8]

The use of such salts produces a metallic salt as waste. Furthermore, it suffers from considerable moisture sensitivity and limited functional group scope. Alternative procedures include two examples of phosphine-free palladium-catalyzed 5-arylation of 2-substituted pyrroles[9] and an example of rhodium-catalyzed direct C-arylation of free NH-pyrrole[10] in the presence of a mild base. The major drawbacks of these methods were low yields of the pre-activated arylated pyrroles and no system tolerance with hindered substrates, respectively. Sanford also applied her recently disclosed arylation procedure to both protected and nonprotected pyrroles by the use of a noncommercially available I^{III} arylating agent in which C-2 arylation occurred selectively in moderate yields.[11] One might therefore expect that general and versatile synthetic methods for direct C-2 arylation of unactivated free NH-pyrroles would find significant utility in organic synthesis.

As part of our continuing efforts in C−H bond functionalization of nitrogen-containing heterocycles,[12] herein we set out to explore a cost-effective and atom-economical regioselective C-2 arylation of free pyrroles. This protocol takes advantage of the regioselectivity for pyrrole C-2 functionalization in the presence of unprotected N−H functionality, compatibility with sterically encumbered iodoarenes, and readily available triethanolamine as base, ligand, and preferred solvent.

To test the feasibility of this reaction, we directed our efforts toward the phosphane-free palladium-catalyzed direct arylation reactions. To this end, iodobenzene **6** and 1*H*-pyrrole were initially treated with $Pd(OAc)_2$ (5 mol %) in triethanolamine (TEA) (unoptimized conditions) which was recently established as an efficient and reusable medium for palladium-catalyzed Heck reactions.[13] To our delight, compound **7** was obtained as a single product in 24% yield. Next, the screening reactions were performed with respect to palladium sources including $Pd(OAc)_2$, $PdCl_2$, $Pd(dba)_2$, and $Pd(OH)_2/C$ which revealed that the last one is superior to other choices. While the yield was further improved by increasing the amount of the catalyst to 10 mol %, a further increase in its amount did not improve the yield beyond that observed with 10 mol %. A substrate ratio screen showed that 1:3 pyrrole/iodoarene ratio was the best. An additional increase of the iodoarene amount had no effect on the yield of the reaction. Subsequent optimization of other reaction parameters, notably, substrate concentration, reaction time, and temperature led to an efficient and selective catalytic system. We were delighted to see that under the optimized reaction conditions iodoarene **6** (3 equiv), $Pd(OH)_2/C$ (10 mol %), in triethanolamine (0.2 M) at 100 °C in a sealed tube for 24 h, the product of the cross-coupling reaction, 2-arylpyrrole **7**, was obtained in 80% yield with excellent regioselectivity (Table 1, entry 1). We next studied the scope and limitations of the phosphane-free regioselective cross-coupling procedure with various substituted iodoarenes (Table 1). The results showed that various electron-withdrawing and electron-donating substituents were tolerated under the optimized reaction conditions. The reactivity of aryl halides was enhanced by the presence of electron-withdrawing substituents. As a decomposition of the product occurred via the purification course, iodobenzene **8** furnished 2-phenylpyrrole **9** in only 56% yield under the standard reaction conditions (Table 1, entry 2). Sterically demanding iodoarenes **10**, **12**, and **14** resulted in the corresponding C-2 arylated pyrroles **11**, **13**, and **15** in moderate to good yields (Table 1, entries 3−5). Even less activated 2-fluoroiodobenzene led to the corresponding product **17** in moderate yield (Table 1, entry 6). Iodoarenes bearing *o*- and *p*-trifluoromethyl and nitro substituents **18** and **20** furnished the desired products **19** and **21** in low and moderate yields, respectively (Table 1, entries 7 and 8). The inferior reactivity of these iodoarenes was as a result of a relatively important amount of biphenyl byproduct formation during the course of the reaction. The reactivity of *o*-methoxy-substituted aryl iodide was also explored. Under the optimized reaction conditions, the 2-arylated pyrrole **23** was obtained, albeit in low yield (Table 1, entry 9). Arylpalladium species with the palladium ortho to a methoxy group can undergo C−H activation with the methoxy C−H bond to form a stable five-membered palladacycle[14] and result in several byproducts. On the other hand, a moderate yield of 46% of **25** was obtained using 4-iodobenzonitrile as a result of significant competing homocoupling reaction and formation of a larg amount of biphenyl-4,4′-dicarbonitrile (Table 1, entry 10).

