The Reductive Coupling of Organic Halide Using Hydrazine and a Palladium Amalgam Catalyst. I. The Preparation of Biaryls

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Synopsis: Iodoarenes could be converted to the corresponding biaryls in high yields by the use of a catalytic amount of a palladium amalgam in place of a palladium–calcium carbonate catalyst in Busch's reaction. The 2,3′-isomer content in the bitolyls obtained by the homo-coupling of *o*-iodotoluene was 15% when palladium was used, while it was 1% when a palladium amalgam was used, and the latter was re-usable. The present method is further applicable to some iodoalkanes.

The preparation of symmetrical biaryls with haloarenes is ordinarily accomplished by either one-step or two-step procedures in which the former uses a metal, as in the Ullmann reaction,[1] or a zerovalent metal complex, as in the reaction discovered by Semmelhack *et al.*;[2] while the latter uses the Grignared reagent. The Ullmann reaction is applicable to ortho-halo-substituted arenes, but it is greatly inhibited or prevented by the presence of such substituents as amino, hydroxyl, and free carboxyl groups.[1] Moreover, the reaction does not usually proceed under mild conditions. In Semmelhack's reaction, the zerovalent complex is very sensitive to air and heat, and the presence of ortho substituents in the haloarenes slows down the reaction velocity.[2] The method reported by Taylor *et al.*,[3] involving the reaction *via* the Grignard reagent, is a good one for the preparation of biaryls in respect to the yield, but it can not be used for ortho-halo-substituted arenes.

In the methods described above, a stoichiometric amount or an excess amount of metal are required, and a reaction which proceeds with a catalytic amount of the metal is desirable for the preparation of biaryls. Busch's reaction[4] has not been used for the preparation of biaryls since the reaction proceeds in accordance with a radical reaction mechanism and the yield of biaryls is low except for biquinolyls,[5–7] which have not been prepared by other methods. On the other hand, Jullia[8] and Norman[9] have recently reported the coupling of haloarenes in the presence of palladium supported on activated charcoal[8] and of palladium metal prepared *in situ* from palladium acetate.[9] However, these reaction conditions are not suitable for the preparation of the biaryls, because the hydrogenation and the dimerization of the haloarenes take place at the same time. This investigation has, therefore, been carried out in order to find suitable conditions for preparing the biaryl.

The reductive homo-coupling of iodoarenes with hydrazine was found to proceed in a high yield under mild conditions by the use of a palladium amalgam catalyst and to be further applicable to ortho-substituted iodoarenes. The present method is simple and easy to operate in comparison with the ordinary method; also, it is a useful method for preparing biaryls.

Results and Discussion

Carriers other than the calcium carbonate in Busch's reaction have been examined for the preparation of biaryls, but no better results were obtained. Although Busch's reaction had not been examined without using a carrier,[4–7] the coupling of iodo-*p*-xylene (**1**) with hydrazine gave 2,2′,5,5′-tetramethylbiphenyl (**2**) in an 18.9% yield and *p*-xylene by the use of the palladium prepared *in situ* from palladium chloride (**3**). The coupling of **1** with a palladium–calcium carbonate catalyst in place of the palladium metal gave **2** in an 11.8% yield. Therefore, the reductive coupling with hydrazine did not always require a carrier. Nickel, copper, and mercury, which had been prepared *in situ* from the corresponding metal chloride, were not observed to catalyze the coupling of iodobenzene under the same conditions. The use of the palladium amalgam prepared *in situ* from mercury(II) chloride (**4**) (0.43 mmol) and **3** (0.50 mmol) as the catalyst enhanced the yield of **2** to 70.6%, about four times as large as that in the absence of mercury. In this case, the hydrogena-

Table 1. Coupling of haloarenes with hydrazine by the use of a palladium amalgam or palladium metal

Haloarene	Yield of biaryl/%[a]	
	Pd–Hg (Method B)	Pd (Method C)
Chlorobenzene		Trace
Bromobenzene	4	30
Iodobenzene	90	49
o-Iodotoluene (T)[b]	67[c]	17[d]
o-Iodotoluene (W)[b]	77[c]	54[e]
m-Iodotoluene	83[f]	28[e]
p-Iodotoluene	102	48
Iodo-*p*-xylene	74	19
3-Iodo-*o*-xylene	64[g]	
4-Iodo-*o*-xylene	78[g]	56[g]
Iodomesitylene	0	0[h]
p-Iodoethylbenzene	82	
p-Iodoaniline	26	
4-Iodo-1,2-dimethoxybenzene	51	

a) Isolated weight. b) Obtained from the Tokyo Chemical Industry Co., Ltd. and Wako Chemical Industries, Ltd., respectively. c—g) The biaryl contained the following isomers: c) 1.3% of the 2,3′-isomer, d) 15.3% of the 2,3′-isomer, e) 16.3% of the 2,3′-isomer, f) 0.7% of the 2,3′-isomer, and g) 0.5% of the 2,3,3′,4′-isomer. h) 2,3′,4,5′,6-Pentamethyldiphenylmethane was detected in a 1% yield.

