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Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides

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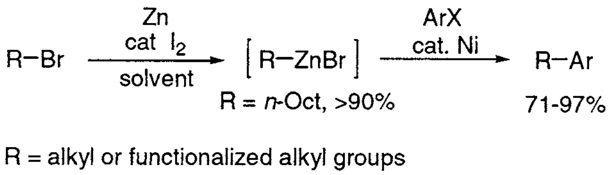
ABSTRACT



Alkylzinc bromides have been efficiently prepared by the direct insertion of zinc metal (dust, powder, granule, shot), activated with 1–5 mol % I_2, into alkyl bromides in a polar aprotic solvent. The zinc reagents thus formed undergo Ni- and Pd-catalyzed cross-coupling with aryl halides to produce functionalized alkylarenes in excellent yields.

Organozinc compounds are very useful and versatile reagents for a variety of transformations in organic synthesis,[1] particularly those involving carbon−carbon bond formation via Pd- and Ni-catalyzed cross-coupling reactions (Negishi coupling).[2] Although alkylzinc compounds can be prepared by various methods,[1] oxidative insertion of zinc metal into alkyl halides is the most direct and attractive. However, unlike alkyl iodides, the less expensive and more accessible alkyl bromides and chlorides are usually unreactive to normal zinc insertion and require the use of highly reactive zinc to achieve oxidative insertion.[3] The only published solution to this problem is the procedure reported by Knochel et al., in which zinc dust is first activated by sequential treatment with 1,2-dibromoethane and Me_3SiCl and then reacted with alkyl bromides in the presence of a catalytic amount of an alkali iodide (0.2 equiv) to generate the corresponding alkylzinc compounds.[4] We report herein a novel, remarkably simple and general procedure for the preparation of alkylzinc compounds from unactivated alkyl bromides and chlorides that uses a catalytic amount of I_2 for activation of zinc (dust, granules, powder, shot).[5]

For illustration, treatment of *n*-octyl bromide with zinc dust (1.5 equiv), activated with I_2 (5 mol %), in *N*,*N*-dimethylacetamide (DMA) afforded *n*-octylzinc bromide in excellent yield (>90%). Formation of the corresponding zinc reagent was established by hydrolysis and iodinolysis of the reaction mixture, producing *n*-octane in 98% yield and

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[1] (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996. (c) Knochel, P., Jones, P., Eds. *Organozinc Reagents: A Practical Approach*; Oxford University Press: New York, 1999. (d) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

[2] (a) Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980. (b) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (c) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002.

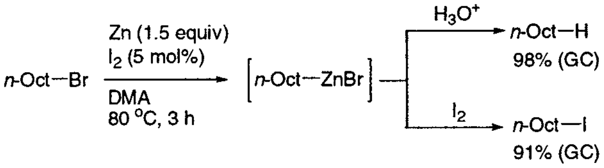
[3] (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155.

[4] Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425.

[5] Although the use of iodine to activate zinc in Reformatsky reactions has been reported, the literature is devoid of examples showing activation of zinc with iodine in the formation of alkylzinc reagents from unactivated alkyl bromides: (a) Newman, M. S. *J. Am. Chem. Soc.* **1942**, *64*, 2131. (b) Palmer, M. H.; Reid, J. A. *J. Chem. Soc.* **1960**, 931.

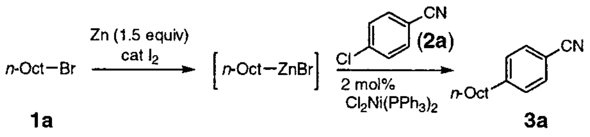
10.1021/ol0272693 CCC: $25.00

Scheme 1



1-iodooctane in 91% yield, respectively (Scheme 1). The *n*-octylzinc bromide thus formed readily participated in the Ni-catalyzed cross-coupling[6] with 4-chlorobenzonitrile (0.8 equiv) to give 4-octylbenzonitrile in 94% yield (Table 1).

