

## The Barbier–Grignard-Type Carbonyl Alkylation Using Unactivated Alkyl Halides in Water

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There has been considerable recent attention toward the development of Barbier–Grignard-type reactions in water.<sup>1</sup> This interest is evident in the number of topical and excellent reviews that have illuminated the advantages of using aqueous organometallic reactions over those occurring in organic solvent<sup>2</sup> in synthesis.<sup>3</sup> For instance, the protection–deprotection processes for certain acidic-hydrogen-containing functional groups can be avoided, which contributes to the overall synthetic efficiency.<sup>4</sup> Additionally, water-soluble compounds, such as carbohydrates, can be directly reacted without the need for derivatization, and water-soluble catalysts can be reused for an extended period of time, which reduces operational cost.<sup>5</sup> However, while the allylation,<sup>6</sup> propargylation,<sup>7</sup> benzylation,<sup>8</sup> arylation/vinylation,<sup>9</sup> and alkynylation<sup>10</sup> of carbonyl compounds, along with the aldol-type reaction,<sup>11</sup> have been successful with various metals in water, a high yield Barbier–Grignard-type carbonyl alkylation with nonactivated halides in water has yet to be developed.<sup>12</sup>

This is largely due to the fact that a highly reactive metal is required to break the nonactivated carbon–halogen bond (as well as to react with the carbonyl once the organometallic intermediate is formed). However, even if the desired intermediate is successfully generated, various competing side reactions may occur when utilizing a highly reactive metal, for example, the reduction of water, the reduction of starting materials, the hydrolysis of the organometallic intermediate, and pinacol-coupling. Essentially, these difficulties have prevented the further development of aqueous organometallic reactions onto simple alkyl halides. Furthermore, on the basis of our unsuccessful attempts in the past, it was ascertained that to overcome this seemingly insurmountable dilemma, a particular balance between metal reactivity and side product conversion must be achieved without severely compromising the yield of the desired alkylated product. Herein, we are gratified to report an efficient Barbier–Grignard-type alkylation of aldehydes in water. In the presence of CuI, Zn, and catalytic InCl, in dilute aqueous sodium oxalate, simple alkyl halides reacted with aldehydes at room temperature, under an atmosphere of air,<sup>13</sup> to yield the desired nucleophilic addition products in moderate to high yields.

The investigation started with the reaction of isopropyl iodide and *p*-cyanobenzaldehyde (Scheme 1), in the presence of InCl and Zn, in water with no desired product (Table 1, entry 1), but we found that with the addition of TBDMSCl and CuBr, there was a 30% isolated yield of the alkylated product (entry 2). Motivated by this initial result, we looked at the usage of other additives such as Bu<sub>3</sub>SnH, (Me<sub>3</sub>Sn)<sub>2</sub>, (Me<sub>3</sub>Ge)<sub>2</sub>, and (Me<sub>3</sub>Si)<sub>2</sub> in water.<sup>14</sup> Even though these reactions, based upon NMR conversions, did give the desired product in varying yields, the reaction conditions were still undesirable because the conversion of aldehyde was not complete and/or there were large amounts of undesired pinacol-coupled product. The addition of organic cosolvents and sodium dodecyl sulfate seemed to hinder the reaction.

Scheme 1

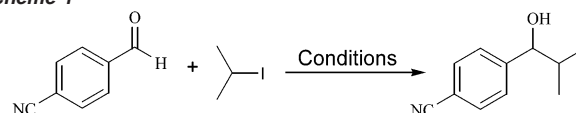


Table 1. Optimization Conditions

entry	conditions <sup>a</sup>	solvent	yield (%) <sup>b</sup>
1	InCl/Zn	H <sub>2</sub> O	0
2	InCl/TBDMSCl/Zn/CuBr	H <sub>2</sub> O	30 <sup>c</sup>
3	InCl/Zn/CuI	H <sub>2</sub> O	13:33:54
4	Zn/CuI	H <sub>2</sub> O	0:38:62
5	InCl/CuBr	H <sub>2</sub> O	no reaction
6	InCl/CuI	H <sub>2</sub> O	no reaction
7	InCl/Zn/CuI	0.07 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0:12:88 <sup>d</sup>
8	InCl/CuBr	0.07 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	no reaction
9	InCl/Zn/CuI	0.07 M K <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	0:25:75
10	InCl/Zn/CuI	0.07 M KOAc	0:36:64
11	InCl/Zn/CuI	0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	6:12:82
12	InCl/CuI	0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	no reaction
13	InCl/Zn	0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	trace
14	Zn/CuI	0.05 M Na <sub>2</sub> C <sub>2</sub> O <sub>4</sub>	13:17:71

