

The reaction of aryl bromides with ethyl cyanoacetate anion catalyzed by palladium complexes with chelated phosphine ligands

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Abstract

A series of chelating phosphines as ligands of palladium complexes was used for the catalytic reaction of bromobenzene with ethyl cyanoacetate anion and it was found that dppe-Pd catalytic system has the highest activity to obtain ethyl phenylcyanoacetate among all ligands. The effects of molar ratio of dppe to catalyst, solvent, temperature and bases on the reaction were discussed. The substituted bromobenzene reacted with ethyl cyanoacetate anion under the appropriate reaction conditions to give the cross-coupling products in considerable yield. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Palladium complex; Catalytic reaction; Chelated phosphine ligands; Nucleophilic substitution; Ethyl aryl cyanoacetates

1. Introduction

Arylated ethyl cyanoacetates are valuable intermediates in the synthesis of some important organic compounds, such as bioactive materials and heterocyclic compounds [1–7]. But it is well known that the synthesis of ethyl aryl cyanoacetates can not be achieved directly through nucleophilic substitution of ethyl cyanoacetate with aryl halides under basic conditions. Uno et al. reported that palladium complex catalyzed reaction of aryl iodide with ethyl cyanoacetate in the presence of potassium *tert*-butoxide gave the arylated products, but ethyl phenylcyanoacetate was obtained in poor yield (8%) from phenyl bromide with ethyl cyanoacetate in the same catalytic reaction conditions [8]. In this paper, we report some recent results on the reaction of bromides with ethyl

cyanoacetate anion catalyzed by palladium complexes with chelated phosphine ligands.

2. Experimental

2.1. General

All arylations were carried out under an atmosphere of dry argon. Solvents were purified by conventional method and distilled under argon. Aryl bromides were distilled under reduced pressure or recrystallized before use. Dichlorobis(triphenylphosphino)palladium [PdCl₂(PPh₃)₂] [9], bis(diphenylphosphino)methane (dppm) [10], bis(diphenylphosphino)ethane(dppe) [10], bis(diphenylphosphino)propane(dppp) [10] were prepared by literature procedure, respectively. All products were purified by TLC using silica GF254 (10–40 μ mesh), identified with ¹H NMR spectral data obtained from a variant GRMINI 300 Hz NMR spectrometer using tetra-methylsilane as an internal standard.

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2.2. Typical procedure. The reaction of bromobenzene with ethyl cyanoacetate

To a suspension of potassium *tert*-butoxide (0.56 g, 5.0 mol) in 1,2-dimethoxyethane (DME) (12 ml), ethyl cyanoacetate (0.34 g, 3.0 mol) was added with stirring. After 10 min, dppe (0.035 g, 0.088 mmol), PdCl₂(PPh₃)₂ (0.056 g, 0.08 mmol) and bromobenzene (0.32 g, 2.0 mmol) were added, then the mixture was heated at reflux for 16 h under argon. After cooling the mixture, 3 N hydrochloric acid was added and the product was extracted with ether (3 × 30 ml). The extract was washed with brine (20 ml) and dried over sodium sulfate. After concentration, the residue was isolated by TLC (20 × 20 cm glass plate with 25–30 g silica GF254, 10–40 mesh) using petroleum ether/ethyl acetate (15/1) as developing solution for three times. Fractions containing product were concentrated to give a clear oil (0.31 g, 82% yield). ¹H NMR (CDCl₃, 300 Hz) δ 1.27 (t, *J* = 7.1 Hz, 3H); 4.24 (q, *J* = 7.1 Hz, 2H); 4.72 (s, 1H); 7.40–7.48 (m, 5H).

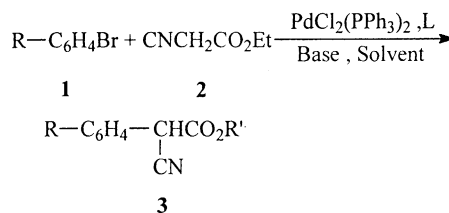
2.3. ¹H-NMR data of 3c-3f

3b oil (68%) ¹H NMR (CDCl₃, 300 Hz) δ 3.79 (s, 3H), 4.75 (s, 1H), 7.39–7.47 (m, 5H). 3c oil (72%) ¹H NMR (CDCl₃, 300 Hz) δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.67 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H). 3d oil (62%) ¹H NMR (CDCl₃, 300 Hz) δ 1.30 (t, *J* = 7.1 Hz, 3H), 3.87 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.03 (s, 1H), 6.90–7.08 (m, 2H), 7.38–7.45 (m, 2H). 3e oil (68%) ¹H NMR (CDCl₃, 300 Hz) δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.82 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.66 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H). 3f oil (54%) ¹H NMR (CDCl₃, 300 Hz) δ 1.35 (t, *J* = 7.1 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.81 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H). 3g oil (52%) ¹H NMR (CDCl₃, 300 Hz) δ 1.30 (t, *J* = 7.2 Hz, 6H), 4.20–4.35 (m, 4H), 4.76 (s, 2H), 7.55 (s, 4H).

