Photoinduced Synthesis of Diorganozinc and Organozinc Iodide Reagents

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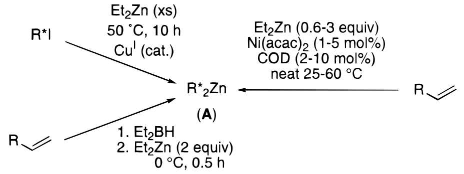
In the past few years, organozinc derivatives have been found to be increasingly useful reagents for carrying out organic transformations.[1] The relatively low reactivity of the carbon−zinc bond toward electrophilic reagents has made them ideal precursors to more reactive species via transmetalation reactions[2] or Lewis acid-catalyzed addition reactions to carbonyl groups.[3] Consequently, one significant advantage of these reagents is that highly functionalized derivatives can be prepared. Although there are several methods to prepare dialkylzincs (**A**) ($R^*{}_2Zn$ where R* is an enantiomercially pure group), they usually require excess Et_2Zn followed by a distillation to remove excess reactants and/or the presence of a transition-metal catalyst (Scheme 1).[4−6] Although mixed diorganozinc reagents (**B**) (R*ZnR′) have been invoked as intermediates,[7,8] very few methods for their clean synthesis are available.[9] Conversely, access to functionalized organozinc halides (**C**) (R*ZnX) has been traditionally accomplished by the direct insertion of activated zinc into a carbon−iodine bond,[10] by treating an organolithium or Grignard reagent with ZnX_2[11] or, more recently, by a Pd-, Mn/Cu− or Ni-catalyzed Et_2Zn insertion into C−X bond.[12]

Our interest in the synthesis of chiral, functionalized zinc carbenoid reagents (**D**) for the cyclopropanation reaction of unfunctionalized olefins prompted us to devise a unified route to diorganozincs (**A**, **B**) and organozinc iodides (**C**). Ideally, this route would avoid the use of excess diethyl- or diisopropylzinc reagent and/or the use of a transition metal as a catalyst. This is an essential requirement since these additional species might jeopardize the subsequent conversion of these reagents into chiral zinc carbenoids (Scheme 2).[13] The accessibility to pure and homogeneous organozinc reagents is an essential first-step toward the efficient synthesis of chiral zinc carbenoid reagents. Herein, we report a new general route to diorganozinc reagents (**A**, **B**) and organozinc iodides (**C**) that is based on the facile equilibration of organozinc reagents and alkyl iodides under photochemical conditions.

Scheme 1



Scheme 2

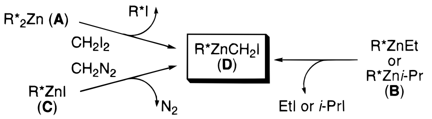
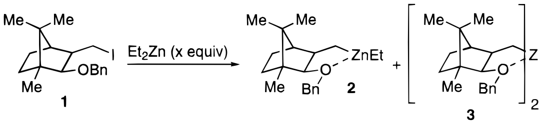


Table 1. Effect of Irradiation on the Conversion of **1** to **2**



entry	*x*	solvent (temp °C)	*t* (h)	convsn to **2**[a] (%)
1	1.0	CD_2Cl_2 (23)	48	<10
2	1.0	neat (80)	48	45 (**3**)[b]
3	2.0	neat (80)	48	70 (**3**)[b]
4	10.0	neat (80)	6	>90 (**3**)[b]
5	1.0	CD_2Cl_2 (23)[c]	3	90

[a] The conversion of **2** was determined by ^1H NMR of the crude reaction mixture. The remaining material was starting iodide 1 and Et_2Zn. [b] Mixed diorganozinc **2** was converted into **3** upon removal of excess Et_2Zn. [c] Reaction mixture was irradiated with a GE sunlamp (275 W) in a pyrex NMR tube.

Our initial target for this study was the mixed diorganozinc **2**. As expected, when iodide **1**[14] was stirred with 1 equiv of diethylzinc in CD_2Cl_2, less than 10% of the desired diorganozinc was observed by ^1H NMR (Table 1, entry 1).

Knochel has previously shown that the use of an excess Et_2Zn without any solvent at 80 °C is necessary to favorably induce the equilibrium on the side of the more stable diorganozinc reagent (or of the more volatile iodoethane). Accordingly, the exchange reaction occurred quantitatively when 10 equiv of Et_2Zn was used to produce **2**. Unfortunately, the mixed diorganozinc **2** was completely converted into the diorganozinc reagent **3** upon removal of excess Et_2Zn and EtI (Table 1, entries 2−4). *However, we have found that a favorable equilibrium occurred in solution at room temperature with only 1 equiv of* Et_2Zn *when a solution of the iodide and* Et_2Zn *in* CH_2Cl_2 *is irradiated at* $\lambda \geq 280$ *nm*

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[1] (a) Knochel, P.; Langer, F.; Longeau, A.; Rottländer, M.; Stüdemann, T. *Chem. Ber.* **1997**, *130*, 1021−1027. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

[2] See, for example: Lipshutz, B. H.; Woo, K.; Gross, T.; Buzard, D. J.; Tirado, R. *Synlett* **1997**, 477−478 and references therein.