Furthermore, we performed a gram-scale experiment employing 2.5 mol % of $Pd(OH)_2/C$ which offered 2-arylpyrrole 21 in 39% yield (Table 1, entry 8).

We next investigated the scope of the reaction using N-protected pyrroles. In this regard, para-substituted electron-rich and -deficient aryl iodides were reacted with 1-methylpyrrole. While with *p*-methoxy-substituted iodoarene **26** C-2-arylated product **27** was obtained in 48% yield, inferior reactivity was associated with electron-deficient aryl iodides **6** and **20** (Table 2, entries 1−3).

Finally, we turned our attention to the synthesis of 1,2-diaryl-1*H*-pyrroles of type **5** which have been also identified as COX-2 inhibitors.[5] Accordingly, 1-iodonaphthalene **14** was reacted with 1-phenylpyrrole. Under the standard

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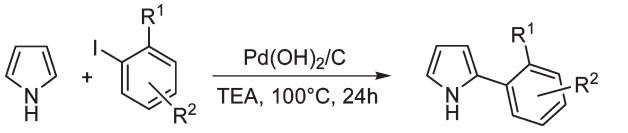
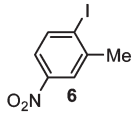
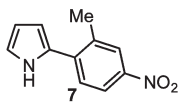
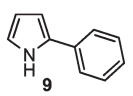
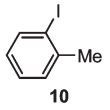
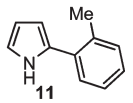
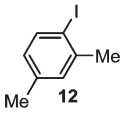
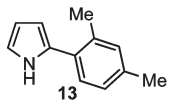
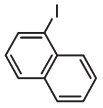
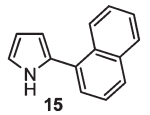
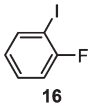
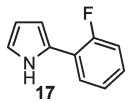
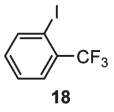
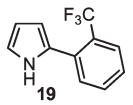
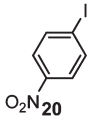
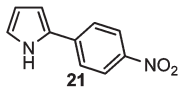
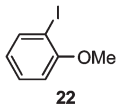
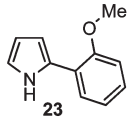
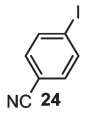
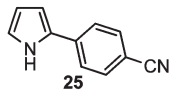
TABLE 1. Scope of the Regioselective Direct C-2 Arylation of Free NH-Pyrroles[a]

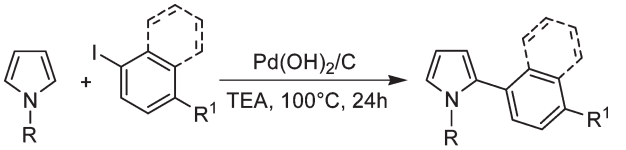


entry	Aryl iodide	product	yield (%)
1	 **6**	 **7**	80
2	 **8**	 **9**	56[b]
3	 **10**	 **11**	60
4	 **12**	 **13**	58
5	 **14**	 **15**	70
6	 **16**	 **17**	43
7	 **18**	 **19**	36
8	 **20**	 **21**	55 39[c]
9	 **22**	 **23**	27[d]
10	 **24**	 **25**	46

