FACILE SYNTHESIS OF BENZYL KETONES BY THE REDUCTIVE COUPLING OF BENZYL BROMIDE AND ACYL CHLORIDES IN THE PRESENCE OF A PALLADIUM CATALYST AND ZINC POWDER
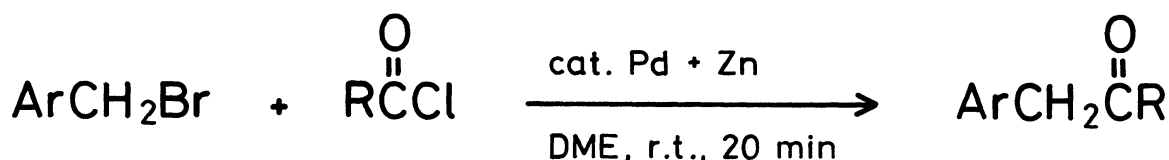
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Benzyl ketones were obtained in good yields from benzyl bromide and acyl chlorides by the combined use of Zn and a palladium catalyst under mild conditions.

Although coupling reaction of acyl halides and organometallic compounds is one of the most fundamental methods for ketone synthesis, the major side reaction is the addition of the organometallic compounds to the produced ketone. The side reaction has been excluded by employing various organometallic reagents such as organomagnesium,[1a,b] cadmium,[1a,c] zinc,[1a] copper,[1d] manganese,[1e] mercury,[1f] aluminum,[1g] rhodium,[1h] boron,[1i] and silicon compounds[1j] under well defined conditions. Recently, palladium-catalyzed coupling reaction of acyl halides and organotin compounds has received considerable attention.[2] Organometallic compounds above-mentioned are generally prepared from the corresponding organic halides. If acyl halides could couple directly with organic halides, it will offer a very convenient method for ketone synthesis.[3] In this paper, we wish to report a simple method for the synthesis of benzyl ketones by the reductive coupling of acyl chlorides and benzyl bromide by means of using zinc and a palladium catalyst.

When a mixture of benzyl bromide (1 equiv) and benzoyl chloride (1 equiv) was added into a suspension of tetrakis(triphenylphosphine)palladium(0) (5 mol%) and zinc powder (2 equiv) in 1,2-dimethoxyethane (DME) at room temperature and stirred for 20 min, the reductive coupling product, benzyl phenyl ketone was obtained in 88% yield. The presence of the palladium catalyst was essential for the reaction; without the palladium catalyst, benzyl phenyl ketone was obtained in less than 4% yield along with many by-products.

$$\text{ArCH}_2\text{Br} \ + \ \text{R}\overset{\displaystyle\text{O}}{\overset{\|}{\text{C}}}\text{Cl} \ \xrightarrow[\text{DME, r.t., 20 min}]{\text{cat. Pd + Zn}} \ \text{ArCH}_2\overset{\displaystyle\text{O}}{\overset{\|}{\text{C}}}\text{R}$$

Various kinds of palladium and nickel compounds were employed as a catalyst for the reductive coupling reaction of benzyl bromide and benzoyl chloride or butanoyl chloride, and the results were summarized in Table I. $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ are fairly superior to $Pd(PhCN)_2Cl_2$, $Pd(OAc)_2$, $PdCl_2$, and $Ni(PPh_3)_2Cl_2$, the use of whose catalysts resulted in forming considerable amounts of the self-coupling product of benzyl bromide, i.e. dibenzyl. In the case of the reaction of

