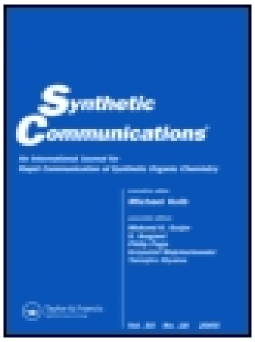

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Nucleophilic Addition of Arylmethylzinc Reagents ($ArCH_2ZnCl$) to Formaldehyde: An Easy Access to 2-(Hetro)arylethyl Alcohols

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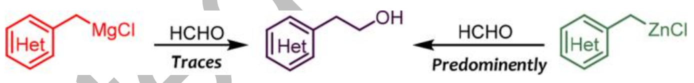
Abstract

The selective addition of arylmethylmagnesium halides with formaldehyde giving arylethyl alcohols is extremely challenging. To circumvent the difficulties, in the current communication we have reported on the nucleophilic addition of benzyl zinc reagents derived from inexpensive and abundant benzyl chlorides to paraformaldehyde. The reaction investigated herein is hitherto unknown and was found to be selective, operationally simple, atom- and step-economical and high yielding to deliver phenethyl alcohols utilized as key perfumery ingredients in 60-83% yields. After successful establishment of the reaction condition, the reaction was also scaled up successfully to deliver a large scale preparation of the phenethyl alcohol.

Graphical Abstract



KEYWORDS: Zn reagents, Nucleophilic addition, 2-(hetro)arylethyl alcohols

INTRODUCTION

Due to indispensable requirement of route scouting in pharmaceuticals, natural products, agrochemicals, commodity chemicals, and flavours and fragrances, the development of new synthetic methodologies have indispensable requirement to accomplish the desired synthetic requirements of the chemical industry.[1] New reagents have been developed to provide the desired novelty in terms of selectivity, reactivity, cost-effectiveness, atom-

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and step-economy, environment benignness, high yield, and high functional group compatibility.

Since last few decades organometallic chemistry has played pivotal role to accomplish the desired synthetic goals.[2] A large number of metals has been used to address the challenges in synthesis.[3] Organometallic addition to electrophiles is ubiquitous and plethora of literature is available to demonstrate the versatility of such transformations.[4] More specifically, the addition of organometallic reagents to carbonyls to form new carbon-carbon bonds has been studied extensively. Interestingly, the addition of a nucleophile containing benzylic organometallic ($ArCH_2M$, M = metal) to an electron deficient carbon is found to be challenging for the installation of benzylic ($ArCH_2$) group in organic compounds. Traditionally, the related organometallics are generated from their corresponding benzylethers or benzyl halides by the reaction of an active metal, for instance Li, Mg, Zn, Mn, Cd, Si.[5] However, this methodology is not straightforward and does poses several practical difficulties. The challenges associated with this type of organometallics are their very high reactivity and lack of stability under normal conditions.

2-Arylethyl alcohols are common perfumery chemicals. 2-Phenylethyl alcohol is used when rose odour is desired. It is used as a preservative in soap because of its stability under basic conditions and antimicrobial property. It is also found in extracts of champaca, neroli, geranium, ylang-ylang, rose, carnation, aleppo pine, hyacinth, and orange blossom.[6]

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Apparently, the most common method to introduce the hydroxymethyl group in a compound is the reaction of a Grignard reagent and formaldehyde. The Grignard reaction of benzyl magnesium chloride **1** and different carbonyl compounds has been extensively investigated by Siegel and Benkeser, independently.[7] However, this reaction with formaldehyde gives largely side products rather than the desired compounds. The reaction of **1** with formaldehyde **2** yields predominantly undesired *o*-tolyl carbinol **4** with a trace of the desired 2-phenethyl alcohol (**3a) (Scheme 1)**. The generation of the by-products is largely depends on the mole equivalent of the formaldehyde and the Grignard reagent used. Alternative methodologies for the synthesis of phenethyl alcohol are also reported in the literature.[8]

DISCUSSION

On the background of this unusual observation and our interest in the synthesis of phenethyl alcohols, we set out to study this reaction. Our hypothesis was that as zinc is less electropositive than magnesium, an organozinc reagent would be better suited to react with formaldehyde to give the desired phenethyl alcohols (Pauling electronegativity Mg 1.31, Zn 1.65). Therefore, the key objective of this work was to address the limitation of this abnormal reactivity of benzyl magnesium chloride with electrophiles and investigating the possibility of using benzyl zinc reagents for the synthesis of phenethyl alcohols. Turbo Grignard reagent is also found to be a valuable tool in metal-halogen exchange having extensive practical utility in the presence of reactive functional groups such as esters, nitriles, ketones, and various unstable heteroaromatics.[9]

