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COPPER(I)-PROMOTED COUPLING REACTION OF ARYL HALIDES WITH SODIUM DIETHYLMALONATE

Jun-ichiro SETSUNE, Kimihiro MATSUKAWA, Hirofumi WAKEMOTO, and Teijiro KITAO
Department of Applied Chemistry, College of Engineering,
University of Osaka Prefecture, Sakai, Osaka 591

Copper(I)-promoted coupling reaction of aryl halides with sodium diethylmalonate occurred smoothly in dioxane. The qualitative trends in the activity of copper(I) salt followed the order : CuBr > CuI > $CuBF_4(CH_3CN)_4$ > CuCl. The activity was lowered in the presence of coordinating molecule such as acetonitrile, pyridine, NaI, phosphine, and sulfide. The reaction was generally applicable to aryl halides with various substituents.

Aromatic halides have recently served to the synthesis of various aromatic compounds of a practical importance coupled with the recent advances in the activation of carbon-halogen bonds by transition metal complexes.[1] The substitution reaction of aromatic halides with a soft nucleophile such as an enolate anion seems to be one of the most intriguing synthetic approaches in view of the utility of α-aryl carbonyl compounds and has so far been reported to occur by (i) the attack of an enolate anion to a benzyne or a aryl radical intermediate generated under an strongly basic reaction condition,[2] (ii) the arylation of lithium ester enolate with aryl halide by a low-valent nickel catalyst,[3] and (iii) copper(I)-catalyzed substitution reactions of mono anionic β-dicarbonyl compounds toward ortho-halobenzoic acids.[4] However, these methods have not yet found a versatile use due to the limitation originated from their rigorous reaction conditions or poor generalities. The nickel-catalyzed arylation was successful only at the very low temperature (-78°C) and unavailable for a softer nucleophile such as active methylene compound. While the Cu(I)-catalyzed coupling reaction reported by Bruggink and Mckillop was effected especially with the aid of the activation by the carboxylic group at the ortho position relative to the reaction center and the use of a large excess amount of β-dicarbonyl compound as a solvent, the general applicability of copper(I) salts to the coupling reaction of aromatic halides and active methylene compounds remains to be uncovered.[5]

We have found that the coupling reactions of aryl halides with sodium diethylmalonate (1) proceed smoothly in dioxane in the presence of copper(I) salts to form phenylmalonic acid diethylester

(2). In the following, we describe the result obtained for this arylation including the effect of solvents, molar ratios of reactants, reaction time, additives, leaving halides, substituents on the aromatic ring, and copper(I) salts.

In a typical experiment, diethylmalonate (12 mmol) was added to the suspension of NaH (12 mmol) in 10 ml of dioxane followed by the successive addition of CuI (12 mmol) and phenyl iodide (10 mmol) under a nitrogen stream. The above heterogeneous reaction mixture was heated for 5 hr at the reflux temperature and the formation of (2) was monitored by GLC analysis using biphenyl as a internal standard. The results are summarized in Table I. Although the reaction mixture is homogeneous in an aprotic polar solvent such as hexamethylphosphoric triamide (HMPA), the reactivity in HMPA has not greatly been improved in comparison with that in dioxane in spite of a partial degradation of (2) to ethyl phenylacetate (3) and the difficulty in the work-up procedure in the HMPA system. The coupling reaction proceeded in diglyme as well as in dioxane, but did not occur in pyridine at all (entry 1-4).

There was found a tendency that the prolonged heating caused the decomposition of the product, the yield of which was also dependent on the amount of CuI. Twice amount of CuI was required to achieve a quantitative conversion, while one half amount of CuI was insufficient for a satisfactory production of (2) even after 10 hr heating (entry 5-9). This observation is explainable in terms of the deactivation of the active copper species due to the complexation with NaI, the concentration of which would increase as the coupling reaction proceeds. In support of this interpretation, the addition of NaI to this system caused the complete inhibition of the coupling reaction. The additives such as triphenylphosphine and dimethylsulfide, which are also capable of coordination to Cu(I), have considerably retarded the rate of the reaction. On the other hand, NaBr was found to be rather innocuous (entry 10-13).

The comparison of the reactivity of phenyl halides was made by using CuI (entry 4,18), CuBr (entry 14,19,23), and $CuBF_4(CH_3CN)_4$ (entry 17,22). This clearly indicates that phenyl halide becomes more reactive as increase with the softness of the leaving halide : PhI > PhBr > PhCl. This tendency is generally noted in the substitution reactions of aryl halide by organocopper reagents.[6] The relative activity of copper(I) salts in this reaction has been estimated for PhI (entry 4,14,16) and PhBr (entry 18,19,22) to be the order : CuBr > CuI > $CuBF_4(CH_3CN)_4$ > CuCl.[7] Inefficiency of $CuBF_4(CH_3CN)_4$ is partly ascribable to the poisoning effect of acetonitrile itself as shown in the experiment of entry 21. CuBr is especially preferable because the amount of CuBr can be reduced without a significant decrease in the yield of (2) in contrast with the case of CuI (entry 6,15,20).

