An Expeditious Synthesis of 1-(4-Chlorophenyl)-3,3-dimethyl-2-butanone by a Ligand-Free Palladium-Catalyzed α-Arylation of Pinacolone: Scale-Up and Effect of Base Concentration

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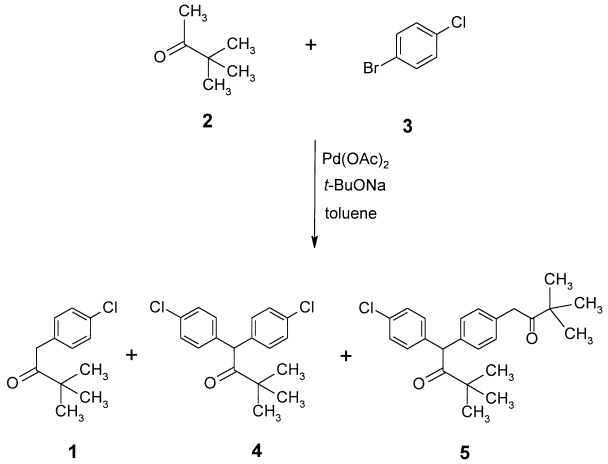
Abstract: An efficient and large-scale synthesis of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**) by an α-arylation of pinacolone (**2**) with 1-bromo-4-chlorobenzene (**3**) in the presence of palladium acetate and sodium *t*-butoxide in toluene is described. An increase in the concentration of sodium *t*-butoxide to 2.5–3.0 equivalents suppressed the formation of over-arylated products. These ligand-free conditions afforded a yield of **1** that was comparable to those obtained by using a ligand.

Keywords: α-arylation; ketones; ligand-free homogeneous catalysis; palladium; pinacolone

Introduction

1-(4-Chlorophenyl)-3,3-dimethyl-2-butanone (**1**) serves as an important intermediate in the synthesis of fungicidal derivatives.[1] The original synthesis of **1** involved the Grignard addition of 4-chlorobenzylmagnesium bromide, which was not commercially available and was prepared from 4-chlorobenzyl bromide and magnesium in diethyl ether, to pivalonitrile followed by the isolation and hydrolysis of intermediate 1-(4-chlorobenzyl)-2,2-dimethyl-propylideneamine hydrochloride with HCl at reflux for 3 h in 52% yield.[2,3] While this three-step route represented a straightforward synthesis of **1**, it was not deemed suitable for large scale due to the use of diethyl ether. In a development program we needed to devise an efficient and economical synthesis of **1** that is amenable for large scale operation.

We rationalized that α-arylation of pinacolone (**2**) with 1-bromo-4-chlorobenzene (**3**) would provide such an efficient and economical synthesis of **1**. The α-arylation of pinacolone (**2**) with bromobenzene was reported in the presence of $FeCl_2$.[4] However, this method was not attractive due to the use of DMSO as the solvent. Other methods were also not considered practical.[5] We were next attracted to the palladium-catalyzed α-arylation of ketones[6] with aromatic halides pioneered by Buchwald[7–9] and Hartwig.[10–12] The synthetic utility of this methodology has been recently reported by others.[13–21] α-Arylation of pinacolone (**2**) with 3-bromofluorobenzene was reported in 74% yield using $Pd_2(dba)_3$ as the catalyst and Xantphos as the ligand,[9] and with bromobenzene in 51% yield using $Pd(dba)_2$ as the catalyst and 1,1′-bis(di-*o*-tolylphosphino)ferrocene (DTPF) as the ligand.[10] Since these catalysts and ligands are expensive, we needed to develop ligand-free conditions using a cheaper palladium catalyst such as palladium acetate. Arylation under ligand-free conditions was also reported by Buchwald.[9] In this paper we describe an efficient and large scale synthesis of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**) by a ligand-free α-arylation of pinacolone (**2**) with 1-bromo-4-chlorobenzene (**3**) in the presence of palladium acetate and an excess (2.5–3.0 equivalents) of sodium *t*-butoxide in toluene (Scheme 1).



Scheme 1.