[3] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.

[4] Preparation of diorganozinc via an iodine−zinc exchange: (a) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956−1958. (b) Micouin, L.; Knochel, P. *Synlett* **1997**, 327−328.

[5] Preparation of diorganozinc from olefins via a nickel-catalyzed hydrozincation: (a) Vettel, S.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 1023−1026. (b) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473−7481.

[6] Preparation of homodialkylzincs via a boron−zinc exchange: (a) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410−412. (b) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229−8243.

[7] Knochel has postulated that mixed diorganozinc reagents were formed as intermediates to homodiorganozinc reagents: (a) ref 4. (b) Micouin, L.; Oestreich, M.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 245−246.

[8] Mixed diorganozinc reagents are prone to undergo the following Schlenk equilibrium: $2R^*ZnR' \rightleftharpoons R^*{}_2Zn + R'_2Zn$. However, when R* contains a functional group that is electron-withdrawing or that can stabilize the zinc center by an intramolecular chelate, the mixed diorganozinc should then be favored over the two other species. For a discussion of the Schlenk equilibrium of organozinc compounds, see: Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539−4549 and references therein.

[9] A method for the preparation of $TMSCH_2ZnR$ has been reported recently: (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496−1498. (b) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895−7898.

[10] Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323−4324.

[11] Boersma, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press: NY 1982; Vol 2, p 823−862.

[12] (a) Stadtmüller, H.; Tucker, C. E.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 7911−7914. (b) Klement, I.; Knochel, P.; Chau, K.; Cahiez, G. *Tetrahedron Lett.* **1994**, *35*, 1177−1180. (c) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743−5753.

[13] Excess diethylzinc would obviously produce an achiral cyclopropanating reagent whereas the presence of a catalytic amount of a transition metal led to the formation of unsuitable reactive species: (a) Kanai, H.; Hiraki, N.; Iida, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1025−1029. (b) Kanai, H.; Nishiguchi, Y.; Matsuda, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1592−1597. (c) Takai, K.; Kakiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671−2673.

[14] Prepared from the known diol in 4 steps (1. TBDMSCl, imidazole; 2. BnBr, NaH; 3. TBAF, THF; 4. Tf_2O, NaI, collidine, CH_2Cl_2, acetone 73% overall yield). For the diol synthesis, see: Wala, R.; Zarnowki, J.; Antkowiak, W. Z. *Rocz. Chem.* **1969**, *43*, 833−844.

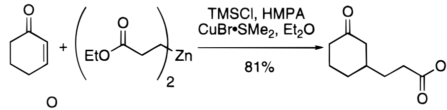
S0002-7863(98)00318-7 CCC: $15.00

(Table 1, entry 5).[15] This spectacular rate enhancement for alkyl group exchange is possible only between dialkylzincs and alkyl iodides.[16]

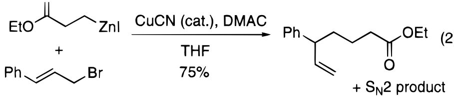
As a follow-up of this observation, several other alkyl iodides were submitted to the reaction conditions to produce the mixed diorganozinc reagents (**B**) (Table 2). In all the cases, control experiments showed that less than 10% of the desired mixed diorganozinc reagent was produced if an equimolar mixture of the alkyl iodide and diethylzinc were stirred under these condition but without irradiation. The alkyl group exchange occurred smoothly and in very high yields with primary iodides containing chelating groups upon irradiation (Table 2, entries 1−5).[17] Even a secondary iodide was transformed into the corresponding mixed diorganozinc reagent in high yield under these conditions (Table 2, entry 2). In cases where the stability of the desired mixed diorganozinc was comparable to that of the starting material, the use of the more reactive diisopropylzinc led to an higher yield for the mixed diorganozinc (Table 2, entries 8 and 9). Access to the diorganozinc reagents (**A**) was achieved by irradiating a solution containing 0.5 equiv of diethyl- or diisopropylzinc and 1 equiv of the alkyl iodide (Table 2, entries 10−13). The double alkyl group exchange occurred rapidly with alkyl iodides containing chelating or basic groups (Table 2, entries 10 and 11). As previously observed, the use of diisopropylzinc was necessary to obtain high conversions with less reactive iodides.

We then turned our attention to the synthesis of organozinc iodides using the same procedure. Gratifyingly, very high conversions to organozinc iodides were observed if R_2Zn ($R =$ Et, *i*-Pr) was substituted with EtZnI or *i*-PrZnI (Table 2, entries 14−20). The reaction times were usually longer that those necessary for the synthesis of the diorganozinc reagents. This observation is probably a consequence of the lower reactivity of EtZnI (or *i*-PrZnI) compared to that of Et_2Zn (or *i*-Pr_2Zn) in this exchange process. Generally, isopropylzinc iodide generally produced higher yields of the corresponding alkylzinc iodide (see Table 2, entries 16 vs 17 and 18 vs 19).