tion was depressed. Some representative results of haloarenes are shown in Table 1. The use of the palladium amalgam in place of palladium increased the yield of biaryl in the coupling of all the iodoarenes listed in Table 1, but decreased that of bromobenzene. It was further found in the coupling of *o*-iodotoluene that the use of the amalgam catalyst hindered the migration of the bonding position which occurred on the intermediate complex [Ph–Pd–X] in the absence of mercury and decreased the contents of 2,3′-dimethylbiphenyl from 15% to 1.3%. The present method was applicable to the synthesis of 2,2′-disubstituted biaryls much like the Ullmann reaction, but iodomesitylene, which had substituents at both ortho positions, did not give the biaryl, in contrast with the Ullmann reaction.

Since **3** as well as **4** was reduced with hydrazine in the initial reaction stage to give the metal, and since the produced amalgam was present throughout the reaction, the reuse of the recovered amalgam as the catalyst was examined for the preparation of **2**. As is shown in Table 1, **1** gave **2** in a 74% yield with **3** and **4**. **2** was obtained in yields of 45% and 53% with the first recovered palladium amalgam (97.5% of the theoretical amount) and with the second recovered one (79.6% of the theoretical amount) respectively. The recoveries of **1** in these reactions were 0.4%, 12.2%, and 1.8% respectively. The use of palladium and mercury in place of these chlorides gave **2** in a 47% yield. Therefore, the following conclusions may be drawn: (1) Both the salts and the metals (amalgam) can be used as catalysts. (2) The activity of the catalyst does not decrease very much even after the reaction, and so the catalyst is re-usable. Since the present method is operationally simple, highly selective, and widely applicable, it offers advantages over the previous methods for the preparation of symmetrical biaryls.

As is shown in Table 2, the present method is also applicable to the reductive coupling of iodoalkanes, but the yield is still unsatisfactory. Further experiments are now in progress.

Experimental

Materials. The reagents and solvent employed were of a commercially available grade except those noted below. Iodo-*p*-xylene,[10] 3-iodo-*o*-xylene,[11] 4-iodo-*o*-xylene,[11] iodomesitylene,[10] *p*-iodoethylbenzene,[10] 4-iodo-1,2-dimethoxybenzene,[12] and 1-iododecane[13] were prepared by the methods given in the literature. The purity of all the halo compounds was determined by GLPC to be over 98%.

Table 2. Coupling of iodoalkanes with hydrazine by the use of a palladium amalgam catalyst (Method B)

Iodoalkane	Coupling product	Yield/%
1-Iodohexane	dodecane	0.2
Iodocyclohexane	bicyclohexyl	6.7
1-Iododecane	eicosane	2.5

Reductive Coupling of **2** *with Palladium (Method A).* A mixture of **1** (21.7 mmol), **3** (0.51 mmol), 85% hydrazine hydrate (**5**) (9.8 mmol), and sodium hydroxide (**6**) (101 mmol) in methanol (12 ml) was refluxed for 6.5 h with stirring. The resulting mixture was filtered, and the residual metal was washed with benzene and water. **2** was obtained by the steam distillation of the filtrate. The amount of **2** was determined by GLPC, using biphenyl as the internal standard. The palladium–calcium carbonate catalyst, prepared by a usual method from calcium carbonate (1.0 g) and **3** (0.51 mmol), was also used in place of **3**.

Reductive Coupling of Organic Halide with a Palladium Amalgam Catalyst (Method B). A mixture of organic halide (25 mmol), **3** (0.50 mmol), **4** (0.50 mmol), and **6** (125 mmol) in 16 ml of methanol containing **5** (15 mmol) was stirred for 6 h under refluxing. The resulting mixture was filtered, and the inorganic residues were washed with benzene and water. After the organic layer had separated from the aqueous layer of the filtrate, the dimer was obtained by either the evaporation of the solvent or distillation *in vacuo*, followed by weighing. After 6 hs' reaction, almost no organic halide was recovered from the reaction mixture. The purity of the reaction products was determined by GLPC to be over 98% except in the case of 4,4′-diaminobiphenyl (97%). The reaction products were identified by their retention time, GC-MS (EI and CI), and NMR spectra in comparison with those of authentic samples.

Reductive Coupling of Haloarenes with a Palladium Catalyst (Method C). The experiment was carried out in the same manner as in Method B except that only **3** (2.5 mmol) was used in place of **3** and **4**.

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