Table 1. Direct Zinc Insertion into *n*-Octyl Bromide under Various Conditions



Zn	I_2 (mol %)	solvents	temp (°C)	time (h)	conversion (%)[a]	yield of **3a** (%)[b]
dust	5	DMA	80	3	>99	94
dust	1	DMA	80	9	>98	89
dust[c]	0	DMA	80	9	20	
dust	5	DMF	80	4.5	>99	88
dust	5	DMSO	80	3	>99	92
dust	5	DMPU	80	3	>99	96
dust	5	NMP	80	6	>98	95
powder	5	DMA	80	3	>99	92
granule	5	DMA	80	3	>98	94
shot	5	DMA	80	12	>98	88

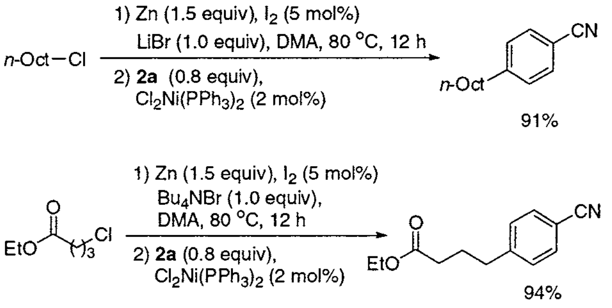
[a] Conversion of *n*-octyl bromide. [b] GC yield. [c] Activated with 1,2-dibromoethane and TMSCl.

The iodine effect is remarkable. Even with the use of 1 mol % I_2, the zinc insertion proceeded smoothly and was complete within 9 h. However, in the absence of I_2, the conversion was only 20% even though zinc dust was activated with 1,2-dibromoethane and Me_3SiCl (Table 1). This zinc insertion can also be performed in other polar aprotic solvents such as DMF, DMSO, DMPU, and NMP, giving comparable results as shown in Table 1. The subsequent Ni-catalyzed cross-coupling reactions with 4-chlorobenzonitrile in these solvents also proceeded readily, with little (<2%) or no formation of homocoupling byproduct 4,4′-dicyanobiphenyl. On the other hand, when less polar solvents such as diethyl ether, THF, dioxane, DME, and acetonitrile were used, virtually no zinc reagent formed under similar conditions. It is noteworthy that other forms of zinc metal such as zinc powder (−100 mesh), granular zinc (−30 + 100 mesh), and even zinc shot (1−2 mm) have been successfully employed in this procedure (Table 1).

Conceptually, the iodine in this process can play a novel dual role: (1) the relative redox potentials between “$I_2 + 2e \rightarrow 2I^-$” and “$Zn \rightarrow Zn^{2+} + 2e$” allows a reaction to occur between iodine and zinc and thus delivers a clean, reactive surface on the metal and (2) the I^- generated can convert the alkyl bromide into the corresponding alkyl iodide, which is a more reactive substrate toward oxidative zinc insertion. Indeed, the formation of small amounts of *n*-octyl iodide was observed during the zinc insertion reaction.

Alkyl chlorides can also be used as substrates in this zinc insertion reaction. The presence of a stoichiometric amount of a bromide salt, as found by Knochel (e.g., LiBr[4] or R_4NBr, etc.), is required in addition to the iodine catalyst (Scheme 2).

Scheme 2



The scope of this zinc insertion reaction is very broad. Not only can many forms of zinc be used but also a variety of functional groups such as halides, ethers, esters, nitriles, amides, acetals, and alkenes are tolerated under the reaction conditions (Table 2). These in situ-generated zinc reagents readily participate in the Ni- or Pd-catalyzed cross-coupling reaction with aryl halides to produce various functionalized alkylarenes in excellent yields.[7] It is noteworthy that organozincs derived from bromides containing a terminal double bond (**1f** and **1g**) produced significant amounts of isomerization and other byproducts (10−20%) from their Ni-catalyzed cross-coupling with 4-chlorobenzonitrile. However, a switch from Ni to Pd led to formation of desired products

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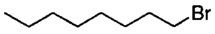
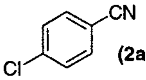
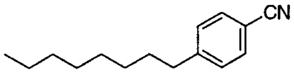
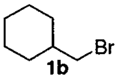
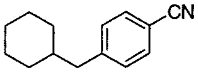
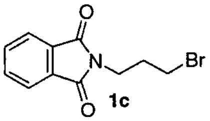
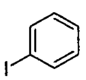
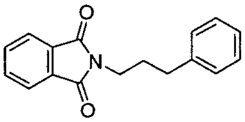
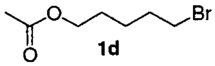
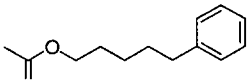
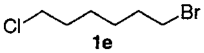
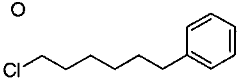
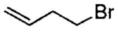
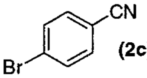
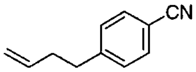
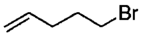
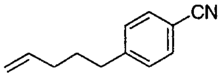
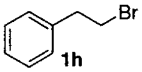
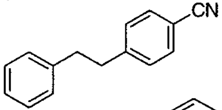
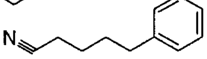
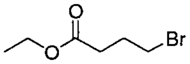
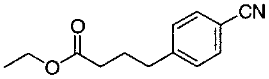
(6) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823. For recent reports on Negishi coupling of alkylzincs with aryl chlorides, see: (c) Lipshutz, B. H.; Blomgren, P. A.; Kim, S. K. *Tetrahedron Lett.* **1999**, *40*, 197. (d) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819. (e) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

