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Unsymmetrical Ketone Synthesis via Palladium Catalyzed Carbonylation of Organic Halides

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Summary. Aryl alkyl (or benzyl) ketones are selectively prepared by the reaction of aryl iodides and alkyl iodides (or benzyl chlorides) in the presence of a stoichiometric amount of zinc-copper couple and a catalytic amount of palladium(0) complex under an atmospheric pressure of carbon monoxide.

Recent development of palladium catalyzed coupling reactions of acyl halides with organotins[1] and aromatic halides or allyl acetates with ketone enolate derivatives[2] is a very useful entry to unsymmetrical ketone synthesis. The ketone synthesis by the use of carbon monoxide is undoubtedly more straightforward and of greater value. Compared with the palladium catalyzed carbonylation of organic halides, providing carboxylic acids, esters, amides, etc.,[3] however, there seems to exist onyl a limited number of methods of unsymmetrical ketone synthesis under carbonylation conditions. Tanaka et al. reported the palladium catalyzed unsymmetrical ketone synthesis by the coupling reaction of aryl and vinyl halides with organotins[4a,b] or terminal acetylenes[4] under medium pressure of carbon monoxide.

In this paper we wish to disclose our preliminary results on an efficient unsymmetrical ketone synthesis which was performed by the coupling reaction of aryl iodides with alkyl- or benzylzinc compounds catalyzed by tetrakis(triphenylphosphine)palladium under an atmospheric pressure of carbon monoxide (eq 1).

$$\mathrm{ArX + RX} \xrightarrow[\mathrm{Zn\text{-}Cu,THF}]{\mathrm{CO,\ Pd(PPh_3)_4}} \underset{1}{\mathrm{ArCOR}} + \underset{2}{\mathrm{ArR}} + \underset{3}{\mathrm{ArH}} + \underset{4}{\mathrm{ArAr}} \qquad (1)$$

The efficiency and utility of the present reaction may be augmented by the ease with which it can be performed (entry 2, Table I). A mixture of tetrakis(triphenylphosphine)-palladium (23.2 mg, 0.02 mmol) and zinc-copper couple[5] (196 mg, 3.0 mmol) was purged with carbon monoxide (equipped with a CO baloon) Into this mixture was added a solution of iodobenzene (408 mg, 2 0 mmol) and 1-iodopropane (374 mg, 2 2 mmol) in 4 ml of dry tetrahydrofuran (THF) The heterogeneous reaction mixture was stirred at 50°C for 24 hours. Vpc analysis showed that a 75% conversion of iodobenzene was attained and n-butyrophenone was formed in 93% yield Usual workup followed by purification by means of column chromatography (silica gel, n-hexane-ethyl acetate gradient) gave the spectroscopically homogeneous ketone in 90% isolated yield based on the conversion of iodobenzene Some representative results, together with the reaction conditions, for other combinations of aryl iodides and alkyl iodides are summarized in Table I, which reveals that the present ketone synthesis can be applied both to primary and secondary alkyl iodides Generally primary iodides showed the higher conversions than the secondary ones, but the selectivity of 1 to other products (2, 3, and 4) was almost the same. With respect to aryl iodides, the aryl iodides with electron donating substituents generally showed better results, judging from conversions and selectivities for 1. As a matter of fact, p-nitrophenyl iodide was unreactive under our reaction conditions and recovered quantitatively. No ketones were formed either for the combination of phenyl bromide and ethyl iodide or for the combination of phenyl iodide and n-propyl bromide.

$$Ar^1I + Ar^2CH_2Cl \xrightarrow[\text{Zn-Cu,THF}]{\text{CO, Pd(PPh}_3)_4} \underset{5}{Ar^1COCH_2Ar^2} + \underset{6}{Ar^1CH_2Ar^2} + \underset{7}{Ar^2CH_2CH_2Ar^2} \qquad (2)$$

In contrast to these, the reaction of benzyl halides and aryl iodides showed rather different reaction features (eq 2) Under the above conditions bibenzyl was obtained in substantial amount e g., 51% of p,p'-dichlorobibenzyl and 44% of phenyl p-chlorobenzyl ketone were obtained by the reaction of phenyl iodide (3 0 mmol) and p-chlorobenzyl chloride (3.0 mmol) at 60°C for 5 hours (Zn-Cu 3 03 mmol, $Pd(PPh_3)_4$ 0 06 mmol cf. entry 2 in Table II) Although the formation of bibenzyl was unavoidable, the amounts of them could be reduced by initiating the reaction at the lower temperatures Results, together with the reaction conditions are summarized in Table II Again in these cases aryl iodides with electron donating substituents showed better yields of unsymmetrical ketones 5 The reaction of methyl o-iodobenzoate with p-chlorobenzyl chloride (-78°C (2h), r.t (1h), 60°C (6h)) provided a mixture of 5 (18%), 6 (21%), and 7 (27%) together with o,o'-dicarbomethoxy-

Table I Unsymmetrical Ketone Synthesis from Aryl Iodides and Alkyl Iodides[a]

