Palladium-Catalyzed Alkoxycarbonylation of Aryl *p*-Toluenesulfonate

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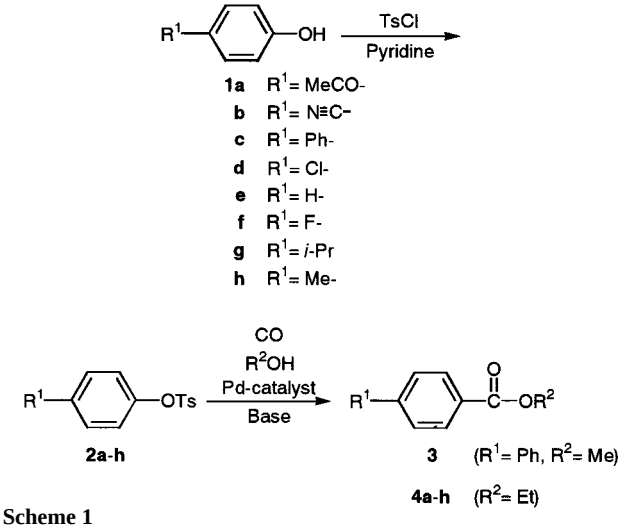
Abstract: Methyl- and ethyl arylcarboxylates were synthesized by palladium-catalyzed alkoxycarbonylation of various aryl *p*-toluenesulfonates (tosylates). Yields were highly dependent on the substituent of aryl tosylates and phosphine ligands used. Ethoxycarbonylation of 4-acetylphenyl tosylate by the use of a bisphosphine ligand gave ethyl 4-acetylbenzoate in quite satisfactory yields.

For the purpose of synthesizing aromatic polyesters (e.g., polyethyleneterephthalate type materials), it is important to investigate the synthetic route to arylcarboxylic acid esters. Carbonylation of aryl halides is one of the most useful methods not only for the preparation of various arylcarboxylate monomers but also for the direct synthesis of aromatic polyesters from dihaloaromatics and diols.[1] We have been focusing on the alkoxycarbonylation of aryl halides[2-5] and the synthesis of aromatic polyesters containing biphenyl moieties by carbonylation-polycondensation.[6,7]

Aryl alkanesulfonates are regarded as synthetic equivalents of aryl halides. For example, palladium-catalyzed alkoxycarbonylation of aryl trifluoromethanesulfonate (triflate) has been reported[8,9] and methyl arylcarboxylates have been synthesized in high yield under mild conditions. This made the direct conversion of a phenolic hydroxy into an alkoxycarbonyl group possible. However, there are very few reports on the alkoxycarbonylation of aryl *p*-toluenesulfonates (tosylates)[10] and no report on that catalyzed by palladium complex. Although tosylates are expected to be less reactive than triflates, investigation of alkoxycarbonylation of aryl tosylates will help us understand the chemistry of this type of reactions, so that the synthesis of polyesters by carbonylation-polycondensation of aryl bisalkanesulfonates will be possible. Another advantage of tosylates is that they are easier to handle than the corresponding triflates because they are more stable and readily crystallize.

We report here the successful synthesis of arylcarboxylic acid esters by the alkoxycarbonylation of aryl tosylates and also the trend of reactivity depending on substrates and reaction conditions. The general schematic of tosylate synthesis and alkoxycarbonylation of the tosylate is shown in Scheme 1.



Scheme 1

It is well documented that palladium-catalyzed alkoxycarbonylation of aryl halides[11] involves oxidative addition of substrate to a palladium(0) species, CO coordination and insertion, and base-assisted alcoholysis yielding ester product and regenerating palladium catalyst.[12] There are some works improving oxidative addition, CO insertion, and alcoholysis step in alkoxycarbonylation of aryl halides with aliphatic alcohols.[13-15]

By analogy with the known carbonylation method, we firstly examined the methoxycarbonylation of 4-biphenyl tosylate (**2c**) as a model system of polyester synthesis (Scheme 1, R^1= Ph, R^2= Me). We have already reported that when a cyclic amidine or guanidine was used for the phenoxycarbonylation of 4-bromobiphenyl, the reaction rate was drastically increased and phenyl 4-phenylbenzoate was obtained in high yields. However, in the case of the methoxycarbonylation of tosylate system the yield of methyl 4-phenylbenzoate (**3**) was low and considerable amount of 4-phenylphenol and its methyl ether were formed when these strong organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used (Table 1). This indicates that the base-mediated ester exchange of sulfonate is prone to occur in the tosylate system. When Et_3N was used as a much weaker base, ester exchange products are not formed but biphenyl was formed as a reduced product. When 1,4-diazabicyclo[2.2.2]octane (DABCO) was used, side reactions were completely suppressed and only the desired product was formed. Ester exchange was also suppressed when ethanol was used as a nucleophile (Table 2). This is ascribed to the bulkiness of the aliphatic alcohol.

