Nickel(II)-Catalyzed Dialkylation of Aromatic Aldehydes with Organozinc Reagents

Yulai Hu, Jin-Xian Wang,* and Wenbo Li
Institute of Chemistry, Department of Chemistry, Northwest Normal University, Lanzhou 730070, P. R. China

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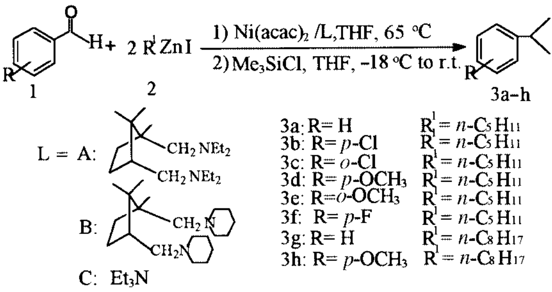
A novel reaction of the dialkylation of arylaldehydes is provided. The reaction of substituted aromatic aldehyde with organozinc halides in the presence of catalytic amount of $Ni(acac)_2$ and a tertiary amine using a silylating agent to give 1-alkyl-1-arylalkanes in satisfactory yields.

Organozinc reagents are versatile organometallic reagents that have found wide applications.[1] Their excellent functional group tolerance, high chemoselectivity and excellent stereoselectivity in many reactions make organozincs ideal organometallic intermediates for the construction of complex polyfunctional molecules. Dialkylzinc compounds are stable and poorly reactive organometallic compounds. R_2Zn reagents are generally inert toward carbonyl compounds, but methods to promote their reaction with aldehydes are well known.[1–3] We have found very few literature reports of dialkylation of carbonyl compounds.[4]

In 1978, Mukaiyama first reported that Et_2Zn could add smoothly to benzaldehyde in the presence of aminoalcohols.[5] After this report, much attention has been given to the reaction,[6] especially the enantioseletive addition reaction[7] of dialkylzinc compounds with aldehydes and ketones. However, in most cases only one of the two alkyl group is transferred, essentially wasting 50% of the precious reagent. Alkylzinc halides RZnX, offer alternatives, the zinc carrying only one alkyl side chain, however, these species are less reactive and often necessitate the use of an additional catalyst.

In 1988, Knochel[8] showed that functional organozinc iodides RZnI could be transmetallated into organozinccopper reagents RCu(CN)ZnI with THF soluble copper salt CuCN·2LiCl, and then coupled with acyl chlorides or conducted 1,4-addition reaction with enones. This report greatly extended the application range of organozinc reagents in organic synthesis. Now these regeants have been successfully used in coupling reactions with organic halides, 1,2-addition reactions with aldehydes or ketones, and 1,4-addition reactions with β-unsaturated carbonyl compound or nitro olefins.[1,6,9] However, stoichiometric CuCN·2LiCl must be used in most of their reactions. Recently, Nickel-catalyzed coupling reaction of halides with organozinc reagents has reported.[10] Addition of alkylzinc to carbonyl compounds is one of the most reliable method to synthesize optically active secondary alcohols.[7,11] In our previous report,[12] we used $Cu(OAc)_2/LiCl$ as a copper salt to carried out the 1,4-addition reaction with enones. Although the method avoided the use of toxic CN^- ion in the reaction, the amount of $Cu(OAc)_2$ used was still stoichiometric. We also reported[13] that the nitro group of 1-aryl-2-nitroethenes can be substituted by organozinc halides under the catalysis of $Ni(acac)_2$ and a tertiary amine to give 1-aryl-1-alkenes in excellent yields.

We have now found that the 1-alkyl-1-arylalkanes can be obtained from substituted aromatic aldehydes with organozinc halides in the presence of catalytic amount of $Ni(acac)_2$ and a tertiary amine using a silylating agent. In this paper, we have reported the new reaction of the dialkylation of aromatic aldehydes by organozinc halides. The reactions are shown in Scheme 1 and the results are summarized in Table1.



