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Preparation of Alkylzinc Bromides Using a New Mn/Cu Catalyzed Bromine-Zinc Exchange Reaction

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Summary: The reaction of functionalized primary alkyl bromides with Et_2Zn *in DMPU in the presence of a catalytic mixed metal system constituted of* $MnBr_2$ *(or* $FeCl_3$*) and CuCl provides functionalyzed alkylzinc bromides (> 80 % yield). In the presence of* $PdCl_2(dppf)$ *or CuCN·2LiCl, these organozinc species react with a range of electrophiles providing various polyfunctional molecules in good yields.*

Organozinc halides are useful organometallic intermediates which tolerate the presence of most organic functionalities and react in the presence of the appropriate transition metal catalyst (Cu, Pd, Ti), with a broad range of electrophiles.[1] They are most conveniently prepared by the insertion of zinc dust into an alkyl iodide.[1,2] Although less expensive and more stable, alkyl bromides and chlorides are generally too unreactive to insert zinc dust.[3] Recently, we have found that a palladium or nickel catalyzed iodine-zinc exchange between an alkyl iodide (FG-R-I) and Et_2Zn allows a particularly smooth preparation of alkylzinc iodides.[4] Herein we wish to report a new reaction which allows to convert directly primary alkyl bromides ($FG\text{-}RCH_2Br$) **1** to the corresponding alkylzinc bromides ($FG\text{-}RCH_2ZnBr$) **2** under mild conditions (several hours at 25 °C) using Et_2Zn and a Mn/Cu mixed-metal catalysis (equation 1). It has been demonstrated that organomanganese chlorides (RMnCl) are alkylated by primary alkyl bromides in THF:NMP mixtures in the presence of catalytic amounts of CuI (3 mol %) in excellent yields.[5] Since polyfunctional zinc reagents are readily available and are good candidates for transmetalations, it was decided to treat dialkylzincs (R_2Zn) with $MnCl_2$ with the hope that the resulting alkylmanganese chlorides (RMnCl) would undergo a coupling reaction with alkyl halides. Surprisingly, we found that the treatment of Et_2Zn (1 equiv.) with octyl bromide (2 equiv.) in the presence of $MnCl_2$ (1 equiv.) and catalytic amounts of CuCl (3 mol % NMP, 25 °C, 4-8 h) did not afford the desired coupling product (Oct-Et), but instead led to OctZnBr as indicated by iodolysis experiments (15 % yield by GC analysis, equation 2 and entry 1 of Table 1).

$$\underset{\mathbf{1}}{\text{FG-RCH}_2\text{Br}} \quad + \quad \text{Et}_2\text{Zn} \quad \xrightarrow[\text{DMPU, 25 °C, 4-10 h} \atop -\,(\text{H}_3\text{C-CH}_3,\ \text{H}_2\text{C=CH}_2)]{\text{MnBr}_2\ (5\ \text{mol\%}) \atop \text{CuCl}\ (3\ \text{mol\%})} \quad \underset{\mathbf{2}\qquad 80\text{-}90\ \%}{\text{FG-RCH}_2\text{ZnBr}} \qquad (1)$$

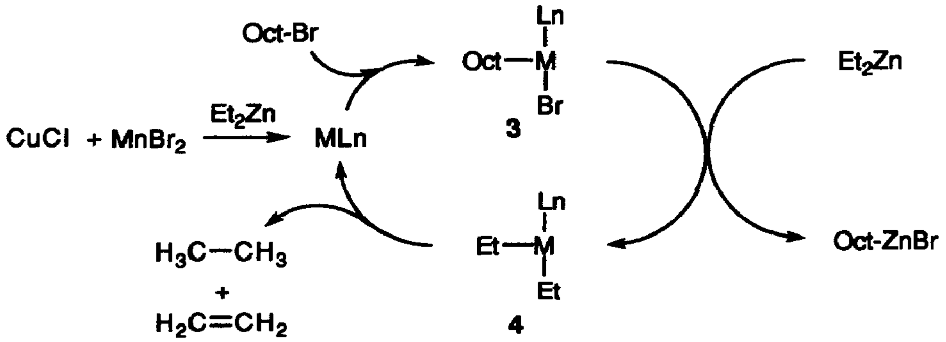
$$\text{Oct-Br} + \text{Et}_2\text{Zn} \xrightarrow[\text{3 \% CuCl; 2) } I_2,\ -15\ °C]{\text{1) MLn cat.; solvent}} \text{Oct-I} \qquad (2)$$

Table 1. Optimization of the Bromine - Zinc Exchange Reaction.

