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Facile synthesis of 3-arylpyrroles by tandem Suzuki–dehydrogenation reaction

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Abstract

Facile method for the synthesis of 3-arylpyrroles is described based on the palladium-catalyzed coupling of trifluoromethanesulfonic acid 1-benzyl-2,5-dihydro-1*H*-pyrrol-3-yl ester with aryl halides. © 2000 Elsevier Science Ltd. All rights reserved.

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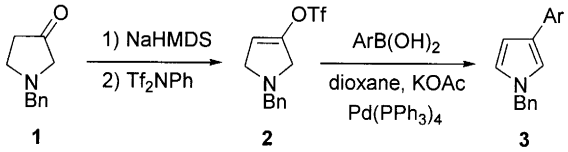
The introduction of substituents into the 3-position of pyrrole has been actively pursued in recent years due to the importance of this class of compound in natural product synthesis.[1] In contrast to the significant number of preparations of polysubstituted 3-arylpyrroles,[2] there are relatively few syntheses of simple 3-arylpyrroles. A literature survey on the preparation of 3-arylpyrrole showed that some of the methods reported involve the reductive cyclization of 2-arylsuccinonitriles,[3] the base-induced ring closure of arylvinamidinium salts,[4] and rhodium-catalyzed hydroformylation of β-alkynylamines with CO/H_2.[5]

We now report that reaction of trifluoromethanesulfonic acid 1-benzyl-2,5-dihydro-1*H*-pyrrol-3-yl ester (**2**) with aryl halides in the presence of palladium-catalyzed leads to the formation of 3-arylpyrroles (**3**) in good yields (see Scheme 1 and Table 1).



Scheme 1.

The synthesis was carried out using commercially available 1-benzyl-3-pyrrolidinone (**1**) as the starting material. Vinyl triflate (**2**)[6] could be prepared in 55% yield from 1-benzyl-3-pyrrolidinone

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Table 1
Tandem Suzuki–dehydrogenation reaction

entry	boronic acid	product (3)[a,b]	yield [c]
1	4-fluorophenylboronic acid	**3a**	69 %
2	4-methoxyphenylboronic acid	**3b**	65 %
3	3-nitrophenylboronic acid	**3c**	73 %
4	1-naphthaleneboronic acid	**3d**	74 %
5	2-furanboronic acid	**3e**	66 %

[a] Reaction was conducted for overnight by using vinyl triflate **2** (0.3 mmol), boronic acid (1.1 eq), $Pd(PPh_3)_4$ (3 mol %), KOAc (3 eq) and dioxane (5 mL). [b] All compounds were characterized by FAB-MS, ^1H-NMR, and ^{13}C-NMR. [c] These isolated yields are not optimized.

(**1**) by trapping the enolate with a triflating reagent, *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh).[7] The regiochemistry of enolization of α-amino ketone has been investigated by A. R. Martin et al.[8] In accordance with his result, when the *N*-substituents are electron-donating groups (methyl, benzyl), only allylamine-type isomers were detected, and if the substituents are electron-withdrawing groups (Cbz, Boc), the enamine-type isomers were exclusively observed. As expected, the reaction took place in such a manner that it gives exclusively allylamine-type triflate (**2**) rather than enamine-type isomer, determined by NOE experiments. We have treated the vinyl triflate (**2**) with boronic acid derivatives in the presence of a catalytic amount of $Pd(PPh_3)_4$ and KOAc in dioxane at 100°C.[9] The reaction mixture provided a compound, which was isolated and characterized to be 3-arylpyrroles. Apparently, after Suzuki coupling, subsequent dehydrogenation was occurred providing 3-arylpyrroles. In general, dehydrogenative aromatizations can be achieved by heating (300~350°C) hydroaromatic compounds with catalytic amounts of palladium on activated carbon.[10] In our reaction, under the Suzuki coupling condition, the dehydrogenative aromatization[11] of the pyrroline (**2**) took place in tandem mode. This could be the first example of tandem Suzuki–dehydrogenation reaction to prepare 3-arylpyrroles from pyrroline.

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7. *Preparation of vinyl triflate* (**2**)*:* To a stirred solution of 1-benzyl-3-pyrrolidinone (**1**) in anhydrous THF under nitrogen at −78°C was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF) dropwise. After stirring at −78°C for 1 h, a solution of *N*-phenyltrifluoromethanesulfonimide in anhydrous THF was quickly added to the mixture. After agitating at −78°C for 10 min, the slurry was warmed slowly to 0°C and stirred at 0°C for 3 h. The solvent was removed, and the crude

residue was taken up in CH_2Cl_2 and washed with water. Drying and evaporation of the organic extracts gave an oil, which was purified by flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 4H), 3.82 (s, 2H), 5.69 (s, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 56.5, 60.2, 113.9, 118.5 (d, *J*=318.9 Hz), 127.4, 128.52, 128.54, 137.9, 145.1.

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9. *Preparation of 3-arylpyrroles* (***3***): A mixture of vinyl triflate, boronic acid, $Pd(PPh_3)_4$ and KOAc in dioxane was heated to 100°C overnight. The product was extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Isolation by flash chromatography gave following compounds. *Representative data for the selected compound* (***3a***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (s, 2H), 6.46 (m, 1H), 6.73 (m, 1H), 6.94 (m, 1H), 7.00–7.49 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 106.9, 115.8 (d, *J*=21.2 Hz), 118.1, 122.8, 124.7, 126.8 (d, *J*=7.7 Hz), 127.5, 128.4, 129.2, 132.4 (d, *J*=3.2 Hz), 138.2, 161.5 (d, *J*=242.0 Hz); FAB-MS *m/z* 252.0 ($[M+H]^+$, calcd 252.3).
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