Synthesis of β-Keto Esters by Carbonylation of Halomethylketones

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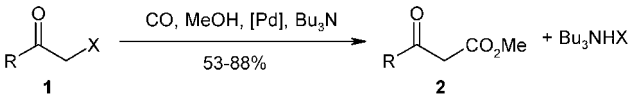
Abstract: A number of β-keto esters were synthesized by Pd-catalyzed carbonylation of halomethylketones in the presence of tributylamine in 68–86% yields. The reaction is completed in 2 hours at 110 °C and 10 bar CO pressure. Chloromethylketones are carbonylated selectively while 2-bromoacetophenone is partly reduced to acetophenone as a byproduct. The reaction can be carried out at atmospheric pressure though the rate stays low. The reaction mechanism is discussed.

Key words: halomethylketones, β-keto esters, carbonylation, palladium, catalysis

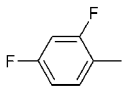
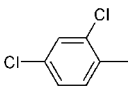
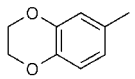
β-Keto esters are valued for their wide applications in organic synthesis, technical chemistry and related areas.[1–3] Condensation of β-keto esters with binucleophiles is a general method for the preparation of pyrimidines and some other heterocycles.[1] β-Keto esters are used in the synthesis of bioactive compounds and their analogues.[2] Preparation of new ligands for homogenous catalysis,[3a] synthesis of chelate complexes for metal microfilms impregnation, for MRI-contrast agents, and polarizers,[3b–e] polymer stabilization,[3f] liquid crystal preparation technology,[3g] preparation of sols and new polymers by sol-gel technology[3h] are some other areas of the uses of β-keto esters. Claisen reaction[4] and related condensations of enolates with alkyl carbonates[5a] and oxalates followed by decarbonylation[5b] are common methods for their preparation. The wide application of β-keto esters stimulates the elaboration of other approaches.[6]

Catalytic carbonylation is widely used for introducing the carbonyl function into molecules. Carbonylation of aryl, allyl, benzyl, and vinyl halides, alcohols, olefins and alkynes into the corresponding aldehydes, ketones, carboxylic acids and their derivatives has been studied in detail.[7] On the contrary, there are a few disembodied data on Pd-catalyzed carbonylation of α-halo ketones in the literature and the yields are generally modest. 2-Bromoacetophenone was carbonylated on $PdCl_2(PPh_3)_2$ at 80 °C and 13 bar CO pressure in the presence of *N*[1],*N*[1],*N*[8],*N*[8]-tetramethyl-1,8-naphthalenediamine yielding methyl benzoylacetate in 64% yield in 48 hours.[8] Ethyl[9] and *tert*-butyl[10] esters of benzoylacetic acid were produced by carbonylation of 2-chloroacetophenone on $PdCl_2(PPh_3)_2$ or $PdCl_2(TPP)_2$ in 25–50% yield. Very recently Cavinato and Toniolo reported their results on ethoxycarbonylation of 2-chlorocyclohexanone to the corresponding β-keto ester on $PdCl_2(PPh_3)_2$–PPh_3.[11] The yield reached 80% at 100 bar but drastically decreased upon decreasing pressure.

Here we report our results on Pd-catalyzed alkoxycarbonylation of halomethylketones **1**. This can be useful for preparing both alkyl acetoacetates and β-aryl-β-keto esters **2**. The reaction proceeds under rather mild conditions, since β-hydride elimination in the substrate is impossible (Scheme 1).



[Pd] = $PdCl_2(PPh_3)_2$, $Pd(dba)_2$–$2PPh_3$
Conditions: 110 °C, 10 bar, 2 h

1, 2	a	b	c	d	e	f
R	Me	Ph				Ph
X	Cl	Cl	Cl	Cl	Cl	Br
Yield	80	86	70	68	88	53

Scheme 1

Optimization of conditions was done with chloroacetone (**1a**) as substrate. The reaction proceeded smoothly in MeOH solution in the presence of 1 mol% of $PdCl_2(PPh_3)_2$ or $Pd(dba)_2$–$2PPh_3$ as a catalyst precursor and Bu_3N as a base under 10 bar CO pressure and 110–130 °C. Under these conditions the reaction was completed in 2 hours with almost quantitative yield of methyl acetoacetate (**2a**) (GC data).

Utilization of phosphine-free palladium such as $PdCl_2$, $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$ seems to be ineffective. No reaction took place without the base. Bu_3N was the most preferable base agent. $CaCO_3$, K_2CO_3 and pyridine gave no satisfactory results, only a trace amount of **2a** was detected. In the presence of Na_2CO_3 the yield was 46%. Use of NaOAc (yield 15%) was accompanied with formation of 2-acetoxyacetone. The concentration of base seemed to be important too. The yield of **2a** decreased from 98% to 53% upon decreasing Bu_3N/**1a** ratio from 1.5 to 1.1.

