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A simple and efficient copper oxide-catalyzed Barbier–Grignard reaction of unactivated aryl or alkyl bromides with ester

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ABSTRACT

of R²O⁻group is discussed.

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Barbier-Grignard-type reaction is one of the most important reactions for carbon-carbon bond formations in organic synthesis.¹ A numerous methods have been reported such as allylation,² benzylation,³ arylation,⁴ propargylation,⁵ and alkynylation⁶ reactions of carbonyl compounds using different metals, but these methods are mainly limited to the use of activated halides, expensive metals, or less convenient materials than halides.⁷ Recently, an effective way of Barbier-Grignard-type reaction by unactivated alkyl iodides was reported, but other less activated bromides and chlorides are not suitable to this reaction.⁸ Therefore, it is still the most difficult challenge to develop a more efficient and practical method for Barbier–Grignard-type reaction of carbonyl compounds with unactivated aryl or alkyl halides. Compared with many studies focused on Barbier-type reaction of aldehydes and ketones,⁹ fewer reports of Barbier-type alkylation of esters with activated halides such as benzyl bromide,¹⁰ iodomethane,¹¹ and *n*-butyl iodide¹² in THF could be found. Herein, we are gratified to report an efficient and highly chemoselective Barbier-Grignard-type reaction of esters with unactivated aryl or alkyl bromides in THF as shown in Scheme 1. To the best of our knowledge, this Barbier-Grignardtype reaction of esters has not been reported.

In the initial study, we chose bromobenzene and ethyl acetate as model starting materials to examine the reaction. As shown in Table 1, FeCl₃ and NiCl₂ were ineffective in giving the desired product (Table 1, entries 1, 2), whereas ZnCl₂ afforded the product 1, 1diphenyl ethanol in low yield of 9% (Table 1, entry 3). A good yield

 R^{1} -Br + R^{2} O^{-} R^{3} Mg, Catalyst THF, 65 °C

 R^1 = aryl, alkyl; R^2 = alkyl; R^3 = alkyl

An efficient one-pot route to synthesize tertiary alcohol compounds using Barbier-Grignard reaction of

unactivated alkyl or aryl bromides with ester in THF at 65 °C catalyzed by CuO has been developed

and systematically investigated. A wide range of substituted tertiary alcohol compounds were obtained

in good to high yields. The reaction is highly chemoselective. The mechanism involving the leaving group

Scheme 1. Magnesium and catalyst mediated Barbier–Grignard reaction of ester with aryl or alkyl bromides.

of 58% was obtained using CuI as catalyst (Table 1, entry 4). The yield was further increased to 61% using CuBr₂ as catalyst (Table 1, entry 5). Encouraged by these exciting results, other copper catalysts also were employed in the reaction. When catalyzed by CuO, the reaction could give product in high yield of 93% (Table 1, entry 6). The other copper catalysts Cu₂O, CuS or CuSe resulted in yields of 85%, 78% or 21% (Table 1, entries 7–9), respectively. And then, we explored the effect of various ligands on the reaction. The results reveal that both phosphorous (e.g., PPh₃, and DPPE) and nitrogen (e.g., TMEDA, TEA, BPy, PMDETA, and BDMAEE) containing ligands are unfavorable for the reaction (Table 1, entries 10–16). Lower reaction temperature than 65 °C resulted in lower yields (Table 1, entries 17, 18). The product could be obtained in yield of 67% using 5% of CuO, but could not be found without catalyst (Table 1, entry 19, 20).

Then, we turned our attention to the effect of PhBr and magnesium amount on the reaction. 2 equiv of PhBr and magnesium to ethyl acetate afforded the product in yield of 65% (Table 2, entry 1). Excess 2.5 or 3.0 equiv of PhBr and magnesium could improve the yield to 81% or 93%, respectively (Table 2, entry 2, 3). 3.5 equiv of PhBr and magnesium could not increase the yield further