Entry	Et_2Zn^a	Solvent	MLn : (mol%)	Yield (%)^b
1	0.5	NMP	$MnCl_2$: 100	15
2	0.5	NMP	$MnCl_2$: 10	22
3	0.5	DMPU	$MnCl_2$: 100	28
4	0.5	DMPU	$MnCl_2$: 10	29
5	1	DMPU	$MnCl_2$: 10	75 (73)
6	1	DMPU	$MnBr_2$: 10	83 (77)
7	1	DMPU	$MnBr_2$: 5	85 (84)
8	1	DMPU	$FeCl_3$: 5	81 (77)

^{a} Number of equivalents (OctBr = 1.0 equiv). ^{b} GC yield of OctI obtained after the iodolysis of OctZnBr, determined using an internal standard. Isolated yields are given in parenthesis.

The use of catalytic amounts of $MnCl_2$ (10 mol %) and the replacement of NMP by DMPU[6] improved somewhat the reaction yield (compare entries 1-4 of Table 1), however a spectacular yield improvement was observed by using one equivalent of Et_2Zn for one equivalent of OctBr (entry 5). We found that the use of $MnBr_2$ instead of $MnCl_2$ led to a further improvement (entry 6) and that the use of only 5 mol % (instead of 10 mol %) of $MnBr_2$ was beneficial. The reaction was complete under these conditions within 2 h (entry 7). A further reduction of the quantity of $MnBr_2$ led to a rate decrease and to lower isolated yields of OctI (after iodolysis). The nature of the copper salt additive was also briefly examined and the use of 1 mol% of CuCl instead of 3 mol % led to a reduced reaction rate and a significant yield decrease (58 % compared to 73 %). The use of $CuBr{\cdot}Me_2S$ instead of CuCl has a similar detrimental effect. Interestingly the use of $FeCl_3$ (5 mol %) as additive gives comparable results as $MnBr_2$, although a slightly slower rate of the bromine-zinc exchange was observed (entry 8). The necessity of having a equimolar stoichiometry between the alkyl bromide and Et_2Zn was explained as we found that ethylene[7] and small quantities of octene (ca. 4 %) were formed during the reaction. This led us to postulate the tentative mechanism depicted in the scheme.



The reaction of CuCl and $MnBr_2$ with Et_2Zn produces the actual catalytic species represented by MLn which undergoes an oxidative addition furnishing an organometallic intermediate **3** which exchanges its octyl and bromide ligands with two ethyl groups leading to OctZnBr and the transition metal complex **4** which after β-hydride elimination and reductive coupling produces ethane and ethylene (Scheme). This new bromine-zinc exchange reaction is of synthetic interest since it allows to convert primary alkyl bromides which are usually reluctant to the direct insertion of zinc dust, into the corresponding alkylzinc bromides under very mild conditions. Thus, for example the addition of Et_2Zn (0.9 equiv) to a DMPU solution of ethyl 4-bromobutyrate **1b** (1 equiv), $MnBr_2$ (5 mol %) and CuCl (3.3 mol %) led to a dark red solution. GC analysis indicates that the bromide-zinc exchange was complete after 3-4 h of stirring at 25 °C. The yield of alkylzinc bromide was estimated to be ca. 85 %. These zinc reagents can be readily coupled with various aromatic iodides and bromides (0.9 equiv) in the presence of catalytic amounts of $PdCl_2(dppf)$[8] (5 mol %) (-30 to 25 °C, 0.5 h, then 65 °C, 12 h) leading to polyfunctional aromatic compounds in 69-75 % yield (entries 1-8 of Table 2).[9] Treatment of the DMPU solution of **2** with $CuCN{\cdot}2LiCl$[2b] afforded copper species which undergo Michael-additions with reactive acceptors such as diethyl benzylidenemalonate (see entries 9-10) or nitrostyrene (entry 11) in 67-68 % yield. The direct reaction with allylic bromides produces the allylated products **5l-n** without the need of a transmetalation or catalysis (68-74 %; entries 12-14 of Table 2).

