Palladium-catalyzed cross-coupling of bromobenzenes, containing an acetyl or a formyl group, with organozinc reagents

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Abstract

The reaction of organozinc halides RZnX (R = Bu, Ph; X = Cl, Br) with m- and p-bromoacetophenones in the presence of $PdCl_2(PPh_3)_2$ in THF/HMPA (THF = tetrahydrofuran; HMPA = N,N,N',N',N'',N''-hexamethylphosphoric triamide) takes place chemoselectively to give the corresponding m- and p-R-substituted acetophenones in high yields. Similarly reaction of RZnX with p-bromobenzaldehyde also proceeds chemoselectively to give the p-R-substituted benzaldehyde in good yields.
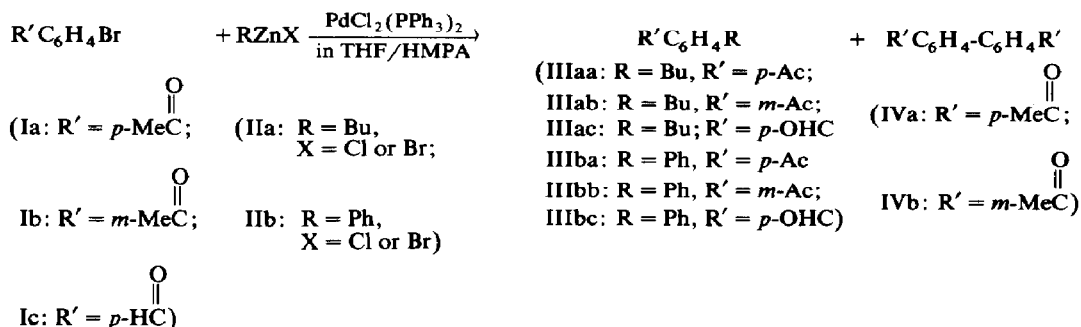
Introduction

It is fairly well known that organozinc reagents, in particular dialkylzincs, react with ketones containing an α-H atom to give aldol condensation products [1]. Acetophenone reacts with diethylzinc to give a dehydrated aldol, β-methylchalcone [2]. On the other hand, the reaction of organozinc reagents with aldehydes gives secondary alcohols [3]. Up to now the cross-coupling of halobenzenes containing a carbonyl group with non-Reformatsky organozinc reagents has not been studied. In this paper we report on the unprecedented chemoselective cross-coupling of bromoacetophenones and bromobenzaldehyde with organozinc halides.

Results and discussion

All reactions were carried out in a mixed solvent of THF and HMPA (THF = tetrahydrofuran; HMPA = N,N,N',N',N'',N''-hexamethylphosphoric triamide) after the observations by Fauvarque et al. that HMPA is an excellent co-solvent in the Ni- or Pd-catalyzed Reformatsky reactions in dimethoxymethane [4].

The reaction of p-bromoacetophenone (Ia) with butylzinc (IIa) or phenylzinc halide (IIb) in the presence of a palladium (II) complex as catalyst gives p-butyl-

$$R'C_6H_4Br \quad + RZnX \xrightarrow[\text{in THF/HMPA}]{PdCl_2(PPh_3)_2}$$

(Ia: R' = p-MeC̈; (IIa: R = Bu,
                         X = Cl or Br;

Ib: R' = m-MeC̈; IIb: R = Ph,
                         X = Cl or Br)

Ic: R' = p-HC̈)

$$R'C_6H_4R \qquad + \quad R'C_6H_4\text{-}C_6H_4R'$$

(IIIaa: R = Bu, R' = p-Ac;
IIIab: R = Bu, R' = m-Ac;   (IVa: R' = p-MeC̈;
IIIac: R = Bu; R' = p-OHC
IIIba: R = Ph, R' = p-Ac
IIIbb: R = Ph, R' = m-Ac;   IVb: R' = m-MeC̈)
IIIbc: R = Ph, R' = p-OHC)

Scheme 1

acetophenone (IIIaa) or 4-acetylbiphenyl (IIIba), respectively, as the major product (Scheme 1).

As shown in Table 1, of the palladium (II) complexes examined, $PdCl_2(PPh_3)_2$ exhibits the highest catalytic activity in the reactions of Ia with II (Entries 1, 8). The analogous Ni complex, $NiCl_2(PPh_3)_2$, however, showed poor activity (Entries 6, 13).