Table I.   Effect of Catalyst on the Reductive Coupling of $C_6H_5CH_2Br$ and RCOCl in
the Presence of Zn Powder[a]

| Catalyst | (mol%) | R | Time | Yield(%)[b] | |
				$C_6H_5CH_2COR$	$(C_6H_5CH_2)_2$
$Pd(PPh_3)_4$	(5)	C_6H_5	20 min	88	trace
	(5)	$n-C_3H_7$	20 min	61	23
$Pd(PPh_3)_2Cl_2$	(5)	C_6H_5	20 min	83	trace
	(5)	$n-C_3H_7$	20 min	84	16
	(2)	$n-C_3H_7$	20 min	55	17
	(10)	$n-C_3H_7$	20 min	66	11
$Pd(PhCN)_2Cl_2$	(5)	C_6H_5	20 min	6	19
$Pd(OAc)_2$	(5)	C_6H_5	2 h	49	33
$PdCl_2$	(5)	C_6H_5	20 min	59	26
$Ni(PPh_3)_2Cl_2$	(5)	C_6H_5	3 h	24	50

[a] All reactions were carried out in 1 mmol scale at room temperature in DME. The molar ratio of $C_6H_5CH_2Br$:RCOCl:Zn = 1:1:2.   [b] Isolated yields by silica gel TLC.

benzyl bromide with butanoyl chloride, $Pd(PPh_3)_2Cl_2$ was found to be superior to
$Pd(PPh_3)_4$. The amount of $Pd(PPh_3)_2Cl_2$ affected the yield, and the use of 5 mol% of
the catalyst gave the best result. Further, the reaction was influenced markedly
by the solvents. When THF, acetonitrile, dioxane, hexamethylphosphoric triamide
and N,N-dimethylformamide were employed as a solvent in the reaction of benzyl
bromide and benzoyl chloride in the presence of 5 mol% $Pd(PPh_3)_2Cl_2$ and zinc powder,
the yields of the corresponding ketone were 76, 72, 65, 27, and 12%, respectively.
DME was found to be the best solvent (83%).

     In order to define the scope and limitation of this new procedure for the
benzyl ketone synthesis, the reaction of various acyl chlorides and benzyl bromide
in the presence of Zn powder catalyzed by $Pd(PPh_3)_2Cl_2$ was examined as shown in
table I. The reaction of aromatic and heterocyclic acyl chlorides gave the corre-
sponding ketones in over 80% yields (entries 1,2,3, and 11). In the case of ali-
phatic acyl chlorides, a linear one gave the desired ketone in a high yield,
whereas sterically hindered branched ones gave poor results (entries 4,5,6, and 7).
Functional groups such as α,β-unsaturated double bond, ester, and arylhalogen in
acyl chlorides were tolerant, but the yields were moderate to good (entries 2,8,
and 9). The reaction of oxalyl chloride and benzyl bromide gave the diketone in
34% yield (entry 10). p-Chloro- or p-methyl substituent in benzyl bromide did not
affect the yields of the corresponding ketones (entries 11,13, and 14), whereas the
reaction of p-methoxy- or p-nitrobenzyl bromide gave poor results (entries 12 and
15). The reaction of phenethyl bromide with nonanoyl chloride gave 2-phenylundecan-
3-one in 55% yield along with considerable amounts of 2,3-diphenylbutane (37%)
(entry 16).

     Instead of benzyl bromide, benzyl chloride was used in the above reaction with
benzoyl chloride, furnishing benzyl phenyl ketone in 22% yield. The reaction of

Table II.   Reductive Coupling of Benzyl Bromides and Acyl Chlorides in the Presence
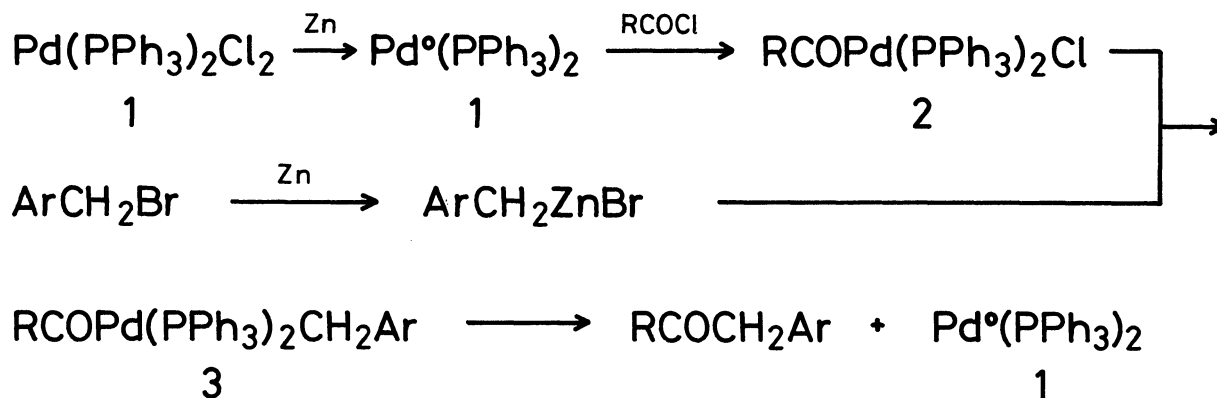of 5 mol% $Pd(PPh_3)_2Cl_2$ and Zn Powder[a]

