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Palladium-Catalyzed Cyanation of Hindered, Electron-Rich Aryl Triflates by Zinc Cyanide

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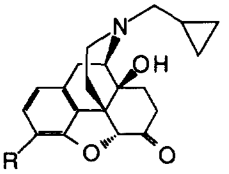
Abstract: We examined the palladium-catalyzed cyanation of hindered, electron-rich aryl triflates by zinc cyanide using 2-methoxyphenyl trifluoromethanesulfonate (**4**) as a model compound. The reaction with two equivalents of $Zn(CN)_2$ and catalytic $Pd(PPh_3)_4$ in DMF at 120°C for 2 hr afforded 2-methoxybenzonitrile (**5**) in 81% yield. The synthesis of 3-cyano-3-desoxynaltrexone (**3**), which had not previouly been obtained by the reaction with potassium or sodium cyanide as a cyanide source, was achieved by applying this procedure to its corresponding triflate **2**. Published by Elsevier Science Ltd.

In the course of our studies on design and synthesis of new, highly selective ligands for opioid receptors, we became interested in 3-cyano-3-desoxynaltrexone (**3**). We have previously synthesized 3-alkyl or aryl substituted 3-desoxynaltrexone by palladium-catalyzed cross-coupling reaction using triflate **2**, which was easily obtained from naltrexone (**1**), as a key intermediate.[1] There are several reports in the literature that describe the formation of aryl cyanides from aryl triflates by the reaction with potassium or sodium cyanide under catalysis by palladium[2-5] or nickel.[2,6-9] We tried these reaction conditions for the synthesis of **3** unsuccessfully. In most cases, the reactions afforded unreacted starting material **2** and/or the phenolic compound (*i.e.* naltrexone (**1**)). The latter is thought to be obtained as a result of sulfur-oxygen bond cleavage *via* nucleophilic attack on the sulfur atom by free cyanide ions.[10,11] It is also reported that high concentrations of cyanide ions are detrimental to the catalytic cycle.[12] Recently, Tschaen *et al.*[13] reported the palladium-catalyzed cyanation of aryl bromides using zinc cyanide, which has a low solubility and higher



1 : R = OH
2 : R = OTf
3 : R = CN

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covalent nature relative to sodium and potassium cyanide, and Selnick *et al.*[14] applied this procedure to the triflate in the course of their synthesis of 6-cyano-1,2,3,4-tetrahydroisoquinoline. These reports prompted us to study this system in detail and apply it to triflate **2**.

As it is well known that sterically hindered, electron-rich aryl triflates are reluctant to undergo palladium-catalyzed reactions,[15] we decided to examine the reaction conditions using 2-methoxyphenyl trifluoromethanesulfonate (**4**) as a model triflate compound. The compound **4** was easily obtained from guaiacol according to the literature.[16]

First, we employed the reported conditions,[14] tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (4 mol %) / $Zn(CN)_2$ (0.7 eq.) / DMF / 80°C, for the cyanation of **4** (Table 1, entry 1). Although it has been reported that 0.6-0.7 equivalents of $Zn(CN)_2$ is sufficient for the complete cyanation of aryl bromides or triflates,[13,14] the yield of our target compound, 2-methoxybenzonitrile (**5**),[17] was low with recovery of significant amounts of unreacted **4** even after prolonged reaction times.

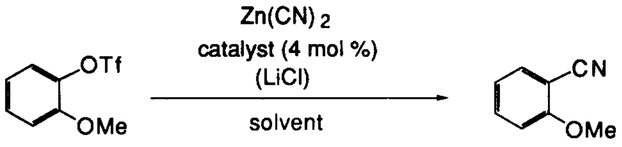
On the other hand, we found the use of two equivalents of $Zn(CN)_2$ enabled nearly complete consumption of the aryl triflate affording **5** in 78% yield (entry 2). Moreover, although the reaction at low temperature did not proceed even with additional amounts of palladium catalyst and reagent (entry 3), it proceeded cleanly by heating the reaction mixture to 120°C. This afforded **5** in 81% yield with a much shorter reaction time (entry 4). The addition of LiCl did not change the course of the reaction dramatically however it showed a slightly advantageous effect (entry 5 and 6). Further, we examined the reaction with several reaction solvents. *N*-Methyl-2-pyrrolidinone (NMP) was less effective (entry 9), and acetonitrile and dioxane were unsuccessful (entry 7 and 8). These results obviously showed that DMF is the most suitable solvent for the reaction. The catalysts were also examined, but neither bis(triphenylphosphine)palladium(II) chloride ($Pd(PPh_3)_2Cl_2$) nor palladium(II) acetate ($Pd(OAc)_2$) gave any of the desired product (entry 10-12) indicating $Pd(PPh_3)_4$ is essential for this cyanation reaction system.