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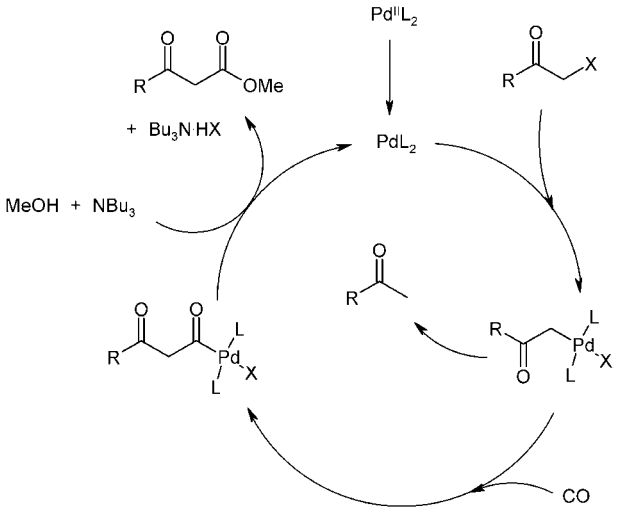
Carbonylation of halomethylketones **1** was carried out under optimal conditions (see Scheme 1). Surprisingly, the reactivity of bromides and chlorides seemed to be different. Chlorides **1a**–**e** were carbonylated selectively. On the contrary, carbonylation of 2-bromoacetophenone (**1f**) in MeOH solution gave only 53% of **2b**. At the same time acetophenone (33%) was formed. Similar results were obtained when EtOH, *t*-BuOH and PhOH were used instead of MeOH.

A plausible scheme of the catalytic cycle (Scheme 2) is based on the Heck mechanism for Pd-catalysed halide carbonylation.[12] The true catalyst is a zerovalent PdL_2 complex, which can be formed from Pd(II) precursor by reduction with CO.[13] Oxidative addition of **1** to PdL_2 followed by CO insertion into the Pd–C bond gives the the acyl intermediate. Nucleophilic attack of MeOH liberates the product **2** closing the catalytic cycle. The base present in carbonylation not only neutralizes the formed hydrohalogenic acid but likely catalyses alcoholysis of the acyl complex.[14] The above mentioned influence of Bu_3N concentration on the reaction rate indicates that alcoholysis of the acyl complex is the rate-limiting step.



R = Me, Ph, substituted Ph
L = CO, PPh_3, NBu_3
X = Cl, Br

Scheme 2

The reduction of the alkylpalladium intermediate (X = Br) leads to acetophenone as the main byproduct. Similarly, the reduction of benzyl halides to toluene was observed in two-phase carbonylation.[15,16] This was explained by homolytic cleavage of Pd–C bond followed by proton abstraction from water. In our case 1,4-diketones must be formed in a radical recombination. However, they were not found in the reaction mixture. This testifies against a single electron tranfer mechanism.

Additional experimentation showed that **1f** can be selectively reduced to acetophenone under reaction conditions in the absence of CO (100% conversion, 73% yield). Moreover, sole Bu_3N or MeOH also can reduce **1f**. Some amount of CH_2O were found in the last case. Detailed mechanism of the reduction is unclear. Anyway, bromides are not appropriate substrates due to their reduction to methylketones. This decreases the yield of the carbonylation product.[8]

It is possible to carry out the synthesis under normal pressure, but the reaction rate stays low. To maintain 110 °C temperature in the reactor at normal pressure we employed BuOH (bp 118 °C) instead of MeOH; the yield of butyl acetoacetate was 25% in 5 hours.

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer with TMS as internal standard. IR spectra were recorded on a Specord M80 spectrophotometer. Mass spectra were recorded on a Cratos MS-30 spectrometer. GC was carried out using Avtochrom UA5 PID, capillar column SE-30 (30 m × 0.25 mm); carrier gas He, *n*-octanol as internal standard.

The initial halides **1** were synthesised by direct halogenation of ketones (**1a**,**b**,**f**) or by acylation of arenes with chloroacyl chlorides (**1c**–**e**).[17]

β-Keto Esters 2; General Procedure

The carbonylation reaction was carried out in a stainless steel reactor equipped with a Teflon liner and magnetic stirrer. The substrate **1** (3 mmol), $PdCl_2(PPh_3)_2$ [or $Pd(dba)_2 + 2PPh_3$] (0.03 mmol), Bu_3N (4.5 mmol), and MeOH (10 mL) were charged in the reactor. The contents were flushed several times with CO and pressurized (10 bar). When the required temperature was attained (110 °C), the stirrer was switched on. The reactor was cooled down in 2 h, depressurised, and unloaded. The solvent was carefully evaporated under reduced pressure. The residue was dissolved in 20% HCl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with H_2O up to pH 7, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by recrystallization or chromatography.