3. Results and discussion

An alternation of the ligand from conventional PPh₃ to dppe improves the catalytic efficiency of palladium complexes to great extent, thereby providing a

convenient method for the preparation of ethyl aryl cyanoacetates from aryl bromides:



3a: R = H, R' = Et

b: R = H, R' = Me

c: R = *p*-CH₃, R' = Et

d: R = *p*-OCH₃, R' = Et

e: R = *o*-OCH₃, R' = Et

f: R = *p*-CO₂Et, R' = Et

g: R = *p*-CH(CN)CO₂R', R' = Et

3.1. The effects of solvent and ligand

At the beginning, the reaction of bromobenzene with ethyl cyanoacetate was studied using PdCl₂(PPh₃)₂ as a catalyst precursor to investigate the effect of ligands and solvents on the progress of Pd-catalyzed reaction (Table 1). In the case of chelating phosphines as ligands of palladium catalysts, the yield was much higher than Ph₃P as ligand (run 1–4, 8). The ligand dppe promoted the reaction to afford ethyl phenylcyanoacetate in satisfactory yield among four chelating phosphines. In this reaction, the effect of the molar ratio of dppe/palladium is obvious. The yields of ethyl phenylcyanoacetate were decreased with the raising or reducing molar ratio to 1.1:1, the yield of the catalytic reaction ascended conspicuously (run 8); the time of reaction did not seem to affect the yield (run 8, 12). The reflux temperature in DME was better (run 8, 13). From Table 1, it is observed that the yield did not increase at reflux temperature in toluene or dioxane, respectively (run 14, 15).

3.2. The effect of base

Table 2 summarized the results for the dppe/Pd catalytic reaction of bromobenzene with ethyl

Table 1
Effects of solvents or ligands on the Pd-catalyzed reaction of bromobenzene with ethyl cyanoacetate^a

Run	Solvent	Ligand(molar ratio of ligand/Pd)	T (°C)/t (h)	Yield (%)
1	DME	PPh ₃ (2)	70/5	8 [8]
2	DME	P(<i>o</i> -anisol) ₃ (2)	70/5	22
3	DME	dppm (1.1)	70/5	21
4	DME	dppp (1.1)	70/5	44
5	DME	dppe (0.5)	70/5	45
6	DME	dppe (0.8)	70/5	54
7	DME	dppe (1.0)	70/6	74
8	DME	dppe (1.1)	70/6	78
9	DME	dppe (1.4)	70/5	61
10	DME	dppe (1.6)	70/5	26
11	DME	dppe (2)	70/6	Trace
12	DME	dppe (1.1)	70/21	78
13	DME	dppe (1.1)	reflux/6	82
14	Toluene	dppe (1.1)	reflux/10	73
15	Dioxane	dppe (1.1)	reflux/10	77

^a Reaction conditions: PhBr (2 mmol); ethyl cyanoacetate (3 mmol); *tert*-BuOK (5 mmol); Pd(PPh₃)₂Cl₂ (0.08 mmol); solvent (10–12 ml) under argon.

cyanoacetate using different kinds of base. From the result, sodium methoxide, from which the ester exchange product was obtained, and sodium hydride were both used as base (run 3, 5), but these yields of cyanophenylacetate ester were less than *tert*-BuOK as base for the present reaction. It seemed that the base must be in a ratio of two and a half times to bromobenzene. And when the nucleophilic reagent to bromobenzene is 1.5:1, the highest yield was obtained.

Table 2
Effect of different kinds of bases on dppe/Pd catalyzed reaction of bromobenzene with ethyl cyanoacetate^a

Run	Base	PhBr:NuH:base	Time	Yield (%) ^b
1	K ₂ CO ₃	1:1.5:2.5	18	0
2	NaOAc	1:1.5:2.5	18	0
3	NaH	1:1.5:2.5	10	64
4	NaOEt	1:1.5:2.5	10	32
5	NaOMe	1:1.5:2.5	10	68 ^c
6	<i>tert</i> -BuOK	1:1.5:2.5	6	82
7	<i>tert</i> -BuOK	1:1.5:2.0	6	46
8	<i>tert</i> -BuOK	1:1:2.5	6	58

^a Reaction conditions: PhBr (2 mmol); PdCl₂(PPh₃)₂ (0.08 mmol); dppe (0.088 mmol); solvent (10–12 ml); at reflux under argon.

^b Isolated yields based on PhBr.

^c The ester exchange product, methyl phenylcyanoacetate (3b) was obtained.

Table 3
The reaction of aryl bromides with ethyl cyanoacetate^a

Run	R-C ₆ H ₄ Br	Time (h)	Product	Yield (%) ^b
1	H	6	3a	82
2	<i>p</i> -CH ₃	15	3c	72
3	<i>p</i> -OCH ₃	15	3d	68
4	<i>o</i> -OCH ₃	15	3e	62
5	<i>p</i> -CO ₂ Et ^c	15	3f	54
6	<i>p</i> -Br	15	3g	52 ^d

^a Reaction conditions: ArBr (2 mmol); ethyl cyanoacetate (3 mmol); *tert*-BuOK (5 mmol); PdCl₂(PPh₃)₂ (0.08 mmol); dppe (0.088 mmol); DME (10–12 ml); at reflux under argon.

^b Isolated yields based on ArBr.

^c NaH was used as base instead of *tert*-BuOK.

^d Di-substituted product was obtained when using at the molar ratio of *p*-BrC₆H₄Br:ethyl cyanoacetate: *tert*-BuOK = 1:3:5.

3.3. The reaction of aryl bromides with ethyl cyanoacetate

On the basis of these results, the standard reaction conditions were fixed for the next investigation. Namely, a mixture of an aryl bromide (2 mmol) with ethyl cyanoacetate (3 mmol) in the presence of PdCl₂(PPh₃)₂ (0.08 mmol), dppe (0.088 mmol) and *tert*-BuOK (5 mmol) in DME (10–12 ml) was refluxed for an appropriate time.

As shown in Table 3, the different available substituted bromobenzene reacted with ethyl cyanoacetate under these conditions to give the cross-coupling products in considerable yield. In the run 5, the base *tert*-BuOK might be too strong for the reaction, resulting in the formation of more byproducts. When NaH was used as base instead of *tert*-BuOK, the yield was better. When an excess of nucleophilic reagent was used and di-substituted benzene was obtained. The yield was higher than that of diiodobenzene [11].

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