Entry	RBr	R'COCl	Yield(%)[b] RCOR'	R-R
1	$C_6H_5CH_2Br$	C_6H_5COCl	83	trace
2	$C_6H_5CH_2Br$	$p\text{-}ClC_6H_4COCl$	90	trace
3	$C_6H_5CH_2Br$	(cyclopropane)COCl	81	trace
4	$C_6H_5CH_2Br$	$n\text{-}C_3H_7COCl$	84	16
5	$C_6H_5CH_2Br$	$(CH_3)_2CHCOCl$	65	28
6	$C_6H_5CH_2Br$	$(CH_3)_3CCOCl$	0	31
7	$C_6H_5CH_2Br$	$n\text{-}C_8H_{17}COCl$	78	17
8	$C_6H_5CH_2Br$	$CH_3CH=CHCOCl$	59	34
9	$C_6H_5CH_2Br$	$CH_2CH_2CO_2Me$ $|$ CH_2CH_2COCl	50	25
10	$C_6H_5CH_2Br$	$(COCl)_2$	34[c]	29
11	$p\text{-}CH_3C_6H_4CH_2Br$	C_6H_5COCl	80	trace
12	$p\text{-}CH_3OC_6H_4CH_2Br$	C_6H_5COCl	13	—
13	$p\text{-}ClC_6H_4CH_2Br$	C_6H_5COCl	80	trace
14	$p\text{-}ClC_6H_4CH_2Br$	$p\text{-}ClC_6H_4COCl$	82	trace
15	$p\text{-}O_2NC_6H_4CH_2Br$	$n\text{-}C_3H_7COCl$	10[d]	—
16	$C_6H_5CH(CH_3)Br$	$n\text{-}C_8H_{17}COCl$	55	37

[a] All reactions were carried out in 1 mmol scale in DME (5 ml) at room temperature for 20 min. The
molar ratio of $RBr:R'COCl:Zn:Pd(PPh_3)_2Cl_2 = 1:1.05:2:0.05$.   [b] Isolated yields by silica gel TLC.
[c] The yield of $(C_6H_5CH_2CO)_2$.   [d] p-Nitrobenzyl bromide was recovered (40%).

methyl iodide and benzoyl chloride gave the reductive coupling product, acetophenone
in a low yield (13%).

Following experiments were carried out in order to explore the reaction course.
When a mixture of benzoyl chloride (1 equiv) and benzyl bromide (1 equiv) was
treated with $Pd(PPh_3)_4$ (1 equiv) in DME at room temperature for 30 min, the glpc
analysis of the supernatant of the reaction mixture showed disappearance of benzoyl
chloride and conservation of benzyl bromide. This fact suggests that the oxidative
addition of benzoyl chloride to palladium(0) is faster than that of benzyl bromide.[4]
On the other hand, when a suspension of benzylzinc bromide[5] in DME was added into a
mixture of benzoyl chloride and 5 mol% of $Pd(PPh_3)_4$ in DME, and stirred for 20 min,
benzyl phenyl ketone was obtained in 59% yield.[6,7] Although the substituent effect
on the reaction course is not clear, the following reaction pathway seems to be the
most plausible based on the above facts. The first step is the oxidative addition
of acyl chloride to a palladium(0) complex (1), produced from $Pd(PPh_3)_2Cl_2$ and Zn,
to afford an acyl palladium(II) complex (2). Then, the complex 2 reacts with benzyl-
zinc bromide, produced from benzyl bromide and zinc *in situ*, generating an acyl-