Similarly, reactions of m-bromoacetophenone (Ib) and p-bromobenzaldehyde (Ic) with RZnX (IIa or IIb) in the presence of $PdCl_2(PPh_3)_2$ gave the corresponding R-substituted acetophenones and benzaldehydes, respectively. GC-MS analyses revealed that no dehydrated aldols of Ia and Ib, (4,4'- and 3,3'-dibromo-β-methylchalcones, respectively), or addition products of II to the formyl group of Ic

Table 1

Catalytic activities of Pd or Ni complexes in the chemoselective cross-coupling of p-bromoacetophenone (Ia) with organozinc halides (II) in THF/HMPA [a]

Entry	Catalyst [b]	RZnX (II) [c] (R =)	Yield of product (III) (%) [d]
1	$PdCl_2(PPh_3)_2$	a (Bu)	aa : 90
2	$PdCl_2(dppb)$	a (Bu)	aa : 49
3	$PdCl_2(dppf)$	a (Bu)	aa : 50
4	$PdCl_2(dppp)$	a (Bu)	aa : 45
5	$PdCl_2$	a (Bu)	aa : 46
6	$NiCl_2(PPh_3)_2$	a (Bu)	aa : 46
7	$NiCl_2(dppp)$	a (Bu)	aa : 45
8	$PdCl_2(PPh_3)_2$	b (Ph)	ba : 98 [e]
9	$PdCl_2(dppb)$	b (Ph)	ba : 70 [e]
10	$PdCl_2(dppf)$	b (Ph)	ba : 75 [e]
11	$PdCl_2(dppp)$	b (Ph)	ba : 60 [e]
12	$PdCl_2$	b (Ph)	ba : 61 [f]
13	$NiCl_2(PPh_3)_2$	b (Ph)	ba : 84 [e]
14	$NiCl_2(dppp)$	b (Ph)	ba : 75 [e]

[a] The molar ratio Ia : II : catalyst = 1.0 : 1.2 : 0.02; the volume-to-volume ratio THF/HMPA = 1/2; at reflux (100°C); for 15 min. [b] Abbrevations for ligands: dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1'-bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane. [c] X = Cl or Br. [d] III = p-CH$_3$COC$_6$H$_4$R; determined by GLC. [e] Trace amounts of 4,4'-diacetylbiphenyl (IVa) were also detected. [f] IVa = 11%.

Table 2

Chemoselective cross-coupling of p- and m-bromoacetophenones (Ia and Ib) and p-bromobenzaldehyde (Ic) with RZnX (II) in the presence of $PdCl_2(PPh_3)_2$ in THF/HMPA [a]

Entry	I (R')	II (R)	Reaction temp	THF/HMPA (ratio)	Yield of III (%) [b]
1	a (p-CH$_3$CO)	a (Bu)	reflux	1/2	aa : 90
15	a (p-CH$_3$CO)	a (Bu)	50 °C	1/2	aa : 80
16	a (p-CH$_3$CO)	a (Bu)	reflux	1/1	aa : 80
17	a (p-CH$_3$CO)	a (Bu)	reflux	1/3	aa : 84
8	a (p-CH$_3$CO)	b (Ph)	reflux	1/2	ba : 98 [c]
18	a (p-CH$_3$CO)	b (Ph)	50 °C	1/2	ba : 76 [c]
19	a (p-CH$_3$CO)	b (Ph)	reflux	1/1	ba : 96 [c]
20	a (p-CH$_3$CO)	b (Ph)	reflux	1/3	ba : 90 [c]
21	b (m-CH$_3$CO)	a (Bu)	reflux	1/2 [d]	ab : 69 [e]
22	b (m-CH$_3$CO)	a (Bu)	50 °C	1/2 [d]	ab : 52 [f]
23	b (m-CH$_3$CO)	b (Ph)	reflux	1/2 [g]	bb : 79 [h]
24	c (p-OHC)	a (Bu)	reflux	1/2	ac : 87
25	c (p-OHC)	a (Bu)	50 °C	1/2	ac : 61
26	c (p-OHC)	b (Ph)	reflux	1/2	bc : 92

[a] The molar ratio I : II : $PdCl_2(PPh_3)_2$ = 1.0 : 1.2 : 0.02; for 15 min. [b] III = R'C$_6$H$_4$R; determined by GLC. [c] Trace amounts of IVa were also detected. [d] For 30 min. [e] 3,3'-Diacetylbiphenyl (IVb) was also detected in 21% yield. [f] IVb = 33%. [g] For 45 min. [h] IVb = trace amounts.

(1-(p-bromophenyl)-1-pentanol and p-bromophenylphenylmethanol) were produced.

As shown in Table 2, the reactions of I with II resulted in the highest yields of chemoselectively cross-coupled products (III), in a mixed solvent of THF/HMPA (volume ratio = 1/2) under reflux (Entries 1, 8). A larger amount of HMPA in the mixed solvent did not give better yields of III (Entries 17, 20).

