Palladium-Catalyzed Direct Arylation for the Synthesis of Indeno[2,1-*b*]-pyrrol-8-ones

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Abstract: Treatment of 2-bromophenyl (*N*-tosylpyrrol-2′-yl)-ketones with $Pd(OAc)_2$, Ph_3P, and K_2CO_3 resulted in the formation of indeno[2,1-*b*]pyrrol-8-ones in moderate to good yields.

Key words: direct arylation, palladium catalyst, acylation, indeno[2,1-*b*]pyrrol-8-one, pyrroles

Transition-metal-catalyzed direct arylation (C–H activation)[1] is an attractive alternative to the classical cross-coupling reactions (e.g., Suzuki–Miyaura,[2] Negishi,[3] Stille,[4] Kumada,[5] Hiyama[6]).

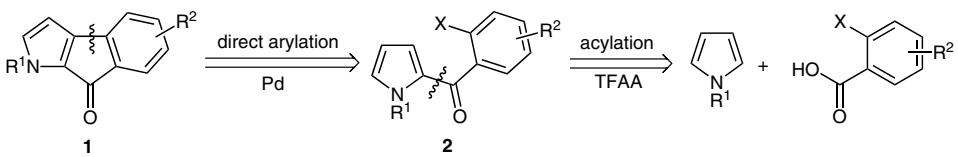
The intramolecular direct arylation reactions have been utilized to construct a series of fluorenone analogues,[7] a class of compounds with important biological activities and also useful synthetic intermediates.[8] Surprisingly, such reactions involving a pyrrole moiety remain unexplored, probably because an efficient strategy to prepare the required precursors is not available yet. Previously, one of us had developed a TFAA-mediated regioselective acylation of *N*-tosylpyrroles using carboxylic acids as acylating agents.[9] Adapting this methodology to 2-halobenzoic acids, we would then be able to develop a simple sequence to indeno[2,1-*b*]pyrrol-8-ones **1** following intramolecular direct arylation reactions of 2-halophenyl pyrrolylketones **2** (Scheme 1).

Initial studies started with acylation of *N*-tosylpyrrole with 2-bromobenzoic acid. Unfortunately, the desired acylation product **2a** (Table 1) was not obtained after refluxing a mixture of *N*-tosylpyrrole, 2-bromobenzoic acid, and TFAA in DCE for 24 hours. Since it was believed that the mechanism for the acylation reaction involved the formation of mixed anhydride,[9] we reasoned that it should be facilitated by the addition of Lewis acids. Indeed, addition of $Sc(OTf)_3$ to the reaction system showed promising results. The reaction was complete within 0.5 hours, and **2a** was obtained in 30% isolated yield. However, the regioselectivity was poor. A substantial amount (12%) of the 3-acylation product was also isolated. Other Lewis acids ($AlCl_3$, $TiCl_4$, BBr_3, CuBr, $SnCl_2$, $FeCl_3$) were then evaluated. Among these, $FeCl_3$ was found to be the most suitable both in terms of productivity and regioselectivity. The desired product **2a** could be isolated in 78% yield, together with a small amount (3%) of the 3-acylation product.

With **2a** in hand, we then carried out the direct arylation reaction. The reaction proceeded slowly in acetonitrile when $Pd(OAc)_2$ was used as catalyst and gave a variety of products upon completion. Addition of Ag_2CO_3 to the reaction system, or using other palladium catalysts such as $Pd(PPh_3)_2Cl_2$ or $Pd_2(dba)_3$, under a variety of conditions all failed to deliver the desired product in acceptable yield. After some optimization, we were delighted to find out that with our initially applied $Pd(OAc)_2$ as catalyst, Ph_3P as ligand, and K_2CO_3 as base, the reaction proceeded smoothly in DMF and gave the detosylated direct arylation product **1a**[10] in 78% isolated yield.

After establishing the reaction conditions, palladium-catalyzed direct arylation of other 2-bromophenyl (*N*-tosylpyrrol-2′-yl)ketones were examined, and the results are collected in Table 1. The desired indeno[2,1-*b*]pyrrol-8-ones could be obtained in moderate to good isolated yields for substrates with sterically hindered (Table 1, entry 2), electron-donating (Table 1, entry 3), or electron-withdrawing substituents (Table 1, entry 4) on the phenyl ring. Under these conditions, direct arylation of substrates with a 5′-arylpyrrolyl moiety (Table 1, entries 5–7) also worked well.

Finally, we tested the palladium-catalyzed direct arylation of 2-bromophenyl pyrrol-2′-ylketone (**3**) (Scheme 2). However, indeno[2,1-*b*]pyrrol-8-one **1a** was not evident



