Efficient C−H Activation of the Methoxy Group of Anisole by a $Pd(OAc)_2/Sn(OAc)_2$ Catalyst System

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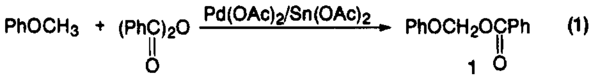
Many examples of the activation of aromatic and aliphatic C−H bonds by transition-metal complexes have appeared over the past few years, offering attractive new routes to organometallic species.[1] Dyker[2] has reported coupling reactions based on palladium-catalyzed C−H activation at a methoxy group, but little other information is available on catalytic C−H activation at heteroalkyl groups. In the course of our study of carboxylation of aromatic compounds, we examined benzoxylation of the methoxy group of anisole. As a result, we succeeded in the benzoxylation of anisole to phenoxymethyl benzoate (**1**) by using a $Pd(OAc)_2/Sn(OAc)_2$ catalyst (eq 1).

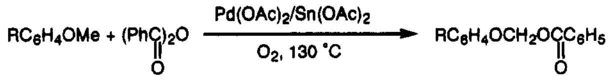


$$\mathrm{PhOCH_3} + (\mathrm{Ph}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}})_2\mathrm{O} \xrightarrow{\mathrm{Pd(OAc)_2/Sn(OAc)_2}} \underset{\mathbf{1}}{\mathrm{PhOCH_2O}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{Ph}} \qquad (1)$$

When $Pd(OAc)_2$ alone was used as a catalyst for the reaction of anisole with benzoic anhydride under an oxygen atmosphere, only a trace amount of **1** was formed. several cocatalysts were examined and $Sn(OAc)_2$ was found to effect a dramatic increase in the yield of **1**. This reaction proceeded with high regioselectivity, and no ring benzoxylation products were obtained. In the absence of oxygen (under argon or CO atmosphere) or $Pd(OAc)_2$, this reaction does not occur; only starting materials were recovered.

Next, we investigated the application of this benzoxylation reaction with a variety of anisole derivatives and these results are listed in Table 1. *p*-Chloroanisole and *p*-dimethoxybenzene reacted with benzoic anhydride to give the corresponding esters **2** and **3** in good yield without formation of ring benzoxylation products. In particular, *p*-dimethoxybenzene gave monobenzoxylation product **3** with very high selectivity. A complex mixture was obtained using *p*-nitrobenzene, and the products were not identified.

Table 1.[a] **Benzoxylation of Anisole and Anisole Derivatives with $Pd(OAc)_2$**



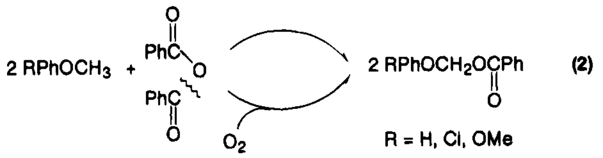
$$\mathrm{RC_6H_4OMe} + (\mathrm{Ph}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}})_2\mathrm{O} \xrightarrow[\mathrm{O_2,\ 130\ ^\circ C}]{\mathrm{Pd(OAc)_2/Sn(OAc)_2}} \mathrm{RC_6H_4OCH_2O}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{C_6H_5}$$

run	R	product	time, h	yield,[b,c] %	turnover number[d]
1	H	**1**	120	108.0	33.8
2	Cl	**2**	312	158.7 (126.3)[e]	49.6
3	OMe	**3**	120	190.5 (151.0)	59.5
4	NO_2	many unidentified products	170	−	−

[a] All experiments were carried out in solution of 25 mmol of anisole derivatives, 0.16 mmol of $Pd(OAc)_2$, 0.6 mmol of $Sn(OAc)_2$, and 5 mmol of benzoic anhydride under oxygen atmosphere at 130 °C. [b] Based on the amount of benzoic anhydride. [c] Yields were determined by GLC. [d] Based on the amount of $Pd(OAc)_2$. [e] Values in parentheses are isolated yields.