As a control experiment, we carried out the reaction of acetophenone with PhZnX (IIb) in the presence of $PdCl_2(PPh_3)_2$ in refluxing THF/HMPA (1/2) for 60 min and found that (E)-β-methylchalcone was produced in 58% yield. Under similar conditions benzaldehyde reacts with IIb to give diphenylmethanol in 63% yield.

The reactions of benzaldehyde and bromobenzene, when both are present in the mixture, with IIb in the $PdCl_2(PPh_3)_2$ at reflux for 30 min, are competitive and give biphenyl in 76% yield; 95% of the benzaldehyde is recovered unchanged. In the absence of $PdCl_2(PPh_3)_2$, the same reaction of benzaldehyde and bromobenzene with IIb at reflux for 60 min gives diphenylmethanol in 61% yield and about 91% of bromobenzene remains unchanged. Moreover, the reaction of a mixture of Ic and bromobenzene with IIb in the presence of $PdCl_2(PPh_3)_2$ at reflux for 15 min gives 80% of 4-biphenylcarbaldehyde (IIIbc) and trace amounts of biphenyl. These results suggest that the reactivity toward PhZnX in the presence of $PdCl_2(PPh_3)_2$ falls in the order: p-OHCC$_6$H$_4$Br (Ic) > C$_6$H$_5$Br > C$_6$H$_5$CHO. The high reactivity of Ic is because of the electron-attracting effect of the p-formyl group, which probably facilitates the oxidative addition by the phenyl–Br bond to the palladium of the catalyst [5], the key step of the cross-coupling reaction. Cross-coupling of I with II is thus much faster than the aldol condensation of acetyl group and addition of II to formyl group in the presence of $PdCl_2(PPh_3)_2$.

In a reaction of Ia with IIb in the presence of $PdCl_2$, 4,4'-diacethylbiphenyl (IVa) is also obtained in 11% yield (Entry 12). Similarly, from a reaction of Ib with IIa, 3,3'-diacethylbiphenyl (IVb) is produced in 21–33% yields (Entries 21, 22). The by-product IVb was scarcely formed in homo-coupling of Ib with $PdCl_2(PPh_3)_2$ and zinc dust in THF/HMPA, in contrast to the observation that the reaction of p-chloroacetophenone with a red-brown mixture, prepared from $NiCl_2$, Ph_3P, and zinc dust in DMAC (N,N-dimethylacetamide) or DMF (N,N-dimethylformamide), gave IVa quantitatively [6].

Thus, IVa and IVb should be produced by the cross-coupling of Ia and Ib with p- and m-acetylphenylzinc halide, respectively, that are formed by halogen–metal exchange of Ia and Ib with II. Similar reasoning has been presented by Beletskaya et al. [7] for the formation of small amounts of 4,4'-dimethoxybiphenyl from p-iodoanisole with PhZnCl in the presence of $PdCl_2(PPh_3)_2$ in THF/Et_2O.

Experimental

General

All reactions were carried out under nitrogen. Organozinc halides (II) were freshly prepared from equimolecular amounts of the corresponding Grignard reagents and $ZnCl_2$ at room temperature in THF under nitrogen. GLC was performed (i) with a Silicone OV-17 column (2 m), with triphenylmethane was the internal standard for the reaction of I with IIa, and (ii) with a Silicone GE SE-54 column (2 m); with acenaphthene as the internal standard for the reaction of I with IIb. All the reactions products described were found to be spectrally identical with authentic samples (^1H NMR (270 MHz), ^{13}C NMR (67.9 MHz), GC-MS (60–600 m/z) and/or IR (4000–400 cm^{-1})). ^1H NMR and ^{13}C NMR spectra were recorded with a JEOL JNM-GX270 NMR spectrometer, GC-MS spectra with a Shimazu GCMS-QP1000 gas chromatograph-mass spectrometer, and IR spectra on a Hitachi 270-30 infrared spectrophotometer.

Reaction of I with II in the presence of $PdCl_2(PPh_3)_2$

A typical procedure (Entry 8) was as follows. To a suspension of Ia (0.60 g, 3.0 mmol) and $PdCl_2(PPh_3)_2$ (0.043 g, 0.06 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml). After having been refluxed at 100°C for 15 min, the reaction mixture was quenched with dilute aqueous HCl. The reaction products were isolated by preparative LC on silica gel with hexane/AcOEt = 5/1 as eluent. IIIba [8], m.p. 120.5–121°C (from EtOH) (lit. m.p. 119–121.5°C); R_f 0.34 (on silica gel TLC with hexane/AcOEt = 5/1). IVa (in 1% yield) [9], m.p. 189–190°C (from C_6H_6) (lit. m.p. 190–191°C); R_f 0.62 (hexane/AcOEt = 10/1).