Entry	ArI	RI	Temp (°C)	Time (h)	Conv[b] (%)	Product (% Yield)[c] 1	2	3	4
1	PhI	MeI	45	24	63	(88)	0	0	0
2	PhI	n-PrI	50	24	75	90(93)	0	0	0
3	PhI	i-PrI	r.t	42	58	(86)	(tr)	0	0
4	PhI	i-BuI	50	28	43	85	0	0	0
5	PhI	n-$C_8H_{17}I$	50	23	49	90	3	0	0
6	PhI	c-$C_6H_{11}I$	50	24	42	63	0	0	4
7	4-$MeOC_6H_4I$	n-PrI	50	22	90	90	0	(tr)	0
8	4-MeC_6H_4I	n-PrI	50	24	80	91	0	0	0
9	2-MeC_6H_4I	n-PrI	50	24	88	56[d]	0	0	0
10	4-BrC_6H_4I	n-PrI	50	8	98	38	0	0	27[e]
11	2-$MeO_2CC_6H_4I$	n-PrI	50	22	100	0	0	23	23

a) Usual scale is as follows ArI (2.0 mmol), RI (2 2 mmol), $Pd(PPh_3)_4$ (0 02 mmol) and Zn-Cu (3.0 mmol) in 4 ml of THF under an atmospheric pressure of CO

b) Based on ArI, consumed

c) Isolated yield based on ArI consumed, and the values in column 4 should be devided by 2 for the comparison of molar ratios with columns 1, 2, and 3 The values in parentheses refer to the vpc yields taking bibenzyl as an internal standard

d) In addition to this, di(o-tolyl) ketone was isolated in 29% yield.

e) In addition to these, di(4-bromophenyl) ketone was isolated in 17% yield

Table II Unsymmetrical Ketone Synthesis from Aryl Iodides and Benzyl Chlorides[a]

Entry	Ar^1I	Ar^2CH_2Cl	Reaction Conditions	Product (% Isolated Yield)[b] 5	6	7
1	PhI	$PhCH_2Cl$	-78°C (2h), rt (1h), 60°C (21h)	57	0	42
2	PhI	4-$ClC_6H_4CH_2Cl$	rt (5h), 60°C (18h)	60	1	15
3	4-$MeOC_6H_4I$	4-$ClC_6H_4CH_2Cl$	-78°C (2h), rt (1h), 60°C (19h)	81	7	9
4	4-MeC_6H_4I	4-$ClC_6H_4CH_2Cl$	60°C (9h)	67	1	9

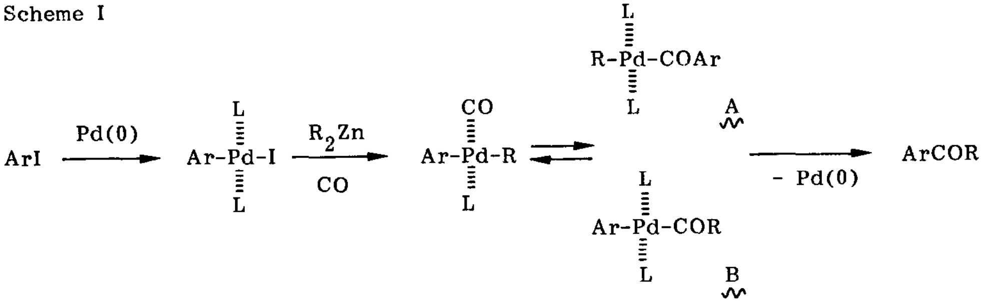
a) Usual reaction scale is as follows Ar^1X (2 0 mmol), Ar^2CH_2Cl (2.2 mmol), $Pd(PPh_3)_4$ (0 04 mmol) and Zn-Cu (3 0 mmol) in 5 ml of THF under an atmospheric pressure of CO The reactions were completed under the conditions shown

b) Yields are based on benzyl chlorides, and hence the values in column 7 should be devided by 2 for the comparison of molar ratios with columns 5 and 6 biphenyl (26%, based on methyl o-iodobenzoate) and methyl bezoate (28%, based on methyl o-iodobenzoate)

Under the same conditions as those for benzyl chlorides, allyl or propargyl bromide did not give the expected ketone in any detectable amounts, resulting in formation of a small amount of cross coupling product detected by vpc

The present reaction may consist of the following sequential reactions (Scheme I) an oxidative addition of palladium(0) species to aryl iodide, a transmetallation of alkyl or benzyl group from organozincs to arylpalladium complex and a migratory insertion of aryl (forming a complex A) and/or alkyl or benzyl group (forming a complex B) on carbon monoxide, followed by a reductive elimination of unsymmetrical ketones to reproduce palladium(0) species The limited success with benzyl chlorides and the unsuccessful results with allyl or propargyl bromide may be partly attributed to a relatively unfavorable equilibrium for the complex(es) A and/or B[6] compared with the R = alkyl cases

Scheme I



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(6) The migratory aptitudes usually are alkyl > benzyl > H and electronegative substituents retard the migration reaction J P. Collman and L. S Hegedus, "Principles and Applications of Organotransition Metal Chemistry", pp 260-298, University Science Books, Mill Valley, California (1980)

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