Palladium-catalyzed Displacement of Aryl Halide by Tin Analogue of Reformatsky Reagent

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Synopsis. Reaction of ethyl α-(tributylstannyl)acetate with aryl bromides in the presence of zinc bromide or chloride and a catalytic amount of dichlorobis(tri-*o*-tolylphosphine)palladium was found to give ethyl arylacetates in good yields except with the aryl bromide having *p*-acetyl or *p*-nitro group.

Transition metal-catalyzed displacement of aryl halides by an enolate-like reagent giving a carbon–carbon bond is of recent interest.[1,2] We have reported the aromatic displacement by enolate-like tin reagents (α-stannyl ketone and/or stannyl enol ether) catalyzed by dichlorobis(tri-*o*-tolylphosphine)-palladium.[3] The nickel or palladium-catalyzed arylation[4] and alkenylation[5] of Reformatsky reagent have also been reported, but these reactions seem to have disadvantage in the low catalytic efficiencies and the limitation in a functional group exsisting in the aryl halide.

In this note, we report the displacement of aryl halides by organotin analogue of Reformatsky reagent in the presence of palladium complex.

$$n\text{-Bu}_3\text{SnCH}_2\text{CO}_2\text{Et} + \text{ArX} \xrightarrow{[\text{Pd}]} \text{ArCH}_2\text{CO}_2\text{Et} + n\text{-Bu}_3\text{SnX}$$

The reaction gave aryl acetate in moderate yields together with 1-arylbutane and biaryl which were formed through butyl transfer from the tin compound and homocoupling of the aryl bromides, respectively. Results are shown in Table 1. Similarly to the reaction of tin enolate, dichlorobis(tri-*o*-tolylphosphine)palladium was the best catalyst among the palladium complexes examined here. However, in contrast with the reaction of tin enolate,[3] proper solvents were polar aprotic ones, such as hexamethylphosphoric triamide (HMPA), *N*-methyl-2-pyrolidone (NMP), *N*,*N*-dimethylformamide (DMF), or dimethyl sulfoxide (DMSO). We chose DMF as a solvent, with which a relatively short reaction time was required.

As can be seen in Table 1, however, the yield was not particularly good, and sometimes was not reproducible. This is probably due to instability of α-stannyl acetate as well as α-stannyl ketone or stannyl enol ether under the reaction conditions. After many trials to overcome the difficulty, the addition of an equimolar amount of zinc bromide or chloride to the reaction system was found to enhance the yield of the product to almost quantitative, as shown in Table 2.

As Table 2 shows, zinc bromide or chloride was an especially effective additive, while other Lewis acids seem to deactivate the catalyst. Based on these results, the best reaction conditions were found to be as follows; a mixture of ethyl α-stannylacetate (1.3 mmol), bromobenzene (1.0 mmol), zinc bromide (1.3 mmol), $PdCl_2[P(o\text{-tolyl})_3]_2$ (0.01 mmol), and DMF (2 cm^3) was heated under argon at 80 °C for 5 h. Usual workup gave ethyl phenylacetate in 71% isolated yield. Table 3 shows the results with various aryl bromides.

The yield was greatly improved compared with

Table 1. Reaction of $Bu_3SnCH_2CO_2Et$ with PhBr in the presence of various palladium complexes[a]

Catalyst[b]	Solvent	Temp/°C	Time/h	Yield/%[c]		
				$PhCH_2CO_2Et$	PhBu	PhPh
None	HMPA	80	20	0		
A	HMPA	80	20	25	4	trace
B	HMPA	80	20	trace	4	8
C	HMPA	80	20	36	10	12
D	HMPA	80	20	59	21	8
D	HMPA	80	5	49		
D	DMSO	100	20	42		
D	NMP	80	5	65		
D	NMP	100	5	52		
D	DMF	80	5	67		
D	DMF	100	5	54		
D	PhH	80	20	25		
D	THF	80	20	34		

a) $Bu_3SnCH_2CO_2Et$ (1.1 mmol), PhBr (1.0 mmol), Catalyst (0.01 mmol), Solvent (0.5 cm^3). b) A; $Pd(PPh_3)_4$, B; $PdCl_2(PhCN)_2$, C; $PdCl_2(PPh_3)_2$, D; $PdCl_2[P(o\text{-tolyl})_3]_2$. c) GLC yield based on bromobenzene.