Table 1. Effect of base on methoxycarbonylation of 4-biphenyl tosylate (**2c**) [a]

Base	Conv./%[b]	Yield/%[b,c]			
		Ester **3**	Ph-C_6H_4-OH-*p*	Ph-C_6H_4-OMe-*p*	Biphenyl
DBU[d]	74	23	27	9	0
DABCO[e]	13	13	0	0	0
Et_3N	50	14	0	0	10

[a] The reaction was carried out with 2.5 mmol of **2c**, 0.1 mmol of $PdCl_2$, 0.2 mmol of 1,3-bis(diphenylphosphino)propane (dppp), 2.75 mmol of the base, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of methanol at 150 °C under 10 bar of CO for 3 h.
[b] Yields and conversions determined by capillary GC.
[c] 4-Phenylbenzoic acid was not observed.
[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[e] 1,4-Diazabicyclo[2.2.2]octane.

Table 2. Methoxy- and ethoxycarbonylation of 4-biphenyl tosylate (**2c**) [a]

R^2	Conv./%[b]	Yield/%[b,c]		
		Ester **3** or **4c**	Ph-C_6H_4-OH-*p*	Ph-C_6H_4-OR^2-*p*
Me	74	23	27	9
Et	60	40	1	0

[a] The reaction was carried out with 2.5 mmol of **2c**, 0.1 mmol of $PdCl_2$, 0.2 mmol of dppp, 2.75 mmol of DBU, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of methanol or ethanol at 150 °C under 10 bar of CO for 3 h.
[b] Yields and conversions determined by capillary GC.
[c] 4-Phenylbenzoic acid and biphenyl were not observed.

In above cases, the yields of target ester were not high. Based on consideration that oxidative addition step is critical in this reaction and the electron density of C-OTs bond would have a large effect on the product yield, we examined the effect of 4-substituent in the ethoxycarbonylation of 4-substituted phenyl tosylates.

Table 3. Ethoxycarbonylation of 4-substituted phenyl tosylate [a]

Aryl tosylate **2**	R^1-	σ [b]	σ^+ [f]	Ester **4**	Yield/%[g]	(Conv./%)[g]
2a	MeCO-	0.502[c]	-	**4a**	81	(91)
2b	NC-	0.660[c]	0.659	**4b**	25	(54)
2c	Ph-	-0.01[d]	-0.179	**4c**	18	(32)
2d	Cl-	0.227[e]	0.114	**4d**	18[h]	(30)
2e	H-	0	0	**4e**	16	(21)
2f	F-	0.062[e]	-0.073	**4f**	6	(17)
2g	*i*-Pr-	-0.151[e]	-0.280	**4g**	6	(17)
2h	Me-	-0.170[e]	-0.311	**4h**	4	(6)

[a] The reaction was carried out with 2.5 mmol of 4-substituted phenyl tosylate (**2a-h**), 0.1 mmol of $PdCl_2$, 0.2 mmol of dppp, 2.75 mmol of DABCO, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of ethanol at 150 °C under 10 bar of CO for 3 h.
[b] Taken from the compilation by D. H. McDaniel and H. C. Brown. Reference 16.
[c] Values based on the ionization of benzoic acid.
[d] The value estimated from dissociation of benzoic acid in 50 % aqueous 2-butoxyethanol.
[e] Values derived from the dissociation constants of benzoic acid.
[f] Electrophilic substituent constants based on the solvolysis of the *t*-cumyl chlorides in 90 % aqueous acetone at 25 °C. Reference 17.
[g] Yields and conversions determined by capillary GC.
[h] A 8 % yield of diethyl terephthalate was obtained.

The results are shown in Table 3. There is obvious tendency that the yield of target ethyl ester increases with increasing the electron withdrawing ability of 4-substituents. The effect of 4-substituents here can be roughly correlated to Hammet σ values. σ (by Mcdaniel and Brown[16]) and σ^+ (by Brown and Okamoto[17]) values are included in Table 3. Acetyl is one of the electron withdrawing groups and the high yield with this substituent at 4-position is consistent with above trend. It should be noted that this high value with acetyl is special among other substituents. For preparative purpose, 4-acetylphenyl tosylates are good substrates of palladium-catalyzed alkoxycarbonylation to give alkyl 4-acylbenzoates and this trend should be extrapolated to other acylaryl tosylates.

