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ARYLATION AND VINYLATION OF 2-CARBOETHOXYETHYLZINC IODIDE AND 3-CARBOETHOXYPROPYLZINC IODIDE CATALYZED BY PALLADIUM

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Summary: By the palladium catalysis 2-carboethoxyethylzinc iodide reacts with aryl iodides and vinyl iodides or triflates to provide the coupling products (ethyl 3-arylpropionates and ethyl 4-pentenoates, respectively) in satisfactory yields. The similar coupling reaction is obserbed for the reaction with 3-carboethoxypropylzinc iodide.

α-Metallocarbonyl compounds ("enolates") are the most popular and the most useful reagents for organic syntheses. Undoubtedly the β- and γ-metallocarbonyl compounds are similarly of great value.[1] However the use of these organometallics is limited mainly due to the lack of their convenient synthetic methods. Recently we reported a simple method for the generation of 2-carboethoxyethylzinc iodide (**1**) and 3-carboethoxypropylzinc iodide (**2**) and their use for the coupling reaction with acid chlorides.[2] These organozincs were prepared by the Reformatsky type direct metallation of ethyl β-iodopropionate or ethyl γ-iodobutyrate with zinc-copper couple. In this communication, we further demonstrate the utilily of these organozinc reagents by the coupling reaction with aryl iodides, vinyl iodides and vinyl triflates.

Palladium Catalyzed Coupling Reaction of 1 and 2 with Aryl Iodides

There have been reported many useful methods to prepare α-aryl[3] and β-aryl[4] ketones via the palladium catalyzed arylation reactions. Interestingly, however, only a few methods are known for the synthesis of aryl esters. Most of them are based on the arylation of unsaturated esters.[5] Here we describe a new synthetic method of β-aryl and γ-aryl esters which was performed by the coupling reaction of aryl iodides with **1** and **2**, respectively.

$$EtO_2C(CH_2)_nZnI \ + \ ArI \longrightarrow EtO_2C(CH_2)_n\text{-}Ar$$

1: n = 2, **2**: n = 3

The typical procedure is as follows: To a solution of **1** or **2** (generated at 60°C in benzene /N,N-dimethylacetamide according to the same procedure as described previously)[2] was added a solution of aryl iodide and a catalytic amount of bis(tri-o-tolylphosphine)-

Table I. Palladium Catalyzed Coupling Reaction of **1** and **2** with Aryl Iodides[a)]

						% isolated yield[c)]	
run	**1** or **2**	XC_6H_4I	catalyst	conditions[b)]	% conv	$Ar(CH_2)_nCO_2Et$	Ar-Ar
1	**2**	X = H	$Pd(PPh_3)_2Cl_2$	0.5 h	91	75	22
2	**2**	X = H	$Ni(PPh_3)_2Br_2$	1 h	72	71	29
3	**2**	X = H	$Pd(PPh_3)_4$	1 h	100	33	66
4	**2**	X = H	$Pd(P(o\text{-}Tol)_3)_2Cl_2$	1 h	96	90	5
5	**1**	X = H	" "	1 h	100	90	0
6	**1**	X = o-Me	$Pd(PPh_3)_2Cl_2$	1 h	100	90	0
7	**2**	X = o-Me	" "	1 h	81	95	5
8	**1**	X = p-OMe	$Pd(P(o\text{-}Tol)_3)_2Cl_2$	1 h	100	96	0
9	**2**	X = p-OMe	" "	1 h	100	75	0
10	**1**	X = o-CO_2Me	" "	1 h	100	95	0
11	**2**	X = o-CO_2Me	" "	0.5 h	80	100	0
12	**1**	X = p-Br	" "	1 h	100	67	0
13	**2**	X = p-Br	" "	0.5 h	90	78	0
14	**1**	X = p-NO_2	" "	1 h	100	80	0

a) The usual reaction scale is as follows: Zn(Cu) 2.3 mmol, Pd catalyst 0.01 mmol or Ni catalyst 0.02 mmol, ethyl 3-iodopropionate or 4-iodobutyrate 1.5 mmol, aryl iodide 1.0 mmol in benzene-DMA (5 mL-0.2 mL).