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Organozinc reagents show excellent reactivity with diverse electrophiles and also are easy to handle. For example, their reactivity exploited in Reformatsky and Simmons-Smith reactions.[10] Apparently, organolithium and organomagnesium reagents have significantly lower functional group compatibility than organozinc reagents.[11] Organozinc reagents have excellent functional group compatibility which can be witnessed in their reactions with electrophile variants.[12] The more the ionic character of the carbon-zinc bond the more reactive is the reagent; due to more negative charge located at the carbon attached to Zn.[13] These considerations prompted us to use zinc in the reaction of arylmethyl halides with formaldehyde, with specific objective of obtaining 2-arylethylalcohols; the reaction would proceed through zinc intermediate $ArCH_2ZnX$.

At the outset, the reaction of benzyl chloride **5a** or benzyl bromide **5b** and paraformaldehyde **7** was selected; the reaction gives 2-phenylethanol **3a** via benzylzinc chloride **6 (Scheme 2).** In a reaction involving organozinc reagent, the quality of zinc affects the reaction to a great extent. Zn dust was used for this reaction and was activated as per the reported method.[14] The reaction was carried out in different solvents using different quantities of zinc, paraformaldehyde is used in excess **(Table 1)**.

Benzyl bromide **5a** (1.0 equiv) and activated Zn dust (1.0 equiv) were heated at 70 °C for 2 h. Paraformaldehyde **7** (3.0 equiv) was added slowly and the reaction mixture was further heated at the same temperature for 6 h. After the work-up and purification 56% isolated yield of **3a** was obtained (**Table 1, Entry 1**). Increasing the quantity of Zn from 1 equiv to 1.5 equiv gave 65% yield of **3a (Table 1, Entry 2).** While using 2.0 equiv of

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the Zn gave 98% GC conversion and 81% yield of the product **(Table 1, Entry 3).** For further work 2.0 equiv of the Zn was used. Benzyl chloride is cheaper than benzyl bromide and has wide ranging commercial availability. Therefore, the reaction using benzyl chloride **5b** (1.0 equiv) and Zn (2.0 equiv) was tested under optimized conditions. The reaction gave 83% yield of **3a (Table 1, Entry 4).** This result showed that benzyl chloride also worked efficiently in the reaction.

Next, the effect of solvent on the reaction was studied. A representative set of ethereal solvents, 2-methyl THF, 1,4-dioxane, methyl *tert*-butyl ether (MTBE), diethyl ether, and cyclopentylmethyl ether (CPME) was screened for the reaction and the reaction was carried out at 70^{o}C (**Entries 4-13**). 2-Methyl THF and cyclopentylmethyl ether (CPME) are considered as green solvents and can be used as suitable replacements of THF, when a high temperature is required. The yield of **3a** was in the range of 55-70%. 2-Methyl THF and CPME did not make any significant impact on the product purity, and gave 70% and 62% isolated yields of the product, while 1,4-dioxane gave less yield of the product **(Table 1, Entries 5-7).**

The effect of temperature on the reaction was studied by performing the reaction first at ambient temperature in diethyl ether. In this reaction only traces of the product were formed **(Table 1, Entry 8).** For the other solvents, the solution was first heated at 70 °C for 2 h and then cooled to ambient-temperature and stirred for 6 h at 70°C, after the addition of paraformaldehyde **(Table 1, Entries 9-12).** The use of THF was found to be advantageous and 76% yield of the product was obtained. 2-Methyl THF was almost

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equally effective, while 1,4-dioxane and MTBE were poor solvents to carry out the desired transformation. The reaction at 0°C showed no conversion of **5**. Paraformaldehyde depolymerises at 60°C. Thus, the optimized conditions were - benzyl chloride (1.0 equiv), Zn dust (2.0 equiv), paraformaldehyde (3.0 equiv), solvent (30 mL), and temperature (70°C), time (6 h).