When *p*-methylanisole was treated under similar reaction conditions, monobenzoxylation occurred at the methyl or the methoxy group and contrary to our expectation ester **5** was obtained in higher yield than **4**. We investigated reaction conditions in order to bring about selective benzoxylation at the methoxy group of *p*-methylanisole. We found that the addition of KOAc and a reaction temperature of 100 °C could depress the benzoxylation at the methyl group. Inspection of the conditions reveals that $Pd(OAc)_2/Sn(OAc)_2$/KOAc/*p*-methylanisole = 0.16/0.6/0.5/25 (molar ratio) was the best choice for increasing the yield of **4**. Addition of a larger amount of KOAc decreased both the product yield and the regioselectivity. At 100 °C, in the absence of KOAc, the ester **5** was obtained as a major product, but at 130 °C, **5** was the major product regardless of the presence or absence of KOAc.

It is worth noting that the corresponding esters were obtained in more than 100% yield based on the amount of benzoic anhydride used. In reactions such as Friedel−Crafts acylation with anhydrides, the anhydride produces an acyl group and a carboxyl group. The yields obtained in the present work suggest that oxygen may be incorporated to produce 2 mol of benzoxyl group from 1 mol of benzoic anhydride (eq 2). Consumption of oxygen was observed in these reactions.



We have found that some aliphatic anhydrides also react with anisole. Under 20 atm of oxygen, *n*-hexanoic anhydride[3] and pivalic anhydride gave the corresponding esters in low yield (<5%)[4] without any other byproducts. In contrast to these results, under 1 atm, many unidentified products were obtained.

Further studies on the application of these reactions to organic synthesis and the elucidation of the reaction mechanism are in progress.

Experimental Section

General. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 60 or 400 MHz. Peak positions are reported in parts per million relative to tetramethylsilane internal standard. Spectra which were recorded with off-resonance decoupling have peaks reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Infrared spectra were recorded as a Nujol (for solid) or liquid film (for liquid). Gas chromatography was performed on a capillary column (CBP 1-W12-100, 0.53 mm i.d. × 12 m) using helium as carrier gas.

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[2] Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 977. Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426. Dyker, G. *Chem. Ber.* **1994**, *127*, 739.

[3] $Pd(PPh_3)_4$ was used instead of $Pd(OAc)_2$ as a catalyst.

[4] Isolated yield. Based on the amount of anhydride.

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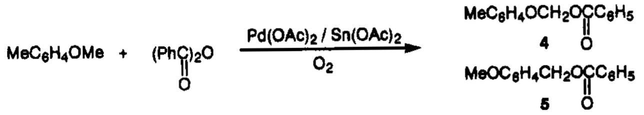
Table 2.[a] **Benzoxylation of *p*-Methylanisole with $Pd(OAc)_2$**



$$MeC_6H_4OMe + (PhC(=O))_2O \xrightarrow[O_2]{Pd(OAc)_2 / Sn(OAc)_2} \underset{\mathbf{4}}{MeC_6H_4OCH_2OC(=O)C_6H_5} + \underset{\mathbf{5}}{MeOC_6H_4CH_2OC(=O)C_6H_5}$$

run	temp, °C	KOAc, mmol	time, h	product	yield,[b,c] %	total yield,[b,c] %	**4**:**5** ratio[d]
1	100		360	**4**	56.7	177.2	3.2:6.8
				5	120.5		
2	100	0.5	336	**4**	46.4	51.6	9.0:1.0
				5	5.2		
3	100	1.0	360	**4**	29.2	37.2	7.8:2.2
				5	8.0		
4	100	2.0	288	**4**	17.5	23.9	7.3:2.7
				5	6.4		
5	100	3.0	288	**4**	8.4	14.2	6.0:4.0
				5	5.8		
6	130		96	**4**	11.7	154.7	0.8:9.2
				5	143.0		
7	130	1.0	48	**4**	9.4	30.4	3.0:7.0
				5	21.0		

[a] All experiments were carried out in solution of 25 mmol of *p*-methylanisole, 0.16 mmol of $Pd(OAc)_2$, 0.6 mmol of $Sn(OAc)_2$, 5 mmol of benzoic anhydride, and KOAc under oxygen atmosphere. [b] Based on the amount of benzoic anhydride. [c] Yields were determined by GLC. [d] Determined by GLC peak area.