<sup>a</sup> 18 h reaction at room temperature, based upon 20 mg (0.153 mmol) of *p*-cyanobenzaldehyde. <sup>b</sup> Yield from crude <sup>1</sup>H NMR, ratio of unreacted aldehyde:pinacol:desired product. <sup>c</sup> Isolated yield. <sup>d</sup> 0.10 equiv of InCl, 3 equiv of CuI, 5 equiv of isopropyl iodide, 6 equiv of Zn.

Further experiments showed that the optimized conditions only utilize Zn, CuI, and a catalytic amount of InCl in 0.07 M aqueous Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub> (entry 7). The use of aqueous Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub> was intended to activate zinc (by dissolving zinc oxide) under neutral conditions. A 12:88% ratio was obtained, as seen from the <sup>1</sup>H NMR of the reaction mixture, of pinacol product to desired alkylated product, respectively, based upon the aldehyde. As seen in Table 1, other aqueous media with KOAc, NaOAc, K<sub>2</sub>C<sub>2</sub>O<sub>4</sub> were also investigated but provided poorer results relative to sodium oxalate. Without zinc, there was no reaction (entry 12); without CuI (entry 13), there was only a trace amount of the alkylated product; without InCl (entry 14), there was an incomplete conversion of the aldehyde. Similar conditions but in water (entries 3–6) showed there was either an incomplete conversion of the aldehyde along with a higher amount of pinacol-coupling product or no reaction. Additionally, when the reaction was carried out in organic solvents such as THF, methanol, and methylene chloride, no desired reaction product was observed. Also, with an even lower concentration of sodium oxalate (entry 11), there was an incomplete conversion of the aldehyde. Therefore, on the basis of these results, we concluded that the best conditions are shown in entry 7.

Subsequently, a variety of aldehydes and alkyl halides were examined to generate the Barbier–Grignard alkylation products by the standard conditions (Scheme 2). Table 2 provides details of the conditions and results of a series of aldehydes<sup>15</sup> and alkyl halides utilized in the methodology. Several conclusions may be drawn from the results obtained.

Scheme 2

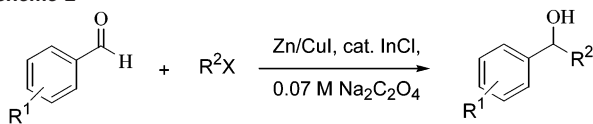
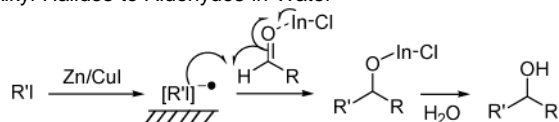


Table 2. Alkylation of Various Aldehydes

entry	RCHO	R <sup>2</sup> X	yield (%) <sup>a</sup>
1	4-CNC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	71
2	4-CNC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl bromide	41
3	4-CNC <sub>6</sub> H <sub>4</sub> CHO	cyclopentyl iodide	67
4	4-CNC <sub>6</sub> H <sub>4</sub> CHO	isopropyl iodide	85
5	4-CNC <sub>6</sub> H <sub>4</sub> CHO	<i>tert</i> -butyl iodide	30
6	4-CNC <sub>6</sub> H <sub>4</sub> CHO	1-iodo-2-methylpropane	32
7	4-CNC <sub>6</sub> H <sub>4</sub> CHO	1-iodohexane	14
8	4-BrC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	58
9	4-ClC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	53
10	PhCHO	cyclohexyl iodide	46
11	3-MeC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	47
12	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	isopropyl iodide	30
13	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	isopropyl iodide	83
14	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	56
15	3-HOC <sub>6</sub> H <sub>4</sub> CHO	isopropyl iodide	47
16	3-ClC <sub>6</sub> H <sub>4</sub> CHO	cyclohexyl iodide	66

<sup>a</sup> Isolated yields were reported.