To establish the scope of the reaction, selected versatile (het)arylmethyl chlorides were reacted with paraformaldehyde in the presence of zinc, under the optimal conditions. The substrates were benzyl chlorides bearing electron-donating and electron-withdrawing groups, and were also heterylmethyl chlorides **(Scheme 3).** All the substrates underwent the reaction smoothly. *Ortho*-, *meta*- and *para*- substituted benzyl chlorides gave good to excellent yields of the products. Tolyl benzyl chlorides (*ortho*- & *meta*-) gave **3b** and **3c** in 74% and 83% yields, respectively. 4-Bromo and 4-methoxy benzyl chlorides gave **3d** (54%**)** and **3e** (81%**)**. Fluoro- and trifluoromethyl groups containing compounds are important in pharmaceuticals for drug designing. Using the optimized conditions, *p*-fluoro and *o*-(trifluromethyl)benzyl chlorides were also found to be susceptible to give **3f** and **3g** in 75% and 71% yield, respectively.

The issue of possible intramolecular competition between more than one chlorine present in the same molecule was addressed by choosing 2,4-dichlorobenzyl chloride, which gave 65% isolated yield of the products **3h,** without any aromatic addition reaction. Thus, this addition is highly selective for benzyl halides and not for the aryl halides. Heterocyclic arylmethyl chlorides 2- and 4-pyridyl methyl chlorides gave59% and 71%

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isolated yields of the products **3i** and **3j,** respectively. The low yield from these compounds may be ascribed to Zn complexing also with adjacent heteroatom nitrogen. The same possibility exists for the 2-chloromethyl derivatives of thiophene and furan. Thus, thiophene and furan derivatives gave 3**k** and **3l** in low yield of 45% and 49%, respectively. Overall, it can be seen that a wide ranging functional group tolerance was observed for the reaction of benzyl zinc chloride and paraformaldehyde in the presence of zinc.

The success of this methodology prompted us to establish a large scale (100 g) practical method for the preparation of the key perfumery ingredient phenethyl alcohol **3a.** The reaction of benzyl chloride with paraformaldehyde was carried out under the optimized conditions and 71% isolated yield of phenethyl alcohol was obtained **(Scheme 4).**

In conclusion, the failure of benzyl magnesium halide to react with formaldehyde to give the expected 2-phenylethyl alcohol gave impetus to the present work. Herein we hypothesized that less electropositive zinc may effectively replace magnesium; i.e. benzylzinc organometallic compound may react with formaldehyde to form the expected 2-phenylethyl alcohol. Hence, we reacted benzyl bromide and benzyl chloride with zinc followed by the reaction of formaldehyde. A range of substituted benzyl chlorides as well heteryl methyl chlorides reacted smoothly and gave the expected products. This protocol is more straightforward than the reported methods and gave high-yield of the phenethyl alcohols. Moreover, this method is proven to be atom- and step-economical, high yielding which can be easily scaled up.

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[CAUTION: On heating, paraformaldehyde generates formaldehyde gas, safety precautions need to be taken by using suitable personal protective equipments (PPEs) to avoid the toxic effects of formaldehyde. This is particularly important while carrying out a large scale operation. The reaction should be performed in a well-ventilated fume hood.]

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EXPERIMENTAL DETAILS

Phenethyl Alcohol (3a)

A two neck Schlenk flask equipped with a magnetic stirring bar and septum was heated with heat gun (~400 °C) for 10 min under high vacuum. After cooling to room temperature, the flask was flushed with argon (3 times). Zn-dust (654 mg, 2.0 equiv, 10.0 mmol) was added followed by THF (20 mL). 1,2-Dibromoethane (5 mol%) was added and the reaction mixture was heated until ebullition occurs. After cooling to rt, chlorotrimethylsilane (1 mol%) was added and the mixture was heated again till ebullition occurs. The flask was again cooled to rt and benzyl chloride (633 mg, 5.0 mmol, 1 equiv) was added as a solution in THF (10 mL) and it was heated at 70 °C for 2 h and cooled to rt. Paraformaldehyde (450 mg, 3.0 equiv. 15.0 mmol) was slowly added at rt and the flask was again heated at 70 °C for 6 h. The solution was cooled to rt and saturated NH_4Cl solution was added. The phases were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with water (20 mL), brine (10 mL) and then dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography using cyclohexane or cyclohexane/ethyl acetate as an eluent to obtain phenethyl alcohol **(3a)** (510 mg, 83%) as a colourless liquid. (b.p. 221-222 °C at 760 torr) (lit. 218-220 °C at 760 torr).[15] The physical data are consistent with the literature values.

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SUPPORTING INFORMATION

Full experimental detail, ^{1}H NMR and mass spectra. This material can be found via the "Supplementary Content" section of this article's webpage.'

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Table 1: The reaction of benzyl chloride/bromide and formaldehyde in the presence of zinc in different solvents.