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Results and Discussion

α-Arylation of pinacolone (**2**, 1.5 equiv.) with 1-bromo-4-chlorobenzene (**3**) in the presence of palladium acetate (1 mol %) and sodium *t*-butoxide (1.6 equiv.) in toluene at 97 °C for 9 h led to satisfactory conversion to **1** (Table 1, entry 1, Method A). These reaction conditions are a modification of Buchwald's conditions.[9] The bromide in **3** reacted selectively over chloride as no bromo analogue of **1** was observed. However, formation of diarylated and diarylated-diketo products (**4** and **5**) was observed. The ratios of **1**, **4**, and **5** are listed in Table 1 and were determined by HPLC using authentic samples as external standards. An authentic sample of **1** was prepared by the Grignard reaction route,[2,3] and **4** was prepared by an α-arylation of **1** with **3**. The pure sample of **5** was obtained by a silica gel chromatography of the reaction mixture from entry 1. The yield of **1** in crude solution, as determined by HPLC, was 64%. Since in our case it was not necessary to isolate pure **1**, we used crude **1** in the next step.[2] An increase in the reaction temperature to 105 °C led to an increase in the diarylation (27.4% of **4** in only 1.5 h, entry 2). However, a decrease in the temperature to 90 °C slowed down the reaction significantly as it required almost 17 h (entry 3). Thus, the conditions in entry 1 were selected for further scale-up. One of the drawbacks with using palladium-catalyzed reactions is the removal of palladium from the product. Activated carbon (PICA P1400) in refluxing toluene was effective in lowering palladium to only 32 ppm, and the desired levels of < 4 ppm could not be achieved.[22] After an extensive study we found that palladium could be reduced to < 4 ppm by washing the crude toluene layer with L-cysteine[23] at 85–90 °C, followed by washing with a solution of L-cysteine and sodium thiosulfate pentahydrate at 78–82 °C. α-Arylation of pinacolone (**2**) with 4-bromochlorobenzene (**3**) was successfully scaled-up to a 14.4-kg scale of **3** (entry 1) in the pilot plant.

Our next goal was to enhance the yield of **1**. Since the lower yield of **1** was due to the further α-arylation of **1** to **4**, some of which then arylated pinacolone (**2**) to **5**, minimizing the formation of **4** and **5** should result in an increase in the yield of **1**. We postulated that the formation of **4**, and in turn of **5**, could be suppressed by using an excess of the base in this reaction. This hypothesis was based on the fact that the α-methylene in the product **1**, being more acidic than in the starting material **2**, would undergo preferential deprotonation. Use of an excess of the base would generate enolates of both **1** and **2** irreversibly, and the enolate of pinacolone (**2**), being a better nucleophile than that of **1**, will undergo preferential α-arylation, thus suppressing the formation of **4**. As expected, use of 3.0 equivalents of sodium *t*-butoxide at 85 °C resulted in a significant decrease in the formation of **4** and **5** (entry 5) and an increase in the yield of **1** to 82% from 64%. A decrease in the amount of sodium *t*-butoxide to 2.5 equivalents (entry 4) did not significantly influence the formation of **4** and **5**, or the yield of **1**. It, however, led to a decrease in the rate of reaction. Use of 2.2 equivalents of base for the monoarylation of acetophenone with bromobenzene was reported by Hartwig.[11] Lowering the reaction temperature to 70 °C did not lead to a complete reaction even after 17 h (entry 6). Since catalytic amounts of water are known[24] to have beneficial effects on organometallic processes and to enhance the regioselectivity of the Heck reaction,[25] we decided to investigate this α-arylation in the presence of catalytic amounts of water. No change in the ratio of **1**, **4**, and **5** or in the yield of **1** was observed in the presence of 0.05 equivalents of water (entry 7). Interstingly, water also did not have any detrimental effect on this reaction. Conditions utilizing 2.5 equivalents of sodium *t*-butoxide (entry 4, Method B) at 85 °C were selected and successfully scaled-up to a multigram scale. At the same time the work-up conditions were also improved. The results with these ligand-free conditions (entries 4 and 5) were comparable to those obtained with $Pd_2(dba)_3$ in the presence of

Table 1. Palladium-catalyzed α-arylation of pinacolone (**2**) with 1-bromo-4-chlorobenzene (**3**).

Entry	$Pd(OAc)_2$ [equiv.]	**2** [equiv.]	*t*-BuONa [equiv.]	Temp. [°C]	Time [h]	Ratio of products [%][a]				Yield [%][a]
						3	**1**	**4**	**5**	
1	0.01	1.5	1.6	97	9.0	0	81.3	12.0	6.7	64
2	0.01	1.5	1.6	105	1.5	55.3	15.9	27.4	1.4	ND[d]
3	0.01	1.5	1.6	90	17.0	2.7	80.7	13.9	2.7	65
4	0.01	1.4	2.5	85	9.5	1.4	91.6	5.0	2.0	81
5	0.01	1.4	3.0	85	8.0	0	91.4	5.3	3.3	82
6	0.01	1.4	3.0	70	18.0	31.7	64.3	2.3	1.7	ND[d]
7	0.01[b]	1.4	3.0	85	7.0	2.7	90.2	5.1	2.0	81
8	$Pd_2(dba)_3$/BINAP[c]	1.4	3.0	85	2.0	0	97.0	1.8	1.2	85

[a] Determined by HPLC.
[b] 0.05 equiv of water was used.
[c] With $Pd_2(dba)_3$ (0.005 equiv.) and BINAP (0.015 equiv.).
[d] ND = not determined.