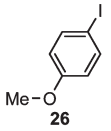
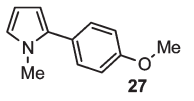
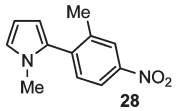
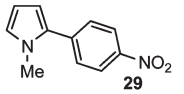
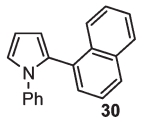
[a]All reactions were run under the following conditions: pyrrole (0.20 mmol, 1 equiv), iodoarene (0.60 mmol, 3 equiv), and $Pd(OH)_2/C$ (10 mol %) in triethanolamine (0.2 M) were heated in a sealed tube at 100 °C for 24 h. [b]Due to decomposition of the product via purification, a rough yield is reported. [c]Pyrrole (0.015 mol, 1.0 g) and $Pd(OH)_2/C$ (2.5 mol %) in triethanolamine (0.2 M) were heated at 100 °C for 48 h. [d]As the product was contaminated by an uncharacterized impurity, an approximate yield is given.

reaction conditions, the corresponding C-2 arylated pyrrole **30** was obtained in 22% yield, presumably due to steric hindrance between adjacent naphthyl and phenyl substituents (Table 2, entry 3).

TABLE 2. Scope of the Regioselective Direct C-2 Arylation of N-Protected Pyrroles[a]



R = Me, Ph

entry	R	Aryl iodide	product	yield (%)
1	Me	 **26**	 **27**	48
2	Me	**6**	 **28**	32
3	Me	**20**	 **29**	30
4	Ph	**14**	 **30**	22

[a]All reactions were run under the optimized reaction conditions.

In summary, we have developed an atom economical and straightforward approach to palladium-catalyzed regioselective direct C-2 arylation of free pyrroles using readily accessible starting materials. The iodoarenes can be widely varied according to their electronic and steric effects, which makes the method versatile for the preparation of these biologically interesting structural motifs, not easily accessible by conventional cross-coupling methods. By establishing phosphane-free conditions, this transformation displayed low moisture sensitivity, which should provide a valuable starting point in sp^2 C−H activation of heteroarenes. Expansion of the derived methodology for direct arylation of other cross-coupling partners is under investigation.

Experimental Section

General Procedure for C-2 Arylation of Pyrroles. A vial equipped with a stir bar was charged with pyrrole (0.200 mmol, 1.0 equiv), aryl iodide (0.6 mmol, 3.0 equiv), and $Pd(OH)_2/C$ (10 mol %). Triethanolamine (0.2 M) was then added, and the vial was capped. The resulting mixture was heated in an oil bath at 100 °C for 24 h, cooled, and then filtered through a short plug of silica. Removal of the solvent gave a crude mixture which was purified by flash column chromatography (hexanes/EtOAc gradient).

2-(2-Methyl-4-nitrophenyl)-1*H*-pyrrole (7). Following the general procedure for the direct C-2 arylation of pyrroles, 5-nitro-2-iodotoluene **6** (158.0 mg, 0.600 mmol) and 1*H*-pyrrole (13.5 mg, 0.200 mmol) were reacted at 100 °C for 24 h. The crude mixture was purified by flash column chromatography on silica gel (EtOAc/hexane, 10%) to afford **7** as a yellowish solid (33 mg,

80%): mp 118−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (s, 3H), 6.38−6.40 (m, 1H), 6.56−6.57 (m, 1H), 6.99−7.00 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 8.08 (dd, J = 8.5, 2.5 Hz, 1H), 8.13 (d, J = 2.5, 1H), 8.5 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 110.7, 112.0, 120.7, 121.8, 126.7, 127.8, 129.6, 136.0, 139.2, 146.0; IR (KBr) 1093, 1324, 1492, 2922, 3378 cm^{-1}; MS m/z 202 ($M^{\bullet+}$, 100), 172 (13), 154 (23), 141 (13), 128 (24). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.51; H, 5.09; N, 13.94.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.