$$\text{Pd(PPh}_3)_2\text{Cl}_2 \xrightarrow{\text{Zn}} \text{Pd}^{\circ}\text{(PPh}_3)_2 \xrightarrow{\text{RCOCl}} \text{RCOPd(PPh}_3)_2\text{Cl} \longrightarrow$$
$$\mathbf{1} \qquad\qquad \mathbf{1} \qquad\qquad\qquad \mathbf{2}$$

$$\text{ArCH}_2\text{Br} \xrightarrow{\text{Zn}} \text{ArCH}_2\text{ZnBr} \longrightarrow$$

$$\text{RCOPd(PPh}_3)_2\text{CH}_2\text{Ar} \longrightarrow \text{RCOCH}_2\text{Ar} + \text{Pd}^{\circ}\text{(PPh}_3)_2$$
$$\mathbf{3} \qquad\qquad\qquad\qquad\qquad\qquad \mathbf{1}$$

benzylpalladium(Ⅱ) complex (3). The last step is the reductive elimination to form ketone along with the regenerated palladium(0) complex. Thus, as a whole a catalytic cycle may be achieved.

In conclusion, the present reaction furnishes a novel and convenient method for the synthesis of benzyl ketones starting from benzyl bromide and acyl chlorides in a single step under very mild conditions.

References

1. a) D. A. Shirley, *Org. Reactions*, **8**, 28 (1954). b) F. Sato, M. Inoue, K. Ogura, and M. Sato, *Tetrahedron Lett.*, **1979**, 4303. c) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley, New York, 1970, p 713. d) G. H. Posner, *Org. Reactions*, **22**, 253 (1975). e) G. Cahiez, D. Bernard, and J. F. Normant, *Synthesis*, **1977**, 130. f) R. C. Larock and J. C. Bernhardt, *J. Org. Chem.*, **43**, 710 (1978). g) T. Mole and E. A. Jeffery, "Organoaluminum compounds," Elsevier, Amsterdom, 1972, p 313. h) L. S. Hegedus, P. M. Kendall, S. M. Lo, and J. R. Sheats, *J. Am. Chem. Soc.*, **97**, 5448 (1975). i) E. Negishi, K. Chiu, and T. Yoshida, *J. Org. Chem.*, **40**, 1676 (1975). j) G. A. Olah, T. Ho, G. K. S. Prakash, and B. G. B. Gupta, *Synthesis*, **1977**, 677.

2. D. Milstein and J. K. Stille, *J. Org. Chem.*, **44**, 1613 (1979), and references cited therein.

3. Only two examples have been reported for reductive coupling of acyl chlorides and alkyl iodide by using tetracarbonylferrate anion: J. P. Collman, S. R. Winter, and D. R. Clark, *J. Am. Chem. Soc.*, **94**, 1788 (1972); Y. Kimura, Y. Tomita, S. Nakanishi, and Y. Otsuji, *Chem. Lett.*, **1979**, 321.

4. Oxidative addition of organic halides, including acyl chloride and benzyl bromide, is well known: P. M. Maitlis, "The Organic Chemistry of Palladium," Vol. 1, Academic Press, New York, 1971, p 72; Y. Becker and J. K. Sille, *J. Am. Chem. Soc.*, **100**, 838 (1978).

5. M. Gaudemar, *Bull. Soc. Chim. Fr.*, **1962**, 974.

6. Without the palladium catalyst, the reaction of benzoyl chloride and benzylzinc bromide in DME at room temperature for 3 h gave only a trace amount of benzyl phenyl ketone.

7. Palladium-catalyzed reaction of benzylzinc bromide with aryl halides has been reported: E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977).