Table 4. Effect of ligand on ethoxycarbonylation of 4-acetylphenyl tosylate (**2a**) [a]

Ligand	Yield/%[b]	(Conv./%)[b]
PPh_3	0	(23)
dppe[c]	8	(14)
dppp	66	(81)
dppb[d]	55	(70)

[a] The reaction was carried out with 2.5 mmol of **2a**, 0.1 mmol of $PdCl_2$, 0.4 mmol of PPh_3 or 0.2 mmol of a bisphosphine ligand, 2.75 mmol of DABCO, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of ethanol at 150 °C under 10 bar of CO for 3 h.
[b] Yields and conversions determined by capillary GC.
[c] 1,2-Bis(diphenylphosphino)ethane.
[d] 1,4-Bis(diphenylphosphino)butane.

Using 4-acetyl derivative, we examined the effect of phosphine ligand (Table 4). It is clear that the bisphosphine ligands are more effective to this reaction than PPh_3. Particularly, the use of 1,3-bis(diphenylphosphino)propane (dppp) gave target ester in the highest yield. In the case of carbonylation of aryl halides and triflates, the difference in the activity has been ascribed to the coordination ability of the ligands to a palladium center.[8,14] The used bisphosphines to form a six-membered chelate, such as dppp, have been reported to have high catalytic activities in the carbonylation of aryl halide and triflates, and some reports describe that both the coordination ability and the flexibility of the chelating ligand are important factors in related reactions.[2,18,19] It is likely that this is also the case in the carbonylation of aryl tosylates. However, it is noteworthy that, unlike in the alkoxycarbonylation of aryl halides, PPh_3 was completely inactive and there was a strong contrast in activity between PPh_3 and dppp in the reaction of tosylates.

Table 5. Effect of CO pressure on ethoxycarbonylation of 4-acetylphenyl tosylate (**2a**) [a]

CO pressure/bar	Yield/%[b]	(Conv./%)[b]
5	74	(86)
10	81	(91)
15	57	(74)
20	60	(74)

[a] The reaction was carried out with 2.5 mmol of **2a**, 0.1 mmol of $PdCl_2$, 0.2 mmol of dppp, 2.75 mmol of DABCO, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of ethanol at 150 °C in the presence of CO for 3 h.
[b] Yields and conversions determined by capillary GC.

Effect of CO pressure is shown in Table 5. The yield of target ester does not increase with increasing CO pressure, indicating that CO insertion is not a rate-determining step. Although yields under various pressures did not differ so much, the highest yield was recorded under 10 bar of CO pressure.

Table 6. Effect of base on ethoxycarbonylation of 4-acetylphenyl tosylate (**2a**) [a]

Base	pK_a[b]	Yield/%[c]	(Conv./%)[c]
DBU	11.2	42[h]	(100)
DBN[d]	11	56[i]	(100)
$(c\text{-}C_6H_{11})_2NEt$	-	70	(79)
$n\text{-}Bu_3N$	10.9	53	(55)
$i\text{-}Pr_2NEt$	-	73	(75)
Et_3N	10.75	52	(68)
Proton Sponge[e]	-	53	(74)
DMAP[f]	9.7	30[j]	(46)
TMEDA[g]	9.15	51	(57)
DABCO	8.2	81	(91)
2,6-Lutidine	6.6	1.8	(3.3)
Pyridine	5.2	0	(2.4)

[a] The reaction was carried out with 2.5 mmol of **2a**, 0.1mmol of $PdCl_2$, 0.2 mmol of dppp, 2.75 mmol of the base, 1.25 mmol of *n*-docosane (internal standard) in 5 ml of ethanol at 150 °C under 10 bar of CO for 3 h.
[b] pK_a values for aqueous solutions of the corresponding conjugate acids. Reference 20.
[c] Yields and conversions determined by capillary GC.
[d] 1,5-Diazabicyclo[4.3.0]non-5-ene.
[e] 1,8-Bis(dimethylamino)naphthalene.
[f] 4-Dimethylaminopyridine.
[g] *N,N,N',N'*-Tetramethylethylenediamine.
[h] A 34 % yield of 4-acetylphenol was also obtained.
[i] A 13 % yield of 4-acetylphenol was also obtained.
[j] A 6 % yield of 4-acetylphenol was also obtained.

Next the effect of base was further investigated (Table 6). Unlike in the phenoxycarbonylation of 4-bromobiphenyl,[3] no obvious trend that the use of base with larger pK_a value[20] gives higher yield of ester was seen in ethoxycarbonylation of 4-acetylphenyl tosylate. Since relatively high temperature is required in this reaction, too strong bases tend to mediate

undesired reactions. The use of simple tetraalkylamines (having ethyl and higher alkyl groups) gave relatively better yields of ester. Too weak bases such as pyridine do not work simply because the lack of ability to absorb acid.