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 $R^1 \rightarrow R^1$





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Table 1

Effects of catalysts, ligands and temperature on the reaction^a



| Entry | Catalyst | Ligand | T (°C) | Yield ^b (%) |
|-------|-------------------|---------|--------|------------------------|
| 1 | FeCl ₃ | None | 65 | Trace |
| 2 | NiCl ₂ | None | 65 | Trace |
| 3 | ZnCl ₂ | None | 65 | 9 |
| 4 | Cul | None | 65 | 58 |
| 5 | CuBr ₂ | None | 65 | 61 |
| 6 | CuO | None | 65 | 93 |
| 7 | Cu_2O | None | 65 | 85 |
| 8 | CuS | None | 65 | 78 |
| 9 | CuSe | None | 65 | 21 |
| 10 | CuO | TMEDA | 65 | 86 |
| 11 | CuO | TEA | 65 | 33 |
| 12 | CuO | BPY | 65 | Trace |
| 13 | CuO | PMDETA | 65 | 85 |
| 14 | CuO | BDMAEE | 65 | 47 |
| 15 | CuO | PPh_3 | 65 | 45 |
| 16 | CuO | DPPE | 65 | 51 |
| 17 | CuO | None | 40 | 47 |
| 18 | CuO | None | 50 | 68 |
| 19 | CuO(5%) | None | 65 | 67 |
| 20 | none | None | 65 | 0 |

 $^a\,$ Reaction conditions: PhBr (7.5 mmol), Mg (7.5 mmol), AcOEt (2.5 mmol), catalyst (15 mol % of AcOEt) and ligand (15 mol %), 15 mL of THF for 4 h.

^b Isolated yield.

(Table 2, entry 4). Better yields could be obtained in dry THF than THF under the same amount of PhBr and magnesium (Table 2, entries 5–7). But when 0.1 mL of water was added in THF, the reaction could be stopped (Table 2, entry 8). Because dry THF needs anhydrous treatment of THF such as sodium, the optimized conditions were chosen as 15% mol of CuO, 3 equiv of PhBr and magnesium, 1 equiv of ethyl acetate, reacting in 15 mL THF at 65 °C for 4 h.

Other aryl halides and esters were examined to explore the scope and limitations of this methodology under the optimized conditions. Different tertiary alcohol compounds were obtained in good to high yields (Table 3).

Table 2

Effect of PhBr and Mg amount on the reaction^a



| Entry | X (equiv) | Solvent (15 mL) | Yield ^b (%) |
|-------|-----------|--|------------------------|
| 1 | 2.0 | THF | 65 |
| 2 | 2.5 | THF | 81 |
| 3 | 3.0 | THF | 93 |
| 4 | 3.5 | THF | 93 |
| 5 | 2.0 | Dry THF | 80 |
| 6 | 2.5 | Dry THF | 92 |
| 7 | 3.0 | Dry THF | 93 |
| 8 | 3.0 | THF/0.1 mL H ₂ O ^c | 0 |

 a Reaction conditions: PhBr (X mmol), Mg (X mmol), AcOEt (2.5 mmol), CuO (15 mol %), 15 mL of THF at 65 $^\circ C$ for 4 h.

^b Isolated yield.

^c Molar ratio of 0.1 mL H₂O to PhBr and Mg: 1:1.3:1.3.

Table 3

Screening of the optimum reacting conditions for synthesis of tertiary alcohol $\mathsf{compounds}^{\mathsf{a}}$

