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Alternative method for alkylation of arylpolyhalomethanes with trialkylborane in the presence of magnesium

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ABSTRACT

Reduction of benzal halide derivatives and α,α,α,-trichloromethylbenzene by magnesium powder in DMAc affords α-halocarbanions which then react with triethylborane to give alkylated products. After oxidation with H_2O_2–NaOH, secondary or tertiary alcohols are obtained. Under the same conditions, 1,1-diphenylpropane is obtained from α,α-dichlorodiphenylmethane.

1. Introduction

We have recently described the electrochemical reaction of decyl dihalo- and trihalo-acetate with trialkylborane leading to α-alkylated esters [1]. The reaction was conducted in an undivided cell fitted with a sacrificial zinc anode, at 20–40 °C in DMAc. We next found that the electrochemical reaction can be applied to the alkylation of benzal chloride (Scheme 1) and after the oxidative work up with hydrogen peroxide, 1-phenyl-propan-1-ol was obtained. Because the potential reduction [2] of benzal chloride (−2.2 V/ECS) is more negative than that of dihalo- and trihalo-acetates (−1.6 V/ECS), zinc rod was replaced by magnesium to allow the formation of the active nucleophilic species. Thus, the reaction presumably occurs by the electrochemical reduction of benzal chloride to give α-chlorobenzylmagnesium chloride. The α-halo anion then reacts with trialkylborane to form an organoborate which evolves by 1,2-alkyl transfer to give a new alkylborane as in the mechanism proposed by Brown [3]. The alkyl arylcarbinol is obtained after oxidation.

Such α-halo anions are usually generated from polyhalo compounds by metal–halogen exchange with *t*-buthyllithium [4], by hydrogen–metal exchange with strong bases [5] or electrochemically [6].

In this laboratory, Oudeyer et al. [7] have shown that, alternatively to the electrochemical route, the cyclopropane formation (Scheme 2) can be performed under Barbier type protocol from polyhalomethyl compounds ($PhCHCl_2$, $PhCCl_3$, $PhCHBr_2$, CCl_3CO_2R) and activated olefins in the presence of magnesium powder suspended in DMF. Under these conditions, the generated α-haloorganomagnesium intermediate reacts faster with the activated olefin than it decomposes by α-elimination of MgX_2 into the corresponding carbene [8].

In continuation of our study on the behaviour of nucleophilic species generated in unusual solvent from polyhalomethylcompounds and magnesium powder in the presence of electrophiles, we wish to report herein the results obtained with triethylborane as the electrophile (Scheme 3).

2. Results and discussion

Initially, the reaction was performed at room temperature by adding dropwise one-third of the mixture of α-benzal chloride (3.5 mmol; 0.45 mL) and triethylborane (1 N in THF, 1.14 equiv.) to a suspension of magnesium powder in the co-solvent (THF, DMAc, DMF, AN) (volume in mL as given in Table 1). The temperature was allowed to rise to 30–35 °C. Then the remaining solution was slowly added by keeping the reaction temperature below 35 °C. After the end of the addition, the reaction mixture was stirred for 30 min at room temperature. The consumption of benzal chloride was checked by GC. The excess of magnesium was filtered off and the oxidation reaction by hydrogen peroxide/sodium hydroxide was performed. The results are reported in Table 1. Two key parameters are indicated: the nature of the co-solvent and the concentration of benzal chloride.

THF, which is the usual solvent for the preparation of organomagnesium as well as for the metal–halogen exchange involving

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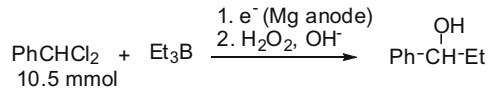
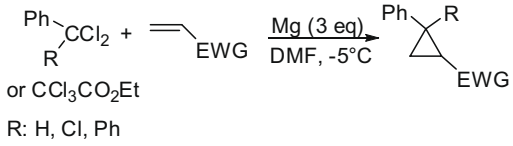
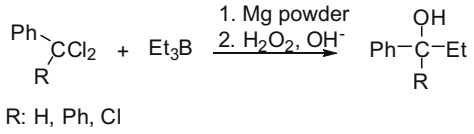


Scheme 1.