(7) **Typical Procedure. Preparation of Ethyl 4-(4-Cyanophenyl)-butyrate (3j).** In a dry 25 mL two-necked flask were charged under N_2 dry DMA (10 mL), I_2 (127 mg, 0.5 mmol), and zinc dust (0.98 g, 15 mmol). The mixture was stirred at 23 °C until the red color of I_2 disappeared (ca. 2 min). Ethyl 4-bromobutyrate (**1j**) (1.95 g, 10 mmol) was added, and the mixture was stirred at 80 °C for 3 h. Completion of the zinc insertion reaction was indicated by GC analysis of the hydrolyzed reaction mixture. The mixture was cooled to 23 °C, and 1.1 g (8 mmol) of 4-chlorobenzonitrile and 105 mg (0.16 mmol) of $Cl_2Ni(PPh_3)_2$ were added successively at 23 °C. The coupling reaction was complete at room temperature after 1 h as checked by GC analysis. The reaction was quenched with 1 N HCl, and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Flash chromatography on silica gel (98:2 hexane/ethyl acetate) gave the cross coupling product **3j** as a clear, colorless oil (1.69 g, 97%).

Table 2. Preparation of Alkylzinc Bromides and Their Subsequent Ni- or Pd-Catalyzed Cross-Coupling with Aryl Halides[a]

entry	alkyl bromide (RBr)	aryl halide (ArX)	product	yield[b] (%)
1	 **1a**	 **(2a)**	 **(3a)**	91
2	 **1b**	**2a**	 **(3b)**	94
3	 **1c**	 **(2b)**	 **(3c)**	71
4	 **1d**	**2b**	 **(3d)**	91
5	 **1e**	**2b**	 **(3e)**	85
6	 **1f**	 **(2c)**	 **(3f)**	86[c]
7	 **1g**	**2c**	 **(3g)**	89[d]
8	 **1h**	**2a**	 **(3h)**	92
9	 **1i**	**2b**	 **(3i)**	93
10	 **1j**	**2a**	 **(3j)**	97

[a] All reactions were carried out in DMA; RBr:Zn(dust):I_2:ArX:$Cl_2Ni(PPh_3)_2$ = 1.0:1.5:0.05:0.8:0.016. [b] Isolated yields based on ArX. [c] $Pd(PPh_3)_4$ (2 mol %) as a catalyst, isomeric purity >97%. [d] $Pd(PPh_3)_4$ (2 mol %) as a catalyst, isomeric purity 95%.

(**3f** and **3g**) with high isomeric purities (entry 6 and 7, Table 2). Formation of zinc reagents from alkyl bromides was usually complete within 1−3 h in DMA at 80 °C. Reaction of bromomethylcyclohexane (**1b**) was rather slow but proceeded to completion within 24 h, and its subsequent cross-coupling with 4-chlorobenzonitrile in the presence of 2 mol % $Cl_2Ni(PPh_3)_2$ produced 4-cyclohexylmethylbenzonitrile in 94% yield. This sluggish zinc insertion may result from a slower iodide−bromide exchange caused by the steric hindrance of cyclohexyl group. For the same reason, the reaction of the secondary alkyl bromide 2-bromooctane was very sluggish. On the other hand, the reaction of the tertiary alkyl bromide 2-bromo-2-methylbutane with zinc dust in DMA at 80 °C was complete within 30 min and did not require the use of a catalytic amount of iodine.[8]

In summary, we have disclosed a simple, general procedure for the preparation of organozinc compounds from unactivated alkyl bromides and chlorides. These organozinc reagents have been shown to be excellent partners in Ni- and Pd-catalyzed cross-coupling reactions. This ready access to versatile alkylzinc reagents should facilitate the further development of organozinc chemistry in organic synthesis.

Acknowledgment. We thank Dr. J. Miller and Dr. J. Dankwardt (DSM Pharmaceuticals) and Professor B. M. Trost (Stanford University) for helpful discussions on this chemistry.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] For the comparison of the reactivity of different types of alkyl bromides, see: ref 3b.