$$R^{1}X + R^{2}COOR^{3} \xrightarrow{CuO, Mg} R^{1} + R^{1}$$

X=I. Cl. Br

| Entry | R ¹ X | R ² COOR ³ | Products | Yield ^b (%) |
|-------|---------------------------------|--|-----------------|------------------------|
| 1 | $R^1 = Ph$ | $R^2 = CH_3$ | 3a | 95 |
| | X = I | $R^3 = C_2 H_5$ | | |
| 2 | $R^1 = Ph$ | $R^2 = CH_3$ | 3a | 93 |
| | X = Br | $R^{3} = C_{2}H_{5}$ | | |
| 3 | $R^1 = Ph$ | $R^2 = CH_3$ | 3a | Trace |
| | X = CI | $R^{3} = C_{2}H_{5}$ | | |
| 4 | $R^1 = 4 - MeC_6H_4$ | $R^2 = CH_3$ | 3b | 90 |
| | $X = B\Gamma$ | $K^{2} = C_{2}H_{5}$ | | |
| 5 | $R^{1}=4-MeOC_{6}H_{4}$ | $R^2 = CH_3$ | 3c | 86 |
| _ | X = BI | $K = C_2 H_5$ | | |
| 6 | $R^{T} = 2 - MeC_6H_4$ | $R^2 = CH_3$ $R^3 = C_1 H$ | 3d | 81 |
| _ | $\Lambda = DI$ | $K = C_2 \Pi_5$ | | |
| 7 | $R^{T} = 2 - MeOC_{6}H_{4}$ | $R^2 = CH_3$ $R^3 = C_1 U$ | 3e | 75 |
| 0 | A = DI | $K^{2} = C_{2}\Pi_{5}$ | | 67 |
| 8 | $R^{1}=2,4$ -dimethylbenzyl | $R^2 = CH_3$ $R^3 = C_1 U$ | 31 | 67 |
| ~ | $\Lambda = DI$ | $R = C_2 \Pi_5$ | | |
| 9 | $K^{*} = 3 - FC_{6}H_{4}$ | $R^2 = CH_3$ $P^3 = C_2 H_2$ | 3g° | 83 |
| 10 | $\Lambda = DI$ | $K = C_2 \Pi_5$ | | 0.5 |
| 10 | $K' = 4 - CIC_6H_4$ | $R^2 = CH_3$ $P^3 = C \Box$ | 3N | 85 |
| | | $R = C_2 H_5$ | | |
| 11 | $R^{*} = 2$ -thienyl | $R^2 = CH_3$ $P^3 = C \Box$ | 31 | 74 |
| 10 | $\Lambda = BI$ | $R = C_2 H_5$ | 21 | 60 |
| 12 | $R^{2} = 1$ -naphtnyl X = Pr | $R^{-} = CH_3$ $P^3 = C_2 H_2$ | 3] | 68 |
| 10 | | $R = C_2 H_5$ | 21- | 00 |
| 13 | $K^{T} = P \Pi$ Y = Br | $K^- = CH_3$ $R^3 = nCH$ | 3K | 89 |
| 14 | $\Lambda = DI$ | $\mathbf{R}^2 = n - \mathbf{C}_4 \mathbf{\Pi}_9$ | 21 | 07 |
| 14 | $R^{2} = PII$ V = Pr | $R^{-} = R - C_{3}H_{7}$ | 31 | 87 |
| 15 | A = DI $P^1 = Db$ | $K = 11 - C_4 \Pi_9$ $R^2 = i C_1 I_1$ | 2 | 05 |
| 15 | K = PII V = Pr | $R = l - C_3 \Pi_7$ $R^3 = C \Pi$ | 2111 | 65 |
| 16 | A = DI $P^1 = Db$ | $R^2 = c_2 H_5$ | 20 | 94 |
| 10 | X = Rr | $R^{3} = C_{2}H_{r}$ | 511 | 04 |
| 17 | $R^1 = Ph$ | $R^2 = PhCH_2$ | 30 | 86 |
| | X = Br | $R^3 = C_2 H_5$ | | |
| 18 | $R^1 = Ph$ | $R^2 = C_2 H_5 O C_2 H_4$ | 3p ^c | 83 |
| | X = Br | $R^3 = C_2H_5$ | -1 | |
| 19 | $R^1 = Ph$ | $R^2 = ClC_2H_4$ | 3α | 81 |
| | X = Br | $R^3 = C_2 H_5$ | | |
| 20 | $R^1 = 4 - MeC_6H_4$ | $R^2 = CH_3$ | 3r | 88 |
| | X = Br | $R^{3} = n - C_{4}H_{9}$ | | |
| 21 | $R^1 = 4 - MeC_6H_4$ | $\mathbf{R}^2 = n - \mathbf{C}_3 \mathbf{H}_7$ | 3s | 83 |
| | X = Br | $R^3 = n - C_4 H_9$ | | |
| 22 | $R^1 = 4 - MeC_6H_4$ | $R^2 = i - C_3 H_7$ | 3t | 81 |
| | X = Br | $R^{3} = C_{2}H_{5}$ | | |
| 23 | $R^1 = 4 - MeC_6H_4$ | $R^2 = c - C_3 H_5$ | 3u | 78 |
| | X = Br | $R^{3} = C_{2}H_{5}$ | | |
| 24 | $R^1 = 4 - MeC_6H_4$ | $R^2 = PhCH_2$ | 3v | 79 |
| | X = Br | $R^{3} = C_{2}H_{5}$ | | |
| 25 | $R^1 = 4 - MeC_6H_4$ | $R^2 = C_2 H_5 O C_2 H_4$ | 3w ^c | 77 |
| | X = Br | $R^{2} = C_{2}H_{5}$ | | |
| 26 | $R^1 = 4 - MeC_6H_4$ | $R^2 = ClC_2H_4$ | 3x | 72 |
| | X = Br | $R^{3} = C_{2}H_{5}$ | | |

 $^a\,$ Reaction conditions: R^1X (7.5 mmol), Mg (7.5 mmol), R^2COOR^3 (2.5 mmol), CuO (15 mol%), 15 mL of THF at 65 $^\circ C$ for 4 h.