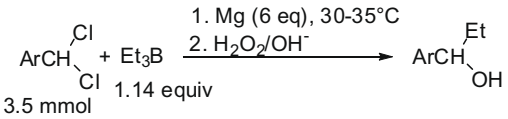


Scheme 2.



Scheme 3.

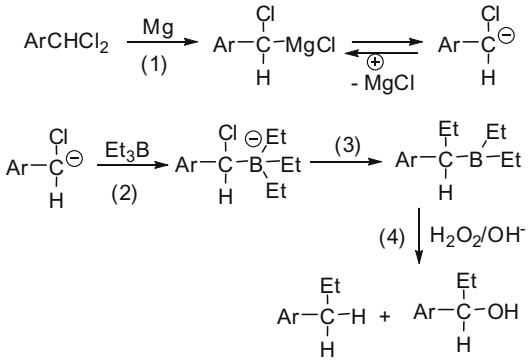
Table 1
Preliminary results for the reaction of benzal chloride with triethylborane in the presence of magnesium powder.



Entry[a]	Co-solvent (V, mL)	Isolated yield% in alcohol
1	THF (5.5 mL)	8
2	DMF (2 mL)	3.5
3	DMAc (5.5 mL)	20
4	DMAc (2 mL)	31 (59%)[c]
5	DMAc (1 mL)	29
6	DMAc (20 mL)[b]	0
7	CH_3CN (1 mL)	0

[a] *Conditions*: slow addition of benzal chloride, triethylborane (1 N in THF) to magnesium powder suspended in DMAc (V, mL).
[b] Reaction performed in the same reaction conditions as electrochemical alkylation reaction of decyl dihalo- and trihalo-acetate.
[c] Determined by GC.

benzal halides [9] or haloform [10], is not suited under this protocol (Table 1, entry 1) since the reaction is not ended after 30 min. This is consistent with the results of Kabalka and co-workers [9], who reported that the reaction of α-haloorganomagnesium chloride, generated from α,α-dichloroarylmethane, with trialkylborane (1 N in THF) in THF is slowly achieved in 10–36 h at room temperature. We also noticed that the reaction cannot be conducted in DMF (Table 1, entry 2) which is a very common solvent allowing formation of organometallic species in electrochemical processes and the solvent for the cyclopropanation reaction in the chemical version [7]. The reaction is best performed in DMAc (Table 1, entries 4 and 5) used as the co-solvent. This evidences that the solvent has a strong influence on the nature and the reactivity of the nucleophilic intermediate species. Also to notice, the course of the reaction is very sensitive to the instant concentration of benzal chloride which must be rather high in the reaction mixture (Table 1, entries 3–6). Also, the reaction conditions for the electrochemical α-alkylation of decyl dichloro- and trichloro-acetate is not adapted (Table 1, entries 6) for benzal halides. Finally,



Scheme 4.

the formation of 1-phenyl-propan-1-ol is not observed in acetonitrile (Table 1, entry 7) and this may be due to the acidity of this solvent.

Regarding the reducing metal, the same rate in the consumption of benzal chloride is observed by replacing magnesium by zinc powder. However traces of 1-phenyl-propan-1-ol (5% in GC) are detected along with toluene, dibenzyle, *E* and *Z*-stilbene as the main products.

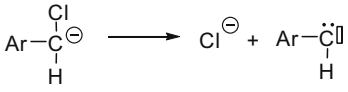
The mechanism of the reaction involves in the first step (Scheme 4, (1)) the reduction of benzal chloride by Mg leading to the α-haloanion.

Then this carbanion reacts with triethylborane to give a new alkylborane (Scheme 4, (2) and (3)) which after oxidation (Scheme 4, (4)) affords 1-phenyl-propan-1-ol. Byproducts resulting from dimerization of the intermediate anion such as (*Z*) and (*E*) stilbene (6%, GC), dibenzyle (2%, GC) and from protonolysis of the newly formed trialkylborane such as 1-phenylpropane (10%, GC) were detected.

Moreover α-haloanions are precursors of carbenes (Scheme 5).