Table 2. Effect of additives

$$Bu_3SnCH_2CO_2Et + PhBr \xrightarrow[\text{in DMF 80 °C, 5h.}]{[Pd]^{a)}} PhCH_2CO_2Et + Bu_3SnBr$$

(1.3 mmol) (1.0 mmol)

Additive (1.3 mmol)	Yield of $PhCH_2CO_2Et$/%[b]
None	67
$ZnBr_2$	100
$ZnCl_2$	100
ZnF_2	53
$TiCl_4$	0
$SnCl_4$	0
$BF_3 \cdot OEt_2$	0

a) $PdCl_2[P(o\text{-tolyl})_3]_2$ (0.01 mmol). b) GLC yield based on bromobenzene.

Table 3. Reaction of $Bu_3SnCH_2CO_2Et$ with ArX

ArX	Isolated yield of $ArCH_2CO_2Et$/%
PhCl	0
PhBr	71
PhI	31*
p-MeC_6H_4Br	93
m-MeC_6H_4Br	60
o-MeC_6H_4Br	71
p-ClC_6H_4Br	89
o-ClC_6H_4Br	66
p-$MeOC_6H_4Br$	47
o-$MeOC_6H_4Br$	82
p-$MeCOC_6H_4Br$	22* mp 61 °C (lit,[4] 62—68 °C)
p-NCC_6H_4Br	67 mp 90 °C (lit,[4] 88 °C)
p-$O_2NC_6H_4Br$	34 mp 62 °C (lit,[4] 64 °C)

* GLC yield based on the halide.

that with Reformatsky reagent. In our case, the best substrate was bromide, and iodide which was a better substrate in Reformatsky reaction gave poor results, and chloride did not react at all. The reaction with aryl bromides having *p*-acetyl or *p*-nito group gave the product in low yields. These tendencies were also observed in other cross-coupling reactions, where the palladium catalyst having tri-*o*-tolylphosphine as a ligand was used.[3,6,7]

The mechanistic role of zinc salts which enhance the yields of the reaction products is not yet clear. The metal exchange between zinc salts and organotin producing Reformatsky reagent seems unlikely, considering the above difference in behaviors of iodobenzene and bromobenzene.

Experimental

IR spectra were recorded on Jasco A-100 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-360 instrument. GLC analyses were carried out with Ohkura 802 instrument, using columns (1.5 m) packed with 10% Silicone SF-96 and SE-30 on Celite 545.

Materials. Ethyl α-(tributylstannyl)acetate was prepared by the reaction of tributyltin ethoxide with ketene.[8] bp 117—119 °C/0.2 mmHg. (lit,[8] 150—152 °C/1.6 mmHg (1 mmHg=133.322 Pa)). Aryl bromides and palladium catalyst have already reported.[3]

Reaction Procedure. Zinc bromide (1.3 mmol) was placed in 10 cm^3 flask, and heated at 140 °C for 1 h under reduced pressure. Then, a mixture of ethyl α-(tributylstannyl)acetate (1.3 mmol), aryl bromide (1.0 mmol), $PdCl_2[P(o\text{-tolyl})_3]_2$ (0.01 mmol), and DMF (2 cm^3) was added into the flask, and heated under argon at 80 °C for 5 h. The reaction mixture was washed with water to remove the solvent, extracted with ether, and dried with anhydrous sodium sulfate. After column chromatography on silica gel, the product was isolated by distillation or crystallization.

Products. All the products were known and their structures were identified with IR and ^1H NMR spectra. Ethyl phenylacetate,[9,10a] ethyl *p*-methylphenylacetate,[10b] ethyl *m*-methylphenylacetate,[10c] ethyl *o*-methylphenylacetate,[10d] ethyl *p*-chlorophenylacetate,[10e] ethyl *o*-chlorophenylacetate,[10f] ethyl *p*-methoxyphenylacetate,[4,10g] ethyl *o*-methoxyphenylacetate,[10h] ethyl *p*-acetylphenylacetate,[4] ethyl *p*-cyanophenylacetate,[4] and ethyl *p*-nitrophenylacetate.[4]

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