Copper(I) malonate is considered to generate in situ forming a cluster as is well known for organocopper reagents. The activity of copper(I) salt in this reaction seems to be dependent on the composition and structure of the cluster. Although organocopper(I) complexes of β-dicarbonyl compound with

Table I. Cu(I)-promoted coupling reaction of phenyl halides with sodium diethylmalonate

$$\mathrm{PhX} + \underset{(\underline{1})}{\mathrm{NaCH(CO_2Et)_2}} \xrightarrow{\mathrm{CuY}} \underset{(\underline{2})}{\mathrm{PhCH(CO_2Et)_2}} + \underset{(\underline{3})}{\mathrm{PhCH_2CO_2Et}}$$

entry	X	Y	molar ratio PhX/(1)/CuY	solvent	time (hr)	temp. (°C)	additive	yield (%)[a] (2)	yield (%)[a] (3)
1	I	I	1.0/1.2/1.2	HMPA	5	120	-	69	7
2	I	I	1.0/1.2/1.2	pyridine	5	105	-	0	0
3	I	I	1.0/1.2/1.2	diglyme	5	105	-	61	0
4	I	I	1.0/1.2/1.2	dioxane	5	101	-	66	0
5	I	I	1.0/1.2/1.2	dioxane	10	101	-	62	0
6	I	I	1.0/2.0/0.5	dioxane	5	101	-	38	tr
7	I	I	1.0/2.0/0.5	dioxane	10	101	-	27	3
8	I	I	1.0/2.0/2.0	dioxane	5	101	-	97	3
9	I	I	1.0/2.0/2.0	dioxane	10	101	-	70	7
10	I	I	1.0/1.2/1.2	dioxane	5	101	NaI(1.2)	tr	0
11	I	I	1.0/1.2/1.2	dioxane	5	101	NaBr(1.2)	61	0
12	I	I	1.0/1.2/1.2	dioxane	5	101	$\mathrm{Me_2S}$(1.2)	52	0
13	I	I	1.0/1.2/1.2	dioxane	5	101	$\mathrm{Ph_3P}$(1.2)	6	0
14	I	Br	1.0/1.2/1.2	dioxane	5	101	-	70	0
15	I	Br	1.0/2.0/0.5	dioxane	5	101	-	60	tr
16	I	Cl	1.0/1.2/1.2	dioxane	5	101	-	25	0
17	I	$\mathrm{BF_4}$	1.0/1.2/1.2	dioxane	5	101	$\mathrm{CH_3CN}$(4.8)	73	0
18	Br	I	1.0/1.2/1.2	dioxane	5	101	-	22	0
19	Br	Br	1.0/1.2/1.2	dioxane	5	101	-	43	0
20	Br	Br	1.0/2.0/0.5	dioxane	5	101	-	39	tr
21	Br	Br	1.0/1.2/1.2	dioxane	5	101	$\mathrm{CH_3CN}$(4.8)	18	0
22	Br	$\mathrm{BF_4}$	1.0/1.2/1.2	dioxane	5	101	$\mathrm{CH_3CN}$(4.8)	10	0
23	Cl	Br	1.0/1.2/1.2	dioxane	5	101	-	0	0
24	Cl	Cl	1.0/1.2/1.2	dioxane	5	101	-	0	0

a) GLC yield using biphenyl as a internal standard.

stabilizing ligands such as amine, phosphine, and isonitrile have been known,[8] the reaction behavior of organocopper(I) species with a soft carbanion is understood less satisfactorily than that of alkyl and arylcopper species. The above result indicates that copper(I) malonate is able to be prepared easily, thermally stable, and shows moderate reactivity even in a heterogeneous reaction condition.

Various aryl halides were allowed to react with sodium diethylmalonate in the presence of CuBr in dioxane and the coupling products were obtained in excellent yields as summarized in Table II. However, we obtained only a tarry substance that could not be analyzed when o-bromoaniline and o-bromoacetanilide were allowed to react through the same procedure. It proved that the coupling reaction proceeded smoothly in the case of aryl halides substituted with electron withdrawing group in particular and ortho-substituted aryl halides were generally more reactive than para-substituted isomers. Improvement

Table II. Cu(I)-promoted coupling reaction of aryl halides with sodium diethylmalonate[a)]

$$\mathrm{ArX} + \mathrm{NaCH(CO_2Et)_2} \xrightarrow[\text{dioxane refl.}]{\text{CuBr}} \mathrm{ArCH(CO_2Et)_2}$$

Ar	X	time (hr)	conv.[b)] (%)	yield[c)] (%)
o-CH_3-phenyl	Br	5	53	58
p-CH_3-phenyl	Br	5	49	61
o-OCH_3-phenyl	Br	5	55	89
p-OCH_3-phenyl	Br	5	45	40
o-NO_2-phenyl	Br	2	94[d)]	96[d)]
p-NO_2-phenyl	Br	2	65[d)]	89[d)]
o-CO_2CH_3-phenyl	Br	2	92	88
p-$COCH_3$-phenyl	Br	2	51[d)]	90[d)]
o-Br-phenyl	I	5	60	77
α-naphthyl	Br	5	52[d)]	90[d)]

a) Reaction conditions not specified were the same as that for phenyl bromide (Table I. entry 19).
b) Mol-% based on the charged aryl halide. c) Product yield based on the converted aryl halide.
d) Determined by HPLC; the other data were determined by GLC.

of the product yield about methyl or methoxy-substituted aryl halide is possible through the use of excess amount of CuBr as noted earlier.

In conclusion, the above mentioned copper(I)-promoted coupling reaction is a facile method for carbon-carbon bond formation in the aromatic system using ordinary reagents and solvent under a relatively mild condition. Further study on its application is now going on.

References and Note

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