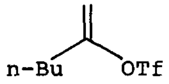
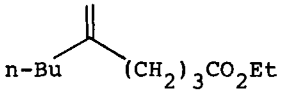
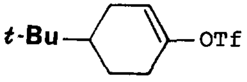
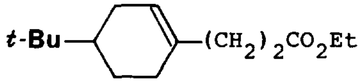
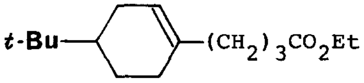
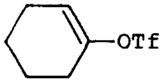
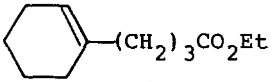
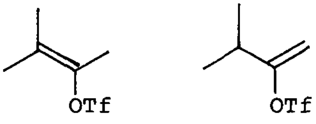
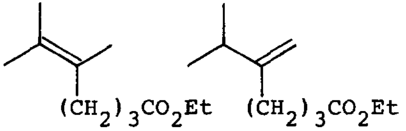
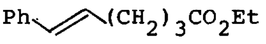
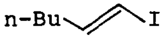
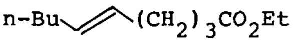
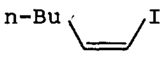
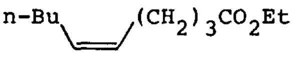
b) The reaction is carried out all through at 60°C.

c) Yield is based on the aryl iodide.

palladium(II) chloride in dry benzene in one portion (for the stoichiometry, see the footnote a in Table I). The reaction was complete within 0.5 - 1 hour at this temperature. Extraction with ethyl acetate followed by purification by means of column chromatography over silica gel (hexane - ethyl acetate gradient) provided the coupling products in the yields listed in Table I.

Both organozincs **1** and **2** showed the similar reactivity. The coupling reaction could be catalyzed by other catalysts, such as bis(triphenylphosphine)palladium(II) chloride, bis(triphenylphosphine)nickel(II) bromide, and tetrakis(triphenylphosphine)palladium(0). All of these catalysts, however, are inferior to bis(tri-o-tolylphosphine)palladium(II) chloride, mainly due to formation of non-negligible amounts of biaryls (runs 1 - 3). The generality and utility of this reaction is apparent by examination of Table I. The reaction tolerates the presence of electron releasing Me and OMe substituents and also strongly electron withdrawing nitro group. Compatibility with reactive ester and bromine[6]

Table II. Palladium Catalyzed Coupling Reaction of **1** and **2** with Vinyl Iodides and Vinyl Triflates[a]

run	**1** or **2**	vinylating agents	products	% isolated[b]
1	**2**			75
2	**1**			74
3	**2**	the same as above		87
4	**2**			89
5	**2**	 (9 : 1)	 (9 : 1)	83
6	**2**			79
7	**2**			71
8	**2**			89

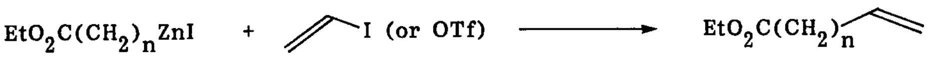
a) The usual scale is as follows: Zn(Cu) 2.3 mmol, $Pd(PPh_3)_4$ 0.04 mmol, ethyl 3-iodopropionate or 4-iodobutyrate 1.5 mmol, vinyl triflate or iodide 1 mmol. Vinyl triflate or iodide is added at 60°C and stirred at this temperature for 30 min.

b) Yield is based on vinyl triflate or iodide.

functions should also be noted.

Palladium Catalyzed Coupling Reaction of 1 and 2 with Vinyl Iodides and Vinyl Triflates

Many standard methods are available for the synthesis of γ,δ-unsaturated esters (e.g., the palladium catalyzed[7] or non-catalyzed[8] alkylation of enolates with allylic substrates, Claisen rearrangement,[9] etc.). Compared with this, the synthesis of δ,ϵ-unsaturated esters, however, is rather complex. From this synthetic point of view, we mostly examined the coupling reaction of **2** with vinyl iodides[10] and triflates[11] to establish a ready access to δ,ϵ-unsaturated esters.



For this coupling reaction, tetrakis(triphenylphosphine)palladium(0) was found to be a suitable catalyst. In the presence of 4 mol% of this catalyst, the reaction of vinyl triflate was very fast, and generally it was consumed within 10 minutes at 60°C after its addition. Vinyl iodides showed the similar reactivity. The reaction was continued for 30 minutes at 60°C for completion, and worked up as described before. The isolated yields of the products after column chromatography are summarized in Table II. The reaction is clean and the yields are uniformly good. The isomeric mixture of triflates afforded the isomeric mixture of products in the same ratio (run 5). As shown in runs 6 - 8, the reaction proceeds with the complete retention of configurations.

As for the synthesis of δ,ϵ-unsaturated esters, the coupling reaction of **1** with allylic substrate seems to be a more reasonable way than the present coupling reaction of **2** with vinylic substrate, because the allyic substrate is much common than the vinylic substrate. Although not successful yet, allylation of **1** and **2** is one of our current interests.[12]

References and Notes

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