Methyl Acetoacetate (2a)

Purified on a silica gel column (eluent: hexane–CH_2Cl_2, 1:5); yield: 0.28 g (80%). Identity with commercial product was confirmed by GC.

Methyl 3-Phenyl-3-oxopropanoate (2b)

Purified on a silica gel column (eluent: hexane–CH_2Cl_2, 1:5); yellowish oil; yield: 0.46 g (86%).

^{1}H NMR ($CDCl_3$): δ = 12.50 (s, 0.1 H, OH in enol form), 7.9–8.0 (m, 2 H, H-2,6), 7.3–7.7 (m, 3 H, H-3,4,5), 5.68 (s, 0.1 H, =CH in enol form), 4.02 (s, 1.6 H, CH_2), 3.80 (s, 0.3 H, CO_2CH_3 in enol form), 3.75 (s, 2.7 H, CO_2CH_3 in keto form). The spectrum corresponds to the one published in the literature.[8]

Methyl 3-(2,4-Difluorophenyl)-3-oxopropanoate (2c)

Recrystallized from hexane; yellowish needles; mp 56 °C; yield: 3.55 g (70%).

IR (KBr): 3424, 3096, 2968, 2832, 1620, 1504, 1448, 1396, 1260, 1232, 1200, 1084, 1068, 976, 856, 836, 792, 604, 544, 423 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 12.63 (s, 0.9 H, OH in enol form), 7.8–8.0 (m, 1 H, H-3), 6.8–7.0 (m, 2 H, H-5,6), 5.81 (s, 0.9 H, =CH in enol form), 3.98 (s, 0.2 H, CH_2), 3.80 (s, 2.7 H, CO_2CH_3 in enol form), 3.76 (s, 0.3 H, CO_2CH_3 in keto form).

MS: *m*/*z* (%) = 214 (M^+, 15), 142 (100), 113 (20), 69 (12), 63 (8), 55 (5), 45 (5).

Anal. Calcd for $C_{10}H_8F_2O_3$ (214.2): C, 56.08; H, 3.77. Found: C, 56.28, H, 4.03.

Methyl 3-(2,4-Dichlorophenyl)-3-oxopropanoate (2d)
Recrystallized from hexane;white solid; mp 70 °C; yield: 0.50 g (68%).

IR (KBr): 3448, 3088, 3008, 2960, 1656, 1632, 1584, 1552, 1476, 1448, 1392, 1368, 1280, 1244, 1204, 1112, 1008, 880, 848, 824, 800, 736, 568, 432 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 12.40 (s, 0.4 H, OH in enol form), 7.20–7.70 (m, 3 H, H-3,5,6), 5.59 (s, 0.4 H, =CH in enol form), 4.04 (s, 1.2 H, CH_2), 3.82 (s, 1.2 H, CO_2CH_3 in enol form), 3.75 (s, 1.8 H, CO_2CH_3 in keto form).

MS: *m*/*z* (%) = 247 (M^+, 4), 213 (31), 211 (75), 177 (25), 175 (92.5), 173 (100), 147 (21), 145 (38), 108 (29), 75 (26), 69 (27), 59 (18), 50 (12).

Anal. Calcd for $C_{10}H_8Cl_2O_3$ (247.1): C, 48.61; H, 3.26, Cl, 28.70. Found: C, 48.93, H, 3.43, Cl, 28.86.

Methyl 3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-oxopropanoate (2e)
Purified on a silica gel column (eluent: hexane–CH_2Cl_2, 1:5); white crystals; mp 66 °C; yield: 0.62 g (88%).

IR (KBr): 2936, 2848, 1744, 1672, 1608, 1584, 1504, 1432, 1328, 1296, 1248, 1152, 1128, 1064, 1020, 928, 912, 896, 880, 856, 832, 812, 704, 656, 624 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 12.52 (s, 0.05 H, OH in enol form), 7.5 (m, 1 H, H-7), 7.3 (m, 1 H, H-5), 6.9 (m, 1 H, H-8), 5.58 (s, 0.05 H, =CH in enol form), 4.3–4.4 (m, 2 H, H-2,3), 3.95 (s, 1.9 H, CH_2), 3.80 (s, 0.15 H, CO_2CH_3 in enol form), 3.76 (s, 2.85 H, CO_2CH_3 in keto form).

MS: *m*/*z* (%) = 236 (M^+, 20), 204 (11.5), 164 (23), 163 (100), 135 (13), 107 (8), 79 (11), 77 (7), 69 (4), 51 (10).

Anal. Calcd for $C_{12}H_{12}O_5$ (236.2): C, 61.02; H, 5.12. Found: C, 60.74, H, 5.35.

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