2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) as the ligand (entry 8).

Since **1** is highly soluble in most solvents, its isolation was not straightforward. We were able isolate **1** in 60% yield by a recrystallization from *tert*-butyl alcohol and in 63% yield from heptane at −15 °C. In both cases the filtration of the product was slow. However, recrystallization from 1-butanol at −5 °C afforded **1** in 53% yield without filtration problem.

Conclusion

In summary, an efficient and large-scale synthesis of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**) by α-arylation of pinacolone (**2**) with 1-bromo-4-chlorobenzene (**3**) in the presence of palladium acetate and sodium *t*-butoxide in toluene is described. An increase in the concentration of sodium *t*-butoxide to 2.5–3.0 equivalents suppressed the formation of over-arylated products. These ligand-free conditions afforded the yield of **1** that was comparable to those obtained by using a ligand.

Experimental Section

Melting points were measured on a Buchi 535 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 instrument. The ratios of **1**, **3**, **4**, and **5** (Table 1) were determined on a Varian (Dynamax) HPLC system using a Phenomenex Luna C18 column (4.6 × 150 mm; 5 μm particle size) and mixture of methanol and water as the mobile phase (gradient: 0–12 min: 30% water in methanol, 12–22 min: 5% water in methanol, 22–25 min: 30% water in methanol) at a flow rate of 1.0 mL/min and UV detector at 225 nm. The retention times of **1**, **3**, **4**, and **5** were 10.5, 11.9, 21.8, and 20.9 min, respectively.

1-(4-Chlorophenyl)-3,3-dimethyl-2-butanone (1)

α-Arylation of Pinacolone (Method A): A 5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, heating mantle, and condenser with a nitrogen inlet-outlet, was charged with sodium *t*-butoxide (100.0 g, 1040.5 mmol) and dry toluene (300.0 mL). The mixture was stirred at 23–27 °C, and a solution of palladium acetate (1.48 g, 6.6 mmol) and 1-bromo-4-chlorobenzene (**3**, 125.0 g, 652.9 mmol) in dry toluene (850.0 mL) was added. The mixture was heated to an internal temperature at 97 °C over a period of 40 min. A solution of pinacolone (**2**, 98.1 g, 979.3 mmol) in dry toluene (300.0 mL) was added over a period of 45 min to 1 h while maintaining the internal temperature at 97 °C. The mixture was stirred at this temperature for additional 9 h. The reaction mixture was cooled to an internal temperature at 23–25 °C over a period of 30 min and a 15% aqueous solution of ammonium chloride (600.0 g) was added over a period of 10 min while maintaining the internal temperature at 20–27 °C. The organic layer was separated and washed with a saturated solution of sodium chloride (600.0 mL). To the organic layer was added a solution of L-cysteine (150.0 g) in water (900.0 mL) and the mixture was heated to an internal temperature at 84–90 °C over a period of 40 min. After stirring for an additional 5 h at this temperature, the mixture was cooled to 23–27 °C. The aqueous layer was discarded and the organic layer was filtered through a pad of Celite (20.0 g). After washing the pad with toluene (200.0 mL), the filtrates were combined. To the combined filtrates was added a solution of L-cysteine (75.0 g) and sodium thiosulfate pentahydrate (2.5 g) in water (600.0 mL). The mixture was heated to an internal temperature at 78–82 °C. White solids formed gradually. The triphasic mixture was stirred at this temperature for additional 5 h, cooled to 23–27 °C, and the organic layer was separated. The organic layer was filtered over a pad of Celite (20.0 g), and the pad was washed with toluene (200.0 mL). The combined filtrates were washed with saturated solution of sodium chloride (400.0 mL). The organic layer was filtered and concentrated to collect about 800.0 mL of solvent and to obtain about 1.0 L of a crude solution of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**), which was used in the next step; yield: 64% (by HPLC); Pd 2 ppm.

This process afforded a 62% yield of **1** on a 14.4-kg scale of 1-bromo-4-chlorobenzene (**3**) in the pilot plant.