All melting points are uncorrected. Column chromatography was done with E. Merck reagent silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed with E. Merck reagent silica gel 60 F-254, 0.25 mm thick.

Anisole, *p*-chloroanisole, *p*-nitroanisole, and *p*-methylanisole were dehydrated over appropriate drying agents and distilled before use. Other reagents were all comercial products and were used without further purification.

General Procedure for the Synthesis of Esters. A flask equipped with an oxygen-filled balloon was charged with $Pd(OAc)_2$ (0.035 g, 0.16 mmol), $Sn(OAc)_2$ (0.142 g, 0.6 mmol), benzoic anhydride (1.13 g, 5 mmol), and anisole (2.72 mL, 25 mmol). The reaction mixture was stirred at 130 °C for 120 h and then quenched with aqueous saturated $NaHCO_3$. After workup, the crude products were purified by silica gel column chromatography. The ester **1** thus obtained was identified by means of its spectral data (IR, NMR, MS). The yields were determined by GLC using biphenyl as an internal standard.

Phenoxymethyl Benzoate (1): ^1H NMR δ 6.75–8.25 (m, 10H), 6.01 (s, 2H); IR (liquid film) 2980, 1730, 1600, 1500, 1410, 1270, 1220, 1180, 1050, 760, 720 cm^{-1}; MS *m/z* (M^+) (rel intensity) 228 (2), 198 (7), 105 (100), 77 (56), 51 (25). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.76; H, 5.44.

(*p*-Chlorophenoxy)methyl benzoate (2): mp 50–52 °C; ^1H NMR δ 6.73–8.11 (m, 9H), 5.98 (s, 2H); IR (Nujol) 2930, 2870, 1740, 1460, 1380, 1280, 1230, 1050, 1030, 960, 840, 720 cm^{-1}; MS *m/z* (M^+) (rel intensity) 264 (0.7), 105 (100), 77 (31). Anal. Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 63.73; H, 4.10.

(*p*-Methoxyphenoxy)methyl benzoate (3): ^1H NMR δ 6.73–8.20 (m, 9H), 5.92 (s, 2H), 3.78 (s, 3H); IR (liquid film) 2950, 1720, 1600, 1500, 1460, 1270, 1210, 1090, 1040, 950, 830, 710 cm^{-1}; MS *m/z* (M^+) (rel intensity) 258 (2), 228 (8), 105 (100), 77 (34). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.88; H, 5.53.

(*p*-Methylphenoxy)methyl benzoate (4): mp 43–44 °C; ^1H NMR δ 6.85–8.30 (m, 9H), 5.98 (s, 2H), 2.30 (s, 3H); IR (Nujol) 2920, 1730, 1610, 1460, 1270, 1210, 1050, 960, 810, 720 cm^{-1}; MS *m/z* (M^+) (rel intensity) 242 (2), 105 (100), 77 (31). Anal. Calcd for $C_{15}H_{14}O_3$: C 74.36; H, 5.82. Found: C, 74.40; H, 5.87.

***p*-Methoxybenzyl benzoate (5)**: mp 31–32 °C; ^1H NMR δ 6.75–8.20 (m, 9H), 5.29 (s, 2H), 3.80 (s, 3H); IR (liquid film) 3000, 1740, 1640, 1300, 1200, 1140, 740 cm^{-1}; MS *m/z* (M^+) (rel intensity) 242 (25), 121 (100), 105 (46), 77 (52), 51 (26).