Entry	$PhCH_2X$ (1 equiv)	Zn metal (equiv)	Solvent	Temp (°C)	Conversion of **5**[a] (%)	Yield of **3**[b] (%)
1	$PhCH_2Br$	1	THF	70	62	56
2	$PhCH_2Br$	1.5	THF	70	70	65
3	$PhCH_2Br$	2.0	THF	70	96	81
4	$PhCH_2Cl$	2.0	THF	70	98	83
5	$PhCH_2Cl$	2.0	2-MeTHF	70	75	70
6	$PhCH_2Cl$	2.0	1,4-Dioxane	70	59	55
7	$PhCH_2Cl$	2.0	CPME	70	65	62
8	$PhCH_2Cl$	2.0	Diethyl ether	Rt	-	traces
9	$PhCH_2Cl$	2.0	MTBE	70	52	47
10	$PhCH_2Cl$	2.0	THF	70	79	76
11	$PhCH_2Cl$	2.0	2-MeTHF	70	75	72
12	$PhCH_2Cl$	2.0	1,4-Dioxane	70	52	44
13	$PhCH_2Cl$	2.0	THF	0	ND	ND

Reaction conditions: $PhCH_2X$ (X = Br of Cl) (5.0 mmol), paraformaldehyde (15.0 mmol), solvent (30 mL). All reactions were run for six hours after formation of benzyl zinc reagent. ND: not detected.

[a]GC conversion, [b]Isolated yield.

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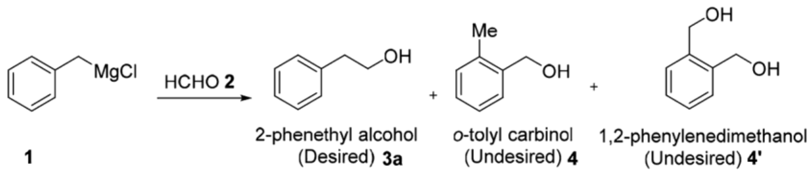
Scheme 1. The addition of benzyl Grignard reagent to formaldehyde.



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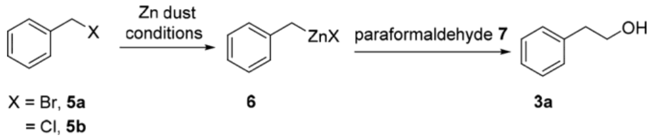
Scheme 2. The reaction of benzyl chloride/bromide with paraformaldehyde (PFA) mediated by zinc.



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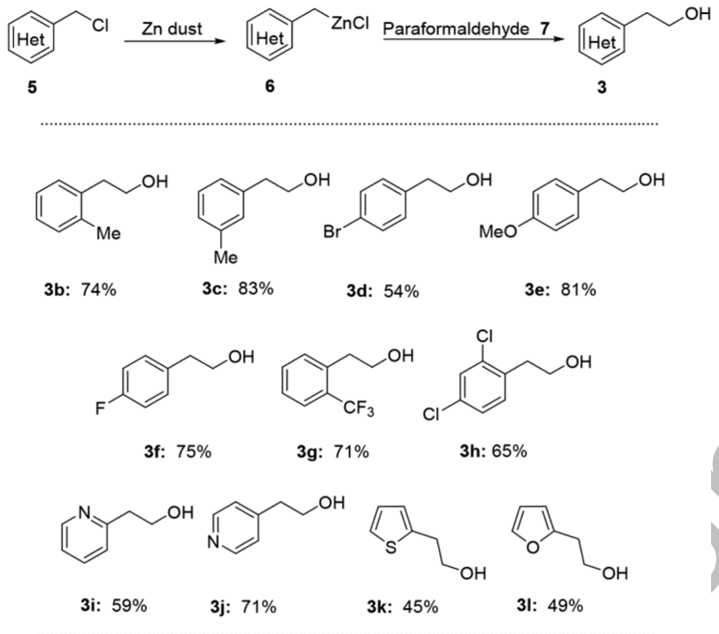
Scheme 3. Products obtained in the reaction of different arylmethyl chlorides with formaldehyde in the presence of zinc. ***Reaction condition:*** Arylmethyl chloride (5.0 mmol), Zn dust (10 mmol), THF (30 mL), paraformaldehyde (15 mmol), Time 6 h



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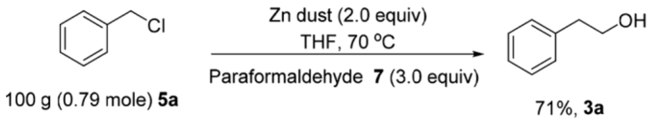
Scheme 4. Large scale preparation of phenethyl alcohol.



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