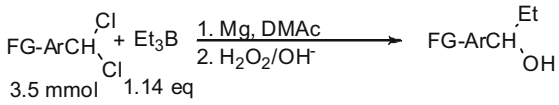
In order to limit the formation of byproducts, the reaction conditions have been improved by several changes in the protocol. In order to favour the reaction of α-halocarbanion with triethylborane, benzal chloride (3.5 mmol) in DMAc (1 mL) was added dropwise to the mixture of 1.14 equiv. triethylborane (1 N in THF, 4 mL) and magnesium in DMAc (1 mL). The reaction temperature was maintained at 32 °C for all over the addition. After the oxidation step, 1-phenyl-propan-1-ol was obtained with 41% isolated yield (Table 2, entry 1). Other results obtained from benzal halide derivatives are also reported in Table 2.

The reaction has been extended to benzal chloride derivatives bearing various substituents (F, CH_3, and OCH_3) on the aryl moiety. The isolated yield is higher when F is at para position (Table 2, entry 4) rather than at meta position (Table 2, entry 6). The best results were found by performing the reaction with 6 equiv. of magnesium (Table 2, entries 4 and 5) and the reaction is also efficient with methyl and methoxy groups as substituents (Table 2, entries 7 and 8). Under these new standard conditions, 1-phenyl-propan-1-ol was not detected by using benzal bromide as starting reagent. We can assume that the α-bromo anion is less stable than the α-chloro anion. However, we found that the slow addition of benzal bromide along with a careful control of the reaction temperature and use of lower amount of magnesium (Table 2, entries



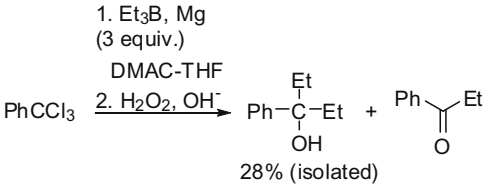
Scheme 5.

Table 2
Preparation of various alkylarylcarbinols



Entry[a]	FG	Temperature (°C)	Metal powder	Isolated yield%
1	H	30	Mg (6 equiv.)	41
2	H[b]	13	Mg (3 equiv.)	19[c]
3	H[b]	27	Mg (3 equiv.)	58
4	pF	32	Mg (6 equiv.)	55
5	pF	34	Mg (3 equiv.)	43
6	mF	33	Mg (6 equiv.)	36
7	pCH_3	33	Mg (6 equiv.)	42
8	$mOCH_3$	32	Mg (6 equiv.)	56

[a] FG-$ArCHCl_2$: 3.5 mmol.
[b] Benzal bromide.
[c] In the previous reaction conditions, the yield was 0%.



Scheme 6.

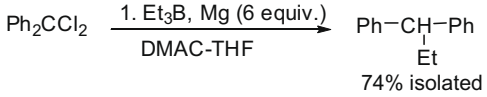
2 and 3) allows to get 1-phenyl-propan-1-ol with 58% isolated yield.

With the successful results obtained in the benzal halides series, we attempted a similar transformation by testing commercially available α,α,α-trichlorotoluene and α,α-dichlorodiphenylmethane.

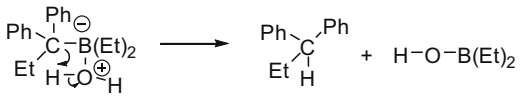
In the reaction of α,α,α-trichlorotoluene with trialkylborane followed by the oxidation step (Scheme 6), toluene (15%, GC), 1-phenyl-propan-1-ol (3%, GC), 3-phenylpentan-3-ol (51%, GC) and 1-phenylpropan-1-one (12%, GC) were identified by mass spectrometry. The main product 3-phenylpentan-3-ol was isolated in 28% yield.

These products are coming from the same newly formed trialkylborane intermediate (Scheme 7). During the H_2O_2/OH^- treatment, either trialkylborane intermediate is oxidized to give *gem* chlorhydrine (way A) which transforms into ketone or a second alkyl transfer reaction mediated by H_2O_2/OH^- occurs (way B) before the completion of the oxidation step.