Improved α-Arylation of pinacolone (Method B): A 2-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, heating mantle, and condenser with a nitrogen inlet-outlet, was charged with sodium *t*-butoxide (125.5 g, 1305.8 mmol) and dry toluene (300.0 mL). The mixture was stirred at 23–27 °C, and a solution of palladium acetate (1.17 g, 5.2 mmol) and 1-bromo-4-chlorobenzene (**3**, 100.0 g, 522.3 mmol) in dry toluene (550.0 mL) was added. The mixture was heated to an internal temperature at 85 °C over a period of 40 min. A solution of pinacolone (**2**, 73.2 g, 731.2 mmol) in dry toluene (150.0 mL) was added over a period of 1 h while maintaining the internal temperature at 85 °C. The mixture was stirred at this temperature for additional 9.5 h. The reaction mixture was cooled to an internal temperature at 0–5 °C over a period of 30 min, and water (500.0 mL) was added over a period of 10 min while maintaining the internal temperature at <25 °C. To the organic layer was added a slurry of L-cysteine (50.0 g) in water (300.0 mL), and the mixture was heated to an internal temperature at 80–86 °C over a period of 40 min. After stirring for an additional 8 h at this temperature, the mixture was cooled to 23–27 °C. The aqueous layer was discarded, and the organic layer was washed with water (300.0 mL) and filtered through a pad of Celite (15.0 g). After washing the pad with toluene (100.0 mL), the filtrates were combined and concentrated to collect about 1.0 L of solvent and to obtain about 300.0 mL of a crude solution of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**); yield: 81% (by HPLC).

Isolation of 1-(4-Chlorophenyl)-3,3-dimethyl-2-butanone (1)

To the residue (300.0 mL) from method B was added 1-butanol (600.0 mL), and the solution was concentrated to obtain about 200.0 mL of residue (collect about 700.0 mL of solvent). This residue was heated to an internal temperature of 40–45 °C over a period of 20 min to obtain a clear solution. The solution was

cooled to an internal temperature at 8–10 °C over a period of 1 h, and the stirring was continued for an additional 5 h. The solids were collected by filtration, washed with precooled (0–5 °C) 1-butanol (100.0 mL), and dried at 40 °C under reduced pressure for 16 h to afford 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**): yield 58.3 g (53%); Pd <3 ppm; mp 47–49 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (s, 9H), 3.76 (s, 2H), 7.09 (d, 2H, J = 8.5 Hz), 7.25 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ = 26.3, 42.4, 44.6, 128.5, 130.9, 132.5, 133.4, 212.4; anal. calcd. for $C_{12}H_{15}ClO$: C 68.4, H 7.18, Cl 16.83; found: C 68.54, H 7.38, Cl 16.86.

1,1-Di-(4-chlorophenyl)-3,3-dimethyl-2-butanone (4)

To a mixture of sodium *t*-butoxide (12.8 g, 133.2 mmol) and palladium acetate (0.213 g, 0.95 mmol) in dry toluene (100.0 mL) was added a solution of 1-bromo-4-chlorobenzene (**3**, 18.0 g, 94.0 mmol) in dry toluene (90.0 mL), and the mixture was heated to an internal temperature at 102 °C. A solution of 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**1**, 20.0 g, 94.9 mmol) in dry toluene (60.0 mL) was added over a period of 15 min, and the stirring was continued at the same temperature for 14 h. The mixture was cooled to 22–27 °C and quenched with a saturated solution of ammonium chloride (80.0 mL) over a period of 30 min while maintaining the internal temperature at 22–35 °C. The organic layer was separated and filtered through a pad of Celite (5.0 g). The pad was washed with toluene (10.0 mL), and the combined filtrates were concentrated to afford a brown solid. To this solid was added heptane (170.0 mL), and the slurry was heated to an internal temperature of 65 °C to obtain a dark solution. The solution was cooled to an internal temperature of −23 °C over a period of 1 h. The stirring was continued at this temperature an additional 15 min, and the solid was collected by filtration, washed with cold heptane (2 × 50.0 mL) and dried at 40 °C under reduced pressure to afford 1,1-di-(4-chlorophenyl)-3,3-dimethyl-2-butanone (**4**); yield: 16.0 g (52.5%); mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (s, 9H), 5.50 (s, 1H), 7.15 (d, 4H, J = 8.5 Hz), 7.30 (d, 4H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ = 26.4, 45.7, 56.1, 128.7, 129.9, 133.2, 137.6, 212.6; anal. calcd for $C_{18}H_{18}Cl_2O$: C 67.3, H 5.65, Cl 22.07; found: C 67.8, H 5.67, Cl 22.52.

1-(4-Chlorophenyl)-1-[4-(3,3-dimethyl-2-oxo-butyl)phenyl]-3,3-dimethyl-2-butanone (5)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.16 (s, 9H), 1.19 (s, 9H), 3.75 (s, 2H), 5.52 (s, 1H), 7.10 (d, 2H, J = 8.30 Hz), 7.18 (d, 2H, J = 8.30 Hz), 7.19 (d, 2H, J = 8.60 Hz), 7.25 (d, 2H, J = 8.60 Hz); ^{13}C NMR ($CDCl_3$): δ = 26.3, 42.7, 44.6, 45.6, 56.5, 128.6, 130.0, 132.8, 133.9, 137.3, 138.2, 212.8; MS: m/e = 385.4 (MH^+).

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