Table 2. Polyfunctional products **5a-n** obtained by the reaction of the alkylzinc bromides **2a-d** with an electrophile.

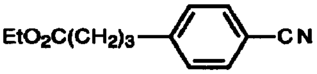
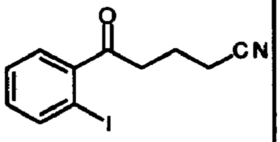
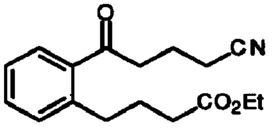
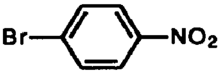
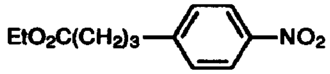
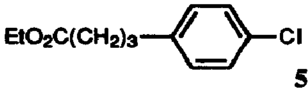
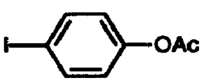
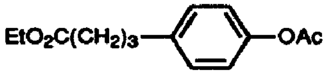
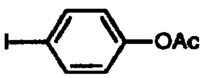
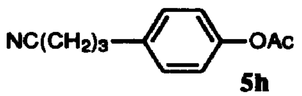
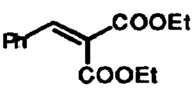
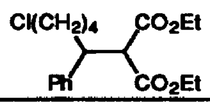
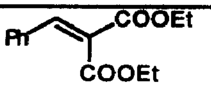
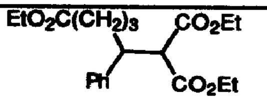
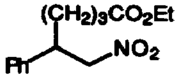
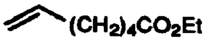
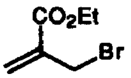
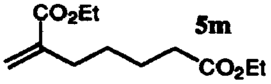
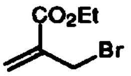
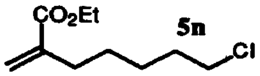
Entry	Alkylzinc Bromide 2	Electrophile	Product 5	Yield (%)[a]
1	OctZnBr **2a**	PhI	Ph-Oct **5a**	71
2	OctZnBr **2a**		 **5b**	70
3	$EtO_2C(CH_2)_3ZnBr$ **2b**		 **5c**	75
4	**2b**		 **5d**	71
5	**2b**		 **5e**	69
6	**2b**		 **5f**	73
7	**2b**		 **5g**	72
8	$NC(CH_2)_3ZnBr$ **2c**		 **5h**	72
9	$Cl(CH_2)_4ZnBr$ **2d**		 **5i**	74

Table 2 (continued)

Entry	Alkylzinc Bromide 2	Electrophile	Product 5	Yield (%)[a]
10	$EtO_2C(CH_2)_3ZnBr$ **2b**		 **5j**	68
11	**2b**		 **5k**	67
12	**2b**		 **5l**	74[b]
13	**2b**		 **5m**	71[b]
14	**2d**		 **5n**	68[b]

[a] Isolated yields of analytically pure compounds. [b] No transmetalation is required.

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7. Determined by detecting 1,2-dibromoethane after the treatment of the reaction mixture with bromine.
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9. *Typical procedure: Preparation of ethyl 4-(p-chlorophenyl)butyrate 5f:* A three-necked flask equipped with a thermometer, a gas inlet and a magnetic stirring bar was charged under argon with $MnBr_2$ (64 mg, 0.3 mmol) in DMPU (5 mL). CuCl (17 mg, 0.2 mmol), ethyl 4-bromobutyrate **1b** (1.17 g, 6.0 mmol) and Et_2Zn (0.54 mL, 5.4 mmol) were successively added. The reaction mixture turned dark red and was stirred for 4 h at 25 °C. GC analysis of a reaction aliquot showed a complete conversion to the zinc reagent **2b**. After cooling to -30 °C a solution of $Cl_2Pd(dppf)$ (185 mg, 0.2 mmol) and 4-chloro-iodobenzene (1.19 g, 5.0 mmol) in THF (5 mL) was slowly added. The reaction mixture was warmed up to 25 °C for 0.5 h and was then stirred at 65 °C overnight and quenched with an aqueous 2N HCl solution (20 mL). After work-up and evaporation of the solvent, the crude residue obtained was purified by flash chromatography (hexane/ether 10:1), yielding 0.82 g (73 %) of **5f** (entry 6 of Table 2).

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