1 2

Scheme 1 Retrosynthetic analysis of indeno[2,1-*b*]pyrrol-8-ones

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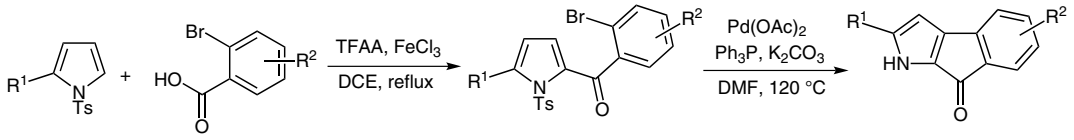
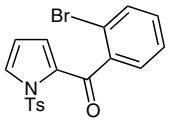
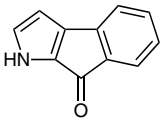
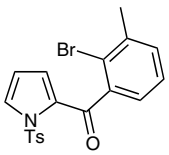
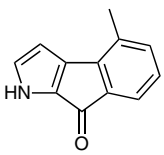
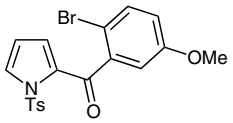
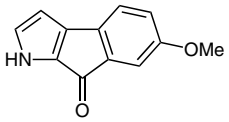
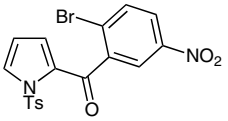
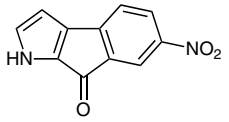
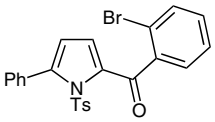
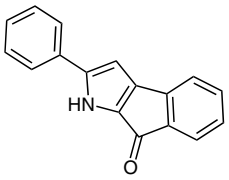
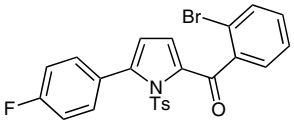
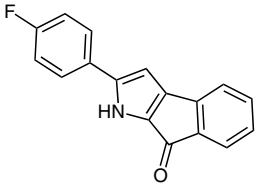
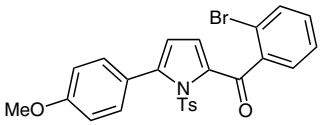
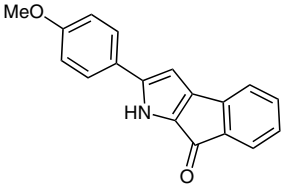
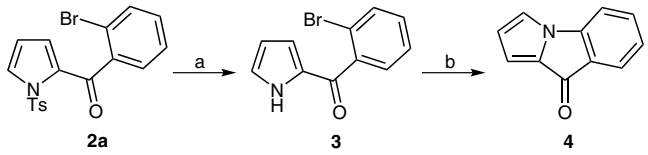
on TLC. After completion of reaction (8.5 h), a major product was isolated, the structure of which was proved to be 9*H*-pyrrolo[1,2-*a*]indol-9-one (**4**),[11] obviously resulting from palladium-catalyzed intramolecular C–N bond formation. This indicated that protection of the pyrrolyl nitrogen was necessary for an efficient direct arylation reaction.

Table 1 Synthesis of Indeno[2,1-*b*]pyrrol-8-ones



Entry	Substrate	Product	Isolated yield (%)
1	 **2a**	 **1a**	78
2	 **2b**	 **1b**	77
3	 **2c**	 **1c**	55
4	 **2d**	 **1d**	54
5	 **2e**	 **1e**	47
6	 **2f**	 **1f**	63
7	 **2g**	 **1g**	47



Scheme 2 *Reagents and conditions*: a) KOH, THF–H_2O, reflux, 12 h, 95%; b) $Pd(OAc)_2$, Ph_3P, K_2CO_3, DMF, 120 °C, 8.5 h, 70%.

Compound **4** is the key precursor to the cytostatic mitomucin family,[8a] and its analogues have shown a broad spectrum of biological activities.[8f,12] Although a number of methodologies for the synthesis of analogues of **4** have been developed,[11,13] those involving a direct arylation reaction are rare.[7d,e] Therefore, our findings may provide a new entry to these polycyclic systems.

In summary, we have developed a novel approach to indeno[2,1-*b*]pyrrol-8-ones through palladium-catalyzed direct arylation reactions of 2-bromophenyl (*N*-tosylpyrrol-2′-yl)ketones. We assumed that the mechanism followed a direct arylation–in situ detosylation, rather than a detosylation–direct arylation reaction sequence. If detosylation was first carried out on the substrates, palladium-catalyzed C–N bond formation of the resulting 2-bromophenyl pyrrol-2′-ylketones would then lead to the formation of the isomeric 9*H*-pyrrolo[1,2-*a*]indol-9-ones. These investigations are currently under way.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) A mixture of **2a** (210 mg, 0.52 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Ph_3P (26 mg 0.10 mmol), and K_2CO_3 (216 mg, 1.56 mmol) in anhyd DMF (11 mL) under N_2 was heated to 120 °C for 9 h and cooled. The mixture was partitioned between EtOAc (60 mL) and H_2O (100 mL). The separated aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography on silica gel (35% EtOAc in PE) to give **1a** (68 mg, 78%) as a red solid; mp 205–206 °C. IR: ν_{max} = 3222, 1690, 1632, 1607, 1509, 1450, 1357, 1319, 1272, 1098 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 6.19 (1 H, m), 6.99–7.27 (5 H m), 12.00 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 103.8, 119.0, 122.6, 126.9, 131.2, 131.7, 133.2, 138.0, 139.1, 142.9, 180.0. ESI-MS: *m/z* (%) = 192 (100) $[M + Na]^+$, 170 (53) $[M + H]^+$. HRMS: *m/z* calcd for $C_{11}H_7NNaO$: 192.0425; found: 192.0416 $[M + Na]^+$.
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