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Ultrasound-Promoted Synthesis of Arylzinc Compounds Using Zinc Powder and Their Application to Palladium(0)-Catalyzed Synthesis of Multifunctional Biaryls

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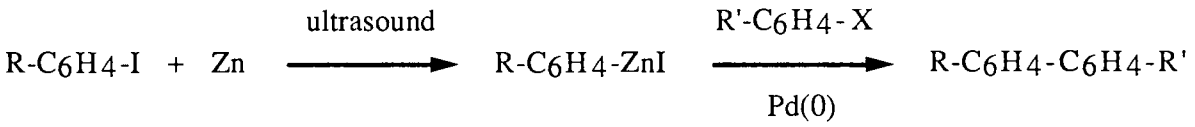
Arylzinc compounds containing electron-withdrawing groups such as CO_2CH_3, $CON(CH_3)_2$, CN, Br, Cl, or CF_3 at ortho position were prepared readily by the ultrasound-promoted reaction of aryl iodides with zinc powder, which were applied to palladium(0)-catalyzed cross-coupling with aryl halides to afford unsymmetrical and multifunctional biaryls in good yields.

Carbon-zinc bonds, characterized by modest reactivities to electrophilic centers, are usually compatible with such reactive substituents as alkoxycarbonyl and cyano groups. In practice, various alkylzinc compounds containing such groups have been prepared and applied to further reactions in the synthesis of multifunctional molecules, not to speak of Reformatsky reaction.[1] Meanwhile, comparable chemistry of arylzinc compounds has been scarcely studied, primarily because they were not readily available.[2] In this paper, we will report a facile synthesis of arylzinc compounds promoted by ultrasound and their application to the synthesis of multifunctional biaryls.[3]



At first, the reaction of methyl o-iodobenzoate (1 equiv.) with zinc powder (2 equiv.) was attempted. Ultrasonic cleaner (Branson 1200, 30W) was used for the irradiation of ultrasound. As shown in Table 1, the reaction proceeded very well at 30 °C[4] under nitrogen in such solvent as NMP, DMF, or TMU and desired arylzinc compound was obtained in a good yield.[5] Without the irradiation of ultrasound, same reaction in TMU needed 15 h to complete. The yield of the arylzinc compound (methyl benzoate / methyl o-iodobenzoate = 16% / 83% after I_2 quenching) was, however, similar to ones in Table 1. Thus, ultrasound shortened the time to reach to

Table 1. Ultasound-Promoted Synthesis of Arylzinc Iodide [a]

R-C_6H_4-I R	Solvent	Temp °C	Time h	Conv.[b] %	Yield / % [b] Ar-ZnI	Ar-H	Chemical Shift C-1 / ppm
o-CO_2CH_3	NMP [c]	30	5	100			
o-CO_2CH_3	DMF [d]	30	5	100			158.6 [e]
o-CO_2CH_3	TMU [f]	30	5	100	87	13	
o-CO_2CH_3	THF	30	5	12			
o-CO_2CH_3	CH_3CN	30	5	7			
o-CO_2CH_3 [g]	TMU	30	5	100	63	36	
o-$CON(CH_3)_2$	TMU	30	20	100	72	8	157.7 [h]
o-CN	TMU	30	8	100	95	4	163.9 [h]
o-Cl	TMU	30	8	100	96	2	154.6 [e]
o-CF_3	TMU	30	5	100	94	5	152.7 [e]
o-Br	TMU	30	12	100	58	2 [i]	
o-$COCH_3$	TMU	30	5	100	38	22	
m-CO_2CH_3	TMU	30	20	30			
m-CO_2CH_3	TMU	50	20	100	75	25	
p-Br	TMU	50	20	100	76	11	
H	TMU	50	20	82			
o-OCH_3	TMU	50	20	61			
p-OCH_3	TMU	50	20	18			

a) Every runs were carried out using 0.4 mmol of aryl iodide, 0.8 mmol of zinc powder, and 0.2 ml of solvent in nitrogen atmosphere under ultrasonic-irradiation conditions. b) Conversion or yield was determined following the method of Ref. 5. c) 1-Methyl-2-pyrrolidinone. d) N,N-Dimethylformamide. e) Run in DMF-d7. Chemical shift was measured with respect to a formyl carbon of DMF-d7 (160.8 ppm). f) 1,1,3,3-Tetramethylurea. g) Run with extra 0.13 equiv. of water. h) DMSO-d_6 was added after the reaction to take NMR spectra. Chemical shift was measured with respect to a center of DMSO-d_6 (39.5 ppm). i) Ortho-diiodobenzene (18%) was also detected after I_2 quenching.

end but kept intact the product.