To further confirm the high conversion observed by NMR or GC, two of these organozinc reagents were prepared on 1-mmol scale and submitted to known transformations (eq 1−2). The irradiation time had to be slightly longer for complete conversion to the desired diorganozinc and the yields for these reactions were similar to those reported in the literature for the same transformations.[18]



(1)

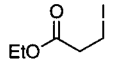
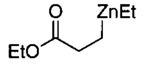
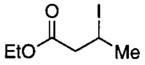
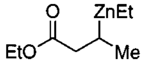
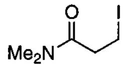
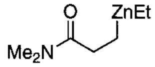
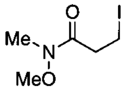
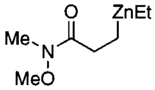
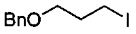
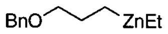
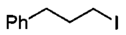
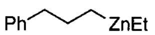
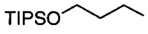
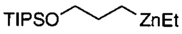
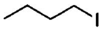
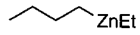
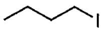
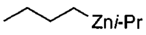
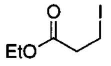
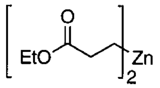
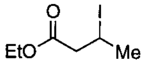
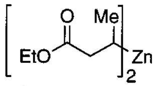
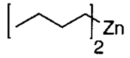
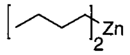
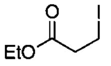
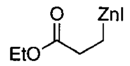
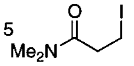
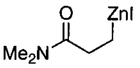
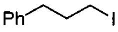
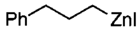
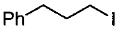
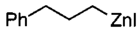
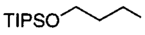
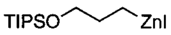
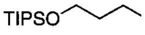
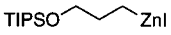
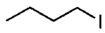
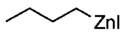
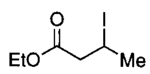
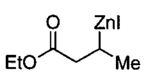


(2)

Application of this methodology to the synthesis of chiral zinc carbenoid reagents is in progress and will be reported in due course.

Table 2. Synthesis of Organozinc Reagents from Alkyl Iodides

$$RI + R'_2Zn \text{ or } R'ZnI \xrightarrow[h\nu]{CD_2Cl_2} R_2Zn,\ RZnR' \text{ or } RZnI$$

Entry	Iodide	R'_2Zn or R'ZnI (equiv)	Product	Conversion[a,b] (rxn time, h)
1		Et_2Zn (1)		>95% (1)
2		Et_2Zn (1)		92% (1)
3		Et_2Zn (1)		>95% (1)
4		Et_2Zn (1)		>95% (1)
5		Et_2Zn (1)		95% (1.5)
6		Et_2Zn (1)		89% (1.5)
7		Et_2Zn (1)		91% (1.5)
8		Et_2Zn (1)		66% (1)
9		*i*-Pr_2Zn (1)		95% (4.5)
10		Et_2Zn (0.5)		95% (1.25)
11		Et_2Zn (0.5)		89% (1.5)
12		Et_2Zn (0.5)		57% (1.5)
13		*i*-Pr_2Zn (0.5)		85% (3)
14		EtZnI (1)		88% (1.5)
15		EtZnI (1)		82% (2)
16		EtZnI (1)		50% (2.5)
17		*i*-PrZnI (1)		83% (3)
18		EtZnI (1)		55% (1.5)
19		*i*-PrZnI (1)		85% (4)
20		*i*-PrZnI (1)		82% (3)
21		*i*-PrZnI (1)		74% (4)

[a] Conversions were determined by ^1H NMR and/or GC analysis of the crude reaction mixture using an internal standard. In all cases, any remaining materials were identified to be the starting reagents. [b] <10% conversions were observed in all the cases if the reactions were not irradiated at ≥280 nm.

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Supporting Information Available: Typical experimental procedures and NMR spectra data of all the compounds (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[15] The mixture was irradiated in a Pyrex NMR tube ($\lambda \geq 280$ nm) with a GE sunlamp (275 W). Photoreactions could also be performed in Pyrex flask or NMR tube ($\lambda \geq 280$ nm) using a Hanovia 450 W Hg medium-pressure UV lamp in a water-cooled quartz immersion apparatus as the light source.

[16] The mechanism for the facile exchange is not known at this time but it might involve the formation of an exciplex between the alkyl iodide and diethylzinc. Both species were recovered unchanged when irradiated separately. For a discussion of the UV spectra of dialkylzincs, see: Young, P. J.; Gosavi, R. K.; Connor, J.; Strausz, O. P.; Gunning, H. E. *J. Chem. Phys.* **1973**, *58*, 5280−5283.

[17] In all cases, a stoichiometric amount of EtI or *i*-PrI was formed and observed by NMR and/or GC.

[18] Experimental details and other control experiments are provided in the Supporting Information.