Scheme 3. Proposed Mechanism for the Metal-Mediated Addition of Alkyl Halides to Aldehydes in Water



First, having an electron-withdrawing group (CN, entries 1–7, Br and Cl, entries 8 and 9, respectively) in the 4-position activates the aldehyde toward alkylation,<sup>16</sup> relative to benzaldehyde. Second, secondary alkyl iodides provide higher yields of the desired products (entries 1, 3, 4) than both primary alkyl iodides (entries 6 and 7) and tertiary alkyl iodide (entry 5). Third, the presence of an electron-withdrawing group appears to increase the yield of the reaction (compare entries 12 and 13).<sup>17</sup> Fourth, an aldehyde bearing a hydroxyl group does not prevent it from reacting under the current reaction conditions.

In summary, we have developed the Barbier–Grignard-type alkylation of aldehydes in water. A tentative mechanism for the reaction is proposed (Scheme 3) in which the alkyl iodide is reacted with zinc (activated by copper as in the case of the zinc–copper couple) to form a radical anion, which then reacts with the aldehyde. A possible electron transfer from the indium(I) to the carbonyl oxygen could generate an indium(II) alkoxylate that hydrolyzes to give the alkylated product, which potentially benefits the alkylation slightly. The scope, mechanism, and applications of this reaction are under further investigation.

**Acknowledgment.** We are grateful to NSF (CAREER) and the NSF-EPA joint program for a sustainable environment for partial support of our research. C.C.K.K. thanks the Louisiana Board of Regents for a Graduate Fellowship.

**Supporting Information Available:** Representative experimental procedure and the full characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919.
- (2) Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Best Synthetic Methods Series; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: San Diego, 1995.
- (3) For representative general reviews regarding organic reactions in water, see: Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59. Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glasgow, 1998. Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. Reissig, H. U. *Org. Synth. Highlights* **1991**, 71. Engberts, J. B. F. N. *Pure Appl. Chem.* **1982**, *54*, 1797.
- (4) For examples, see: Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 6674. Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747. Chappell, M. D.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2003. Warwel, M.; Fessner, W. D. *Synlett* **2000**, 865. Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206.
- (5) For a recent asymmetric example, see: Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919.
- (6) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. For an asymmetric example, see: Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277.
- (7) Issac, M. B.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003. Yi, X. H.; Meng, Y.; Li, C. J. *J. Chem. Commun.* **1998**, 449. Mitzel, T. M.; Palomo, C.; Jendza, K. *J. Org. Chem.* **2002**, *67*, 136.
- (8) Bieber, L. W.; Storch, E. C.; Malvestiti, I.; Sila, M. F. *Tetrahedron Lett.* **1998**, *39*, 9393.
- (9) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450. Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. Li, C. J.; Meng, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9538.
- (10) Wei, C. M.; Li, C. J. *Green Chem.* **2002**, *4*, 39. For a leading reference on alkyne-carbonyl addition in organic solvent, see: Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373 and references cited therein.
- (11) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505.
- (12) Conjugated addition and imine additions have been reported before; however, unlike the aldehyde addition, the intermediates in these reactions are stabilized by the carbonyl or the aryl groups, respectively; for examples, see: Huang, T. S.; Keh, C. C. K.; Li, C. J. *J. Chem. Commun.* **2002**, 2440. Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131.
- (13) Li, C. J. *Acc. Chem. Res.* **2002**, *35*, 533.
- (14) Further details are provided in the Supporting Information.
- (15) No reaction was observed with aliphatic aldehydes such as undecanal, 2,2-dimethylpropionaldehyde, cyclohexancarboxaldehyde. Ketones such as benzophenone, acetophenone, 2-hexanone, cyclohexanone, and cyclopentanone also did not result in the desired product along with unsaturated carbonyls such as 4-hexen-3-one and 2,2-dimethyl-4-pental.
- (16) When 4-nitrobenzaldehyde was used, the reaction mixture <sup>1</sup>H NMR showed an inseparable mix of reduced products. This was attributed to some reduction of the nitro group under the reaction conditions.
- (17) 2,4-Dimethylbenzaldehyde and 2,4-bis(trifluoromethyl)benzaldehyde were compared in an analogous manner but had poor isolated yields of 17 and 8%, respectively, possibly due to steric effects.

JA029649P