Encouraged by these results, the ultrasound-promoted reaction was extended to other aryl halides. As shown in Table 1, aryl iodides containing such EWG as $CON(CH_3)_2$, CN, Cl, or CF_3 at ortho position reacted with zinc powder at 30 °C under the ultrasonic-irradiation conditions to afford the corresponding arylzinc compounds in good yields except for o-iodoacetophenone.[6] For the reaction of aryl iodides containing EWG at meta or para position, ultrasonic irradiation at 50 °C was necessary

Table 2. Pd(0)-Catalyzed Synthesis of Biaryls [a]

R-C6H4ZnI R	R'-C6H4-X R'	X	Temp °C	Time h	Yield / % [b] R-C6H4-C6H4-R'
o-CO2CH3	H	Br	70	8	71
o-CO2CH3	p-CO2C2H5	Br	70	4	100
o-CO2CH3	p-COCH3	I	45	4	85
o-CO2CH3	p-NO2	I	45	4	88
o-CON(CH3)2	p-CO2CH3	Br	70	2	88
o-CN	p-Cl	I	45	10	84

a) Every runs were carried out using 2 mol% of Pd(PPh3)4 in situ generated and 1-2 mmol of aryl halide in TMU under N2. Molar ratio of ArZnI / Ar'X = ca. 1-1.1.
b) Isolated yields.

to reach to end. Electron-donating groups (EDG) diminished the reactivities of aryl iodides greatly, so that the reaction did not reach to end under the ultrasonic-irradiation conditions even at 50 °C. It is to be noted that arylzinc compounds thus obtained were stable enough for at least months in the reaction mixture at ambient temperature to be safely used in further synthesis (vide infra).

To see if our arylzinc compounds can participate in further reaction in the similar manner as conventional organozinc compounds, cross-coupling with aryl halides was tried. Here, it has been well established that the conventional arylzinc compounds, which are derived from aryllithium compounds and zinc(II) salts, couple with aryl halides in the presence of palladium(0) catalysts.[7] As shown in Table 2, our compounds did not cause any trouble in the participation in the palladium(0)-catalyzed reaction with aryl halides: multifunctional and/or unsymmetrical biaryls containing such reactive substituents as alkoxycarbonyl, cyano, N,N-dimethyl-carbamoyl, acyl, chloro, and nitro groups on either or both rings were obtained in good yields. In conclusion, ultrasonic irradiation is proved to be effective for the synthesis of arylzinc compounds from aryl iodides containing EWG at ortho position. This synthetic method is simple and facile, since 1) laboratory ultrasonic cleaner serves well and 2) any troublesome pre-treatments are not required for zinc source. The arylzinc compounds might provide useful, otherwise not easily accessible, functionalized-aryl nucleophiles to a variety of synthetic manipulation, as exemplified by biaryl syntheses.

Typical procedure is as follows: A mixture of methyl o-iodobenzoate (0.37 ml, 2.5 mmol), Zn powder (327 mg, 5.0 mmol), and TMU (1.25 ml) was irradiated for 5 h at 30 °C under nitrogen in an ultrasonic cleaner. Then, the yellow-supernant was transferred through a cannula to a mixture of p-nitroiodobenzene (498 mg, 2.0 mmol) and

$Pd(PPh_3)_4$ prepared in situ from $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), Zn powder (13 mg, 0.2 mmol), and TMU (2 ml). The resultant brown solution was stirred at 45 °C for 4 h under nitrogen, from which 453 mg (88%) of methyl 4'-nitro-1,1'-biphenyl-2-carboxylate was obtained after silica-gel column-chromatography (Hexane / Ethyl acetate = 19 / 1) as white solid. Mp 79-79.5 °C (lit.,[8] 78-79 °C). IR 1742, 1518, 1350, 858cm^{-1}.

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2) It had long been believed that the direct reaction between aryl halides and zinc metal did not take place but, in 1980, we had first reported that zinc powder can react with methyl o-iodobenzoate to afford the corresponding arylzinc compound. However, the reaction needed the harmful solvent (HMPA) and the heating (50 °C): K. Takagi, N. Hayama, and S. Inokawa, Bull. Chem. Soc. Jpn., 53, 3691 (1980). Recently, similar reaction between aryl halides and activated-zinc metal have been reported: T. N. Majid and P. Knochel, Tetrahedron Lett., 31, 4413 (1990); L. Zhu, R. M. Wehmeyer, and R. D. Rieke, J. Org. Chem., 56, 1445 (1991); H. T. Teunissen and F. Bickelhaupt, Tetrahedron Lett., 33, 3537 (1992); T. Sakamoto, Y. Kondo, N. Murata, and H. Yamanaka, ibid., 5373 (1992). See also, C. E. Tucker, T. N. Majid, and P. Knochel, J. Am. Chem. Soc., 114, 3983 (1992).

3) For the use of ultrasound in organometallic synthesis, see for example: D. Bremner, "The Application of Sonochemistry in the Formation and Reactions of Metal-Carbon Bonds," in "The Chemistry of the Metal-Carbon Bond," ed by F. R. Hartley, John Wiley & Sons, Chichester (1989), Vol. 5, p. 3.

4) Water temperature of cleaner was maintained at cited ones throughout the reaction in whole runs.

5) The conversion was determined by quenching the reaction mixture with acidic solution, followed by the GLC analysis of the amount of methyl benzoate. Small amount of methyl benzoate was present in the reaction mixture before this quenching presumably owing to the hydrolysis of the arylzinc compound produced with accidental water in the solvent et al (see Table 1). The yield of arylzinc compound was determined by quenching the reaction mixture with iodine, followed by the GLC analysis of the amount of aryl iodide.

6) For the synthesis of arylzinc compounds containing acyl groups, the method using activated zinc metal gave better results than ours. See, T. N. Majid and P. Knochel, Tetrahedron Lett., 31, 4413 (1990); L. Zhu, R. M. Wehmeyer, and R. D. Rieke, J. Org. Chem., 56, 1445 (1991).

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8) D. H. Hey, F. C. Saunders, and G. H. Williams, J. Chem. Soc., 1961, 554.

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