Finally, we turned to the synthesis of the original target, 3-cyano-3-desoxynaltrexone (**3**). Although the addition of LiCl was deleterious to the formation of **3** in this case, **3** was obtained by treatment of **2** with two equivalents of $Zn(CN)_2$ and catalytic $Pd(PPh_3)_4$ in DMF at 120°C in moderate yield (eq 1).[18]

$$\mathbf{2} \xrightarrow[\substack{\text{DMF / 120°C / 9 hr} \\ 39\%}]{\text{Pd(PPh}_3\text{)}_4\text{ (4 mol \%) / Zn(CN)}_2\text{ (2 eq.)}} \mathbf{3} \qquad (1)$$

In conclusion, we examined the palladium-catalyzed cyanation of aryl triflates using zinc cyanide as a cyanide source. The results demonstrated that this system is effective for the cyanation of hindered, electron-rich aryl triflates. The synthesis of 3-cyano-3-desoxynaltrexone, which had not previouly been obtained by the reaction with potassium or sodium cyanide, was achieved by applying this procedure to its triflate precursor.

Table 1. Palladium-Catalyzed Cyanation of **4** with Zinc Cyanide



4 **5**

entry[a]	conditions					yield (%)[b]	
	catalyst	solvent	$Zn(CN)_2$ (eq.)	temp. (°C)	time (hr)	**5**	recovered **4**
1	$Pd(PPh_3)_4$	DMF	0.7	80	40	34	32
2	$Pd(PPh_3)_4$	DMF	2.0	80	15	78	4
3 [c]	$Pd(PPh_3)_4$ [d]	DMF	3.0	50	48	—[e]	85
4	$Pd(PPh_3)_4$	DMF	2.0	120	2	81	—[e]
5 [c]	$Pd(PPh_3)_4$	DMF	2.0	80	24	80	—[e]
6 [c]	$Pd(PPh_3)_4$	DMF	2.0	120	2	83	—[e]
7	$Pd(PPh_3)_4$	acetonitrile	2.0	80	24	—[e]	76
8	$Pd(PPh_3)_4$	dioxane	2.0	80	24	—[e]	81
9	$Pd(PPh_3)_4$	NMP	2.0	80	24	26	35
10	$Pd(PPh_3)_2Cl_2$	DMF	2.0	80	24	—[e]	89
11 [c]	$Pd(PPh_3)_2Cl_2$	DMF	2.0	80	24	—[e]	73
12	$Pd(OAc)_2$	DMF	2.0	80	24	—[e]	94

[a] Carried out in the same manner as described in the text, unless otherwise stated. [b] Isolated yield. [c] Reaction run in the presence of 3 equiv of LiCl. [d] 10 mol % of catalyst was used. [e] Not detected by TLC.

A typical procedure is as follows: To the mixture of **4** (400 mg, 1.6 mmol) and zinc cyanide (367 mg, 3.1 mmol) in deoxygenated dry DMF (2 ml) was added tetrakis(triphenylphosphine)palladium(0) (72 mg, 0.06 mmol). The mixture was then stirred at 120°C under an argon atmosphere for 2 hr. After cooling, the reaction mixture was partitioned between saturated sodium bicarbonate and EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with hexane-EtOAc (15:1) as an eluent to give 168 mg (81%) of 5.

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18. **3**: mp 211-213°C (EtOAc); $[\alpha]^{20}_{D}$ -209 (*c* 0.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.12-0.22 (2H, m), 0.55-0.63 (2H, m), 0.88 (1H, m), 1.48-1.63 (2H, m), 1.88-2.12 (2H, m), 2.30-2.53 (4H, m), 2.65 (1H, dd, *J* = 19.5, 5.7 Hz), 2.75 (1H, m), 2.99-3.18 (2H, m), 3.25 (1H, d, *J* = 5.7 Hz), 4.84 (1H, s), 6.78 (1H, d, *J* = 7.8 Hz), 7.30 (1H, d, *J* = 7.8 Hz); IR ($CHCl_3$) 3685, 2401 cm^{-1}; EIMS m/z 350 (M^+), 55 (base). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.74; H, 6.35; N, 7.93.