Scheme 1.

Table 1. Nickel (II) catalyzed reaction of R-ZnI with aromatic aldehydes in the presence of silylating agents

Entry	R	L	Product[a]	Yield /%[b]
1	H	A	3a	76
2	H	B	3a	74
3	H	C	3a	80
4	*p*-Cl	C	3b	76
5	*o*-Cl	C	3c[14]	78
6	*p*-OCH_3	C	3d	65
7	*o*-OCH_3	C	3e	50
8	*p*-F	C	3f	74
9	H	C	3g	85
10	*p*-OCH_3	C	3h	82

[a]The structures were determined by IR,^{1}H-NMR, ^{13}C-NMR and MS. [b]Isolated yield.

The organozinc reagents, obtained by the Knochels procedure,[8] were added into a mixture of $Ni(acac)_2$ and a tertiary amine at room temperature. The reactions were carried out at −18 °C to room temperature. In the course of the reactions, the reaction mixture became slightly brown from milky white. In the absence of $Ni(acac)_2$ and a tertiary amine, the reaction was not successful. For example, no product was isolated after the reaction of aromatic aldehyde and *n*-$C_5H_{11}ZnI$ without $Ni(acac)_2$ and a tertiary amine or chlorotrimethylsilane. Me_3SiCl plays an important role for activation of the organozinc reagent in the reaction. We have also found that this reaction is sensitive to molecular structure of aldehydes and ketones. For example, under the same conditions, the use of aliphatic aldehydes, ketones, and aromatic ketones led several side reactions.

In a typical case, under nitrogen atmosphere, a mixture of zinc (1 g , 1.5 mmol), 1,2-dibromoethane (0.2 cm^3) and THF (2 cm^3) in a three-neck flask was heated to 60–70 °C for 2–3 min and then cooled to room temperature. Chlorotrimethylsiane (0.2 cm^3) was added, and the mixture was stirred at room temperature for 15 min. A solution of RI (1.2 mmol) in THF (10 cm^3) was then added, and the mixture was stirred for 12 h at 35–40 °C. The resulting solution of RZnI in THF was ready to use. In another three-neck flask, Ni(acac)$_2$ (1.2 mmol), L (2.4 mmol for A and B, 4.8 mmol for C), and THF (10 cm^3) were added and heated at 60 °C for 10 min. The solution of RZnI in THF obtained as above was added at room temperature, and the resulting mixture was cooled to –18 °C. A solution of aromatic aldehyde (8 mmol) was added drop by drop and the temperature was allowed to rise to room temperature. After stirring for 12 h, saturated NH$_4$Cl solution (10 cm^3) and Et$_2$O (10 cm^3) were added and the mixture was stirred for 10 min. The organic layer was separated, dried over anhydrous MgSO$_4$ and concentrated. The product was isolated from the crude reaction mixture by chromatography on a silica-gel column using pertroleum/diethyl ether as an eluent.

In summary, compared with the similar reaction of dialkylzincs, the reaction reported here has the following advantages: easier availability of organozinc iodides than dialkylzincs and higher yields of products and provides a new method to form the products of dialkylation.

Further investigations on the utilization of this reaction and the mechanism are now in progreess.

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14 Spectroscopic data for **3c**: colorless liquid; ^{1}H NMR (80 MHz, CDCl$_3$):δ = 7.44–6.99 (m, 4H), 3.35–3.19 (m, 1H), 1.59–0.68 (m, 22H); ^{13}C NMR (100MHz, CDCl$_3$): δ = 143.712, 134.646, 129.302, 127.638, 126.774, 126.595, 40.661, 36.240, 32.009, 26.927, 22.561, 14.043; IR ν_{max} (neat)/cm^{-1}: 3017, 2956, 2928, 2857, 1466, 1441, 1378, 1103, 751, 734, 682; EI-MS (*m/z*): 266 (M), 268 (M+2).