Other reactions of I with II were carried out in the same way IIIaa [10], b.p. 95–95.5°C/0.1 Torr (lit. 167°C/33 Torr); R_f 0.56 (hexane/AcOEt = 5/1). m-Butylacetophenone (IIIab), b.p. 103–105°C/6 Torr; R_f 0.41 (hexane/AcOEt = 5/1); ^1H NMR (CDCl$_3$): δ 0.93 (t, 3H), 2.58.(s, 3H); ^{13}C NMR (CDCl$_3$): δ 137.2 (C-1 in Ar), 143.4 (C-3 in Ar); m/z: 176 (20%, M^+), 161 (100%, $M^+ - CH_3$), 133 (25%, $M^+ - CH_3CO$); IR (neat): 1686 cm^{-1} (ν(C=O)), 794 and 693 cm^{-1} (δ(CH)); Anal. Found: C, 81.67; H, 9.30. $C_{12}H_{16}O$ calcd.: C, 81.77; H, 9.15%. p-Butylbenzaldehyde (IIIac) [11], b.p. 96–98°C/5 Torr (lit. b.p. 160–165°C/44 Torr); R_f 0.56 (hexane/AcOEt = 10/1). 3-Acetylbiphenyl (IIIbb) [12], b.p. 160–164°C/3

Torr (lit. b.. 148–151°C/1 Torr); R_f 0.39 (hexane/AcOEt = 5/1). IIIbc [13], m.p. 59–60°C (from hexane) (lit. m.p. 60–61°C); R_f 0.41 (hexane/AcOEt = 5/1). IVb [14]: m.p. 123–124°C (from EtOH) (lit. m.p. 122–123°C); R_f 0.67 (hexane/AcOEt = 3/1).

Reaction of acetophenone with IIb

The reaction of acetophenone (0.37 g, 3 mmol) with freshly prepared IIb (3.6 mmol) in the presence of PdCl$_2$(PPh$_3$)$_2$ (0.043 g, 0.06 mmol) in a mixture of THF (9 ml) and HMPA (18 ml) was carried out at reflux for 60 min. (E)-β-Methylchalcone [15] was obtained in 58% yield; b.p. 157–162°C/1 Torr (lit. b.p. 150–155°C/1 Torr); R_f 0.64 (hexane/AcOEt = 3/1).

A reaction of benzaldehyde (0.32 g, 3 mmol) with IIb (3.6 mmol) was carried out under similar conditions, diphenylmethanol [16] was obtained in 63% yield; m.p. 67–68°C (from EtOH/H$_2$O) (lit. m.p. 68°C); R_f: 0.40 (hexane/AcOEt = 3/1).

The competition between benzaldehyde and bromobenzene for reaction with IIb

To a mixture of benzaldehyde (0.32 g, 3 mmol), bromobenzene (0.47 g, 3 mmol), and PdCl$_2$(PPh$_3$)$_2$ (0.043 g, 0.06 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml) and the mixture was refluxed for 30 min. Biphenyl [17] was obtained in 76% yield; m.p. 69.5–70.5°C (from EtOH) (lit. m.p. 70.5°C); R_f 0.60 (hexane/AcOEt = 50/1). Benzaldehyde was recovered unchanged (95%).

The competitition between bromobenzene (0.47 g, 3 mmol) and Ic (0.56 g, 3 mmol) for reaction with IIb (3.6 mmol) was left to take place during 15 min under similar conditions. IIIbc was obtained in 80% yield and biphenyl was formed in trace amounts. About 92% of bromobenzene remained unchanged.

The competition between benzaldehyde and bromobenzene for reaction with IIb in the absence of PdCl$_2$(PPh$_3$)$_2$

To a mixture of benzaldehyde (0.32 g, 3 mmol) and bromobenzene (0.47 g, 3 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml) and the mixture was refluxed for 60 min. Diphenylmethanol was obtained in 61% yield and about 91% of bromobenzene was recovered unchanged.

Homo-coupling of Ib with PdCl$_2$(PPh$_3$)$_2$ and zinc dust

This reaction was attempted by way of the procedure used to make IVa from p-chloroacetophenone and NiCl$_2$/Ph$_3$P/Zn in DMAC or DMF [6]. A suspension of Ib (0.60 g, 3 mmol), PdCl$_2$(PPh$_3$O$_2$ (43 mg, 0.06 mmol), and zinc dust (0.30 g, 4.6 mmol) in a mixed solvent of THF (9 ml) and HMPA (18 ml) was refluxed for 3 h. IVb was obtained in only 0.2% yield and 93% Ib was recovered unchanged.

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