^b Isolated yield.

^c New compound.

As shown in Table 3, most aryl halides could give the expected products in yields of over 70%. Iodobenzene or bromobenzene afforded the product in high yields of 95% or 93% respectively, although chlorobenzene was not a suitable substrate for this reaction (Table 3, entries 1–3). Compared with bromobenzene, the electron donating group of Me or MeO resulted in slightly

decreasing yield of 90% or 86% (Table 3, entries 4, 5), respectively. Due to steric hindrance, *o*-bromotoluene and *o*-bromoanisole gave lower yields than their para isomers (Table 3, entries 4–7). The stronger electron donating group of MeO resulted in lower yields than Me (Table 3, entries 4, 6 compared with entries 5, 7 respectively). Compared with 4-methyl or 2-methyl bromobenzene (entry 4 or 6), 2, 4-Dimethyl bromobenzene gives lower yields of 67% (Table 3, entries 9 and 10), respectively, which indicates small difference between these electron withdrawing and donating groups. Other aryl bromides such as 1-bromonaphthalene or 2-bromothiophene afforded the corresponding product in good yields of 68% or 74% (Table 3, entries 11–12), respectively.

To further evaluate the scope of this reaction, a variety of esters were exploited as the reactants. Bromobenzene and bromotoluene could give the corresponding products in good to high yields (Table 3, entries 13–26). The steric hindrance on alcohol or acid parts of esters has resulted in slightly decreasing yield of over 80% (Table 3, entries 13–19). The structure difference of secondary or tertiary α carbon of esters did not cause a deal of difference in yields. Although alkyl chloride could form Grignard reagent also, ethyl 3-chloropropanoate could still obtain better yields of 81% (Table 3, entry 19). The possible reason is the less reactivity of alkyl halide in this reaction, which could be supported by the results in Table 4. Displaying the similar rule with bromobenzene, 4-bromotoluene reacted with different esters to afford corresponding products in slightly lower yields of 88–72% (Table 3, entries 20–26) than those of bromobenzene.

Although Grignard reagent could be reacted with the ester to give tertiary alcohol compounds, the addition of phenyl or 4-methylphenyl Grignard reagent to ethyl acetate could only give the corresponding product in lower yields of 56%¹³ or 26%,¹⁴ respectively. In order to gain high yields, more reactive but expensive ketones have to be employed.¹⁵ Obviously, the method in this paper is more simple, convenient, economic, and effective.

We have also applied butyl bromide in the reaction. However, the yield of the product obtained was only 41% under the same optimized conditions as above (Table 4, entry 1). We tried to improve the yield via increasing the amount of butyl bromide. As shown in Table 4, 6 equiv of butyl bromide and magnesium to ethyl acetate could give good yield of 74% (Table 4, entry 4). Further increasing the amount of butyl bromide and magnesium

Table 4

Effect of butyl bromide and Mg amount on the reaction^a



| Entry | CH ₃ CH ₂ CH ₂ CH ₂ Br, Mg (equiv) | Solvent (15 ml) | Yield ^b (%) |
|-------|---|--------------------|---------------------------|
| 1 | 3.0 | THF | 41 |
| 2 | 4.0 | THF | 54 |
| 3 | 5.0 | THF | 61 |
| 4 | 6.0 | THF | 74 |
| 5 | 7.0 | THF | 75 |
| 6 | 3.0 | Dry THF | 57 |
| 7 | 4.0 | Dry THF | 73 |
| 8 | 5.0 | Dry THF | 75 |

 a Reaction conditions: $n\mbox{-BuBr}$ (X mmol), Mg (X mmol), AcOEt (2.5 mmol), CuO (15 mol %), 15 mL of THF(THF or dry THF) at 65 $^\circ C$ for 4 h.

^b Isolated yield.

to 7 equiv resulted in the close yield of 73% (Table 4, entries 5). Meanwhile, 4 equiv of butyl bromide and magnesium could give the good yield of 74% in dry THF (Table 4, entries 6–8).

Under this conditions, 2-bromobutane, benzyl bromide, bromocyclohexane, and 2-bromomethyl-1, 3-dioxolane could react with ethyl acetate to give the products in medium yields of 51–61% (Table 5, entries 2–5), which indicate the effect of steric hindrance. The steric hindrance of ester also results in medium yields of the reactions of butyl bromide with butyl butyrate and ethyl 2-methyl propanate (Table 5, entries 6–7).