In the reaction of dichlorodiphenylmethane with triethylborane (Scheme 8), the standard hydrogen peroxide procedure does not lead to the expected alcohol. Indeed, it has previously been noted that trialkylboranes, able to yield stable carbanions after deboronation, are readily protonolyzed by base (NaOH in diglyme) [11] at



Scheme 8.



Scheme 9.

room temperature or by NaOH/tetrabutylammonium hydroxide [12]. Because of the particular position of boron atom in the newly formed trialkylborane, the dealkylation occurred easily in the presence of HCl 1 N affording 1,1-diphenylpropane as the main product in 74% yield. This product was identified by comparison with an authentic commercial sample.

The proposed mechanism for the formation of 1,1-diphenylpropane is depicted in Scheme 9.

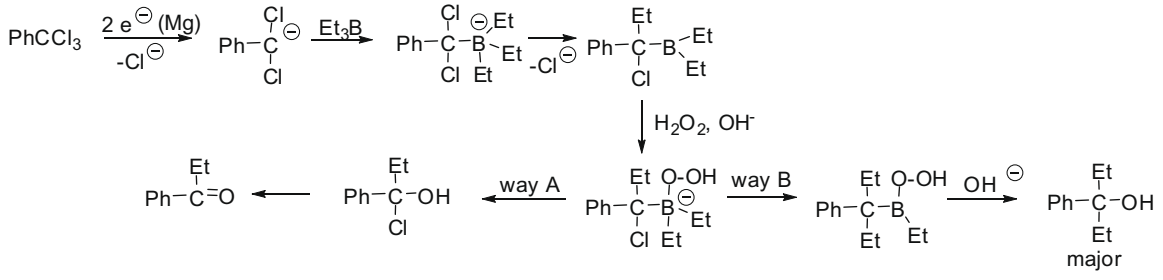
3. Conclusions

We have shown that benzal chloride and its derivatives can be reduced in the presence of trialkylborane by magnesium powder in DMAc to give after oxidation step secondary alcohols. Compared to Kabalka and co-workers reaction conditions [9], the reaction time is shortened thanks to the addition of DMAc as co-solvent. The scope of this improved method covers the alkylation of benzal bromide, α,α,α,-trichlorotoluene and α,α-dichlorodiphenylmethane. It was also reported that α-bromo(chloro)benzyl anions can be prepared by *in situ* deprotonation of benzal halide derivatives with dicyclohexylamide [5b]. Compared to our method carried out at room temperature in one step, this faster method required the use of strong base and the control of the temperature (−78 °C).

Magnesium powder cannot be replaced by weaker reducing reagent such as zinc powder.

4. Experimental

Unless indicated, all solvents and reagents were purchased from commercial sources and used as received. N,N-dimethylacetamide (DMAc) was stored under argon. 3-Fluoro-, 4-fluoro-, 4-methyl- and 3-methoxy-benzal chlorides were prepared according to the known procedures [13]. ^1H, ^{13}C, ^{19}F spectra were recorded on a Brucker Avance-II 400 MHz. Chemical shifts are quoted in parts per million (ppm). Mass spectra were obtained with a GCQ Thermoquest Spectrometer coupled to a chromatograph fitted with a 25-m CPSIL5 CB capillary column. The infrared spectra were recorded on a Perkin–Elmer FT-IR Spectrometer 1720X. Elemental



Scheme 7.

analyses and high resolution mass spectral analyses were made by the Service Central d'Analyse (CNRS, Lyon).

Typical procedure: the synthesis of 1-(3-fluorophenyl)propan-1-ol is representative. To a suspension of magnesium powder (21 mmol) in DMAc (1 mL) is added triethylborane (1 N in THF, 4 mmol). The temperature is allowed to rise to 32 °C in few minutes. The solution of 3-fluorobenzal chloride (0.63 g; 3.5 mmol) in DMAc (1 mL) is slowly added (7 drops per minutes). The reaction temperature rises slowly for a while; the reaction mixture turns to yellow. Then the reaction temperature is controlled and maintained below 35 °C. After 30 min, the remaining magnesium is filtered off. NaOH (3 N, 2 mL) and H_2O_2 (3 mL) are carefully added at 0 °C to the filtrate, while keeping the temperature below 50 °C. After stirring for 1 h at 50 °C, the mixture is cooled down; saturated $NaHCO_3$ aqueous solution (30 mL) and diethylether are added. The aqueous layer is extracted twice with diethylether (30 mL). The collected organic layers are washed with distilled water and NaCl saturated solution. The product is dried over $MgSO_4$ and after the evaporation of the solvent, is purified by column chromatography.