In conclusion, palladium-catalyzed methoxy- and ethoxycarbonylation of aryl tosylates successfully proceeded to give the corresponding arylcarboxylates. When 4-position of aryl tosylate is substituted by an electron withdrawing group in the case of ethoxycarbonylation, the yield of ethyl ester considerably increased. Especially, the ethoxycarbonylation of 4-acetylphenyl tosylate gave the corresponding ethyl ester in high yield which is satisfactory for preparative purpose. It can be said that this reaction is particularly applicable to acylphenyl tosylates to give alkyl acylbenzoates. Methoxycarbonylation of aryl tosylates occurred with some base-mediated side reactions.

Typical procedure:

Synthesis of 4-acetylphenyl tosylate (**2a**):

To a suspension of 4-acetylphenol (9.99 g, 73.4 mmol) in pyridine (70 ml), 16.8 g of TsCl (88.1 mmol) was added portionwise at room temperature and the whole mixture was stirred at 45 °C for 14h. After cooling to room temperature, 100 ml of water was added to the mixture and stirred at room temperature for 3 h. This mixture was diluted with benzene (1000 ml) and washed with water (500 ml), 10 % aqueous HCl (500 ml x 3), water (500 ml x 2), saturated aqueous $NaHCO_3$ (500 x 2), and brine (500 ml x 2), and then dried over Na_2SO_4. After filtration, solvent was evaporated in vacuo to give a white solid (20.9 g). Recrystallization from benzene (20 ml)-hexane (40 ml) gave 4-acetylphenyl tosylate (**2a**) as colorless fine needles (17.7 g, 83 %). mp 62.5-63.5 °C. IR (KBr): 1682, 1379 cm^{-1}. *Anal.* Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 62.02; H, 4.77. ^1H NMR ($CDCl_3$) δ: 2.46 (3H, s, Ar-C$\underline{H}_3$), 2.58 (3H, s, C$\underline{H}_3$CO), 7.09 and 7.90 (each 2H, dt, *J*=8.9, 2.4 Hz), 7.33 and 7.71 (each 2H, dt, *J*=8.3 Hz, 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.66 (<u>C</u>H$_3$-Ar), 26.55 (<u>C</u>H$_3$CO), 122.50, 128.47, 129.92 and 130.04 (aromatic <u>C</u>H), 132.09, 135.68, 145.79 and 152.98 (aromatic <u>C</u>), 196.69 (<u>C</u>=O).

Ethoxycarbonylation of **2a**:

In a 50 ml stainless-steel autoclave were placed 725.9 mg (2.5 mmol) of **2a**, 17.7 mg (0.1 mmol) of $PdCl_2$, 82.5 mg (0.2 mmol) of dppp, 388.3 mg (1.25 mmol) of *n*-docosane, 5 ml of ethanol, and 308.5 mg (2.75 mmol) of DABCO. Carbon monoxide was introduced at 10 bar of an initial pressure and then heated with stirring at 150 °C in an oil bath for 3h. After excess carbon monoxide was purged, the reaction mixture was diluted by chloroform. Ethyl 4-acetylbenzoate (**4a**) and unreacted **2a** were found in the mixture by a GC analysis. They were separated by column chromatography on silica gel (eluent: hexane-ethyl acetate) to give 355 mg (74 %) of **4a** and 71 mg (11 %) of **2a**. **4a** was recrystallized from hexane and obtained as colorless pillars. mp 55.5–56.5 *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.88; H, 6.34. MS m/z: 192 (M^+), 177 ($M^+ - CH_3$), 147 ($M^+ - OCH_2CH_3$). IR (KBr): 1717, 1684 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (3H, t, *J*=7.2 Hz, C$\underline{H}_3$-CH$_2$-), 2.65 (3H, s, C$\underline{H}_3$CO), 4.41 (2H, q, *J*=7.2 Hz, CH$_3$-C$\underline{H}_2$-), 8.01 and 8.13 (each 2H, dt, *J*=8.8, 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.17 (<u>C</u>H$_3$-CH$_2$-), 26.79 (<u>C</u>H$_3$CO), 61.38 (O-<u>C</u>H$_2$-), 128.13 and 129.74 (aromatic <u>C</u>H), 134.23 and 140.11 (aromatic <u>C</u>), 165.72 (ester <u>C</u>=O), 197.59 (ketone <u>C</u>=O).

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