The reaction results in better yields in dry THF than THF and is restrained by adding even 0.1 mL of water in 15 mL of THF (Tables 2 and 4). Thus, we conjecture that the reaction may involve the formation of Grignard reagent. Another possible way is the copper reduced by magnesium participates in the reaction. But when copper was employed directly, the reaction would not occur. To further probe the role of CuO. the reactions of bromobenzene with iso-butanal, cyclohexanone and acetyl chloride were carried out under the optimized conditions for esters. No products of iso-butanal and cyclohexanone could be detected. Acetyl chloride gave product 3a in 85% yield also. When 1 equiv of CuO based on ester was employed, the reaction of phenyl bromide with iso-butanal or cyclohexanone, resulted in less than 10% of GC yield for iso-butanal or no product was detected for cyclohexanone, respectively. When other copper catalysts such as CuI or CuBr₂ were employed, the reaction of phenyl bromide with iso-butanal or cyclohexanone could yield 40-60% of products, which indicates the unique role of CuO. According to the reaction of Grignard reagent, aldehyde, ketone, and acyl chloride are more reactive than ester, and acyl chloride should yield some amount of ketone product. Thus, we could infer that the reaction process catalyzed by CuO is obviously different with the typical nucleophilic addition of Grignard reagent. It may involve the leaving groups RO of ester or Cl of acetyl chloride in the reacting process.

On the basis of the mechanistic studies, a plausible reaction pathway is proposed in Figure 1. Initially, RX reacts with magnesium to form RMgX, then CuO inserts into RMgX to form compound 1,¹⁶ which reacts with RMgX to give organocopper 2.¹⁷ It reacts with ester to yield addition intermediate 3. Negative ion 5 could be formed by intramolecular nucleophilic substitution of the leaving group RO with R, which gives product **6** after gaining

Table 5

Screening of the optimum reacting condition for synthesis of tertiary alcohol compounds $^{\rm a}$

| R ¹ Br + | | $R^2 O R^3$ | CuO, Mg | |
|---------------------|---|-------------|------------|------------------|
| | + | | THF, 65 °C | R' + R' R^2 |

| Entry | R ¹ Br | R ² COOR ³ | Products | Yield ^b (%) |
|-------|--|--|----------|------------------------|
| 1 | $R^1 = n - C_4 H_9$ | $R^2 = CH_3$ | 5a | 74 |
| 2 | $\mathbf{R}^1 = i - \mathbf{C}_4 \mathbf{H}_9$ | $R^{3} = C_{2}H_{5}$ $R^{2} = CH_{3}$ $R^{3} = C_{2}H_{5}$ | 5b | 51 |
| 3 | $R^1 = c - C_6 H_{11}$ | $R^2 = CH_3$ $R^3 = C_1 H_3$ | 5c | 55 |
| 4 | $R^1 = PhCH_2$ | $R^{2} = C_{15}$ $R^{2} = CH_{3}$ $R^{3} = C_{2}H_{5}$ | 5d | 72 |
| 5 | $\mathbf{R}^1 = n - \mathbf{C}_4 \mathbf{H}_9$ | $R^2 = n - C_3 H_7$ | 5e | 58 |
| 6 | $\mathbf{R}^1 = n - \mathbf{C}_4 \mathbf{H}_9$ | $R^{3} = n-C_{4}H_{9}$ $R^{2} = i-C_{3}H_{7}$ $R^{3} = C_{2}H_{5}$ | 5f | 52 |

^a Reaction conditions: $R^{1}Br$ (15 mmol), Mg (15 mmol), $R^{2}COOR^{3}$ (2.5 mmol), CuO (15 mol %). 15 mL of THF at 65 °C for 4 h.

^b Isolated yield.



Figure 1. Plausible pathway for aryl or alkyl halides addition to ester.

proton. The released CuO 4 from intermediate 3 would participate in the reaction again.

In conclusion, we have developed an experimentally simple and efficient Barbier-Grignard reaction of unactivated bromides addition to ester catalyzed by CuO in THF at 65 °C. This methodology is highly chemoselective. Under the optimized conditions, the more reactive aldehyde and ketone in Grignard reagent reaction would not react with bromides. Furthermore, this reaction allows the preparation of a wide range of substituted tertiary alcohol compounds in good yields. Meanwhile, this is the first report to developed Barbier-Grignard-type reaction of ester using unactivated halides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12. 042.

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