1-(3-Fluorophenyl)propan-1-ol: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.16 (m, 1H), 6.93 (m, 3H), 4.38 (t, 1H, J = 6.52 Hz), 3.00 (sbroad, 1H, OH), 1.58 (m, 2H), 0.75 (t, 3H, J = 7.42 Hz). ^{19}F NMR (380 MHz, $CDCl_3$) δ ppm: −113.13. ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.10 (d, $^1J_{C-F}$ = 233.9 Hz), 146.35 (d, $^3J_{C-F}$ = 8.10 Hz), 128.75 (d, $^3J_{C-F}$ = 8.10 Hz), 120.6 (d, $^4J_{C-F}$ = 2.80 Hz), 113.10 (d, $^2J_{C-F}$ = 21.40 Hz), 111.8 (d, $^2J_{C-F}$ = 21.40 Hz), 74.15 (d, $^4J_{C-F}$ = 1.60 Hz), 30.8, 8.9. MS: m/z (%) 154, 138, 125, 97 (100%), 77.

1-(4-Fluorophenyl)propan-1-ol: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (m, 2H), 7.03 (m, 2H), 4.56 (t, 1H, J = 6.57 Hz), 2.25 (sbroad, 1H, OH), 1.85–1.66 (m, 2H), 0.88 (t, 3H, J = 7,42 Hz). ^{19}F NMR (380 MHz, $CDCl_3$) δ ppm: −115.38. ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.1 (d, $^1J_{C-F}$ = 244.49 Hz), 140.29 (d, $^4J_{C-F}$ = 3.02 Hz), 127.59 (d, $^3J_{C-F}$ = 8.05 Hz), 115.1 (d, $^2J_{C-F}$ = 21.13 Hz), 75.3, 31.9, 10.0. MS: m/z (%) 154, 137, 125 (100%), 109, 97, 77. IR (NaCl): ν 3353, 2966, 2933, 2878, 1604, 1500, 1460, 1220, 832 cm^{-1}. Anal. Calc. for $C_9H_{11}FO$: C, 70.11; H, 7.19; F, 12.32. Found: C, 70.11; H, 7.41; F, 12.58%.

1-(4-Methylphenyl)propan-1-ol: Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (d, 2H, J = 7.82 Hz), 7.07 (d, 2H, J = 7.82 Hz), 4.46 (t, 1H, J = 6.60 Hz), 2.26 (s, 3H), 1.86 (sbroad, 1H), 1.68 (m, 2H), 0.82 (t, 3H, J = 7.40 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 140.6, 136.1, 128.0, 124.9, 74.8, 30.8, 20.1, 9.2. MS: m/z (%) 150, 133, 121 (100%), 105, 93, 91, 77. IR (NaCl): ν 3363, 2962, 2926, 2874, 1513, 1455, 1097, 1039, 1011, 813 cm^{-1}. HRMS (M+Na) m/z: Calcd for $C_{10}H_{14}ONa$ calcd 173.0942; found: 173.0945.

1-(3-Methoxyphenyl)propan-1-ol: Oil; ^{1}H MR (400 MHz, $CDCl_3$) δ ppm: 7.19 (t, 1H, J = 8.09 Hz), 6.84 (m, 2H), 6.74 (m, 1H), 4.50 (t, 1H, J = 6.58 Hz), 3.74 (s, 3H), 1.71 (m, 2H), 1.20 (sbroad, 1H), 0.85 (t, 3H, J = 7.42 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.7, 146.4, 129.4, 118.3, 112.9, 111.4, 76.0, 55.2, 31.8, 10.2. MS: m/z (%) 166, 137, 109 (100%), 94, 77, 51. HRMS (M+Na) m/z: Calcd for $C_{10}H_{14}O_2Na$ calcd 189.0891; found: 189.0893.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2009.09.022.

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