



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



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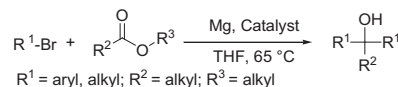
ABSTRACT

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 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 alkylation⁶ 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–Grignard-type 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, 1-diphenyl ethanol in low yield of 9% (Table 1, entry 3). A good yield



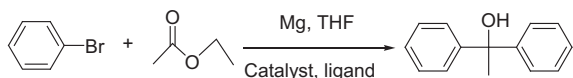
Scheme 1. Magnesium and catalyst mediated Barbier–Grignard reaction of ester with aryl or alkyl bromides.

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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Table 1
Effects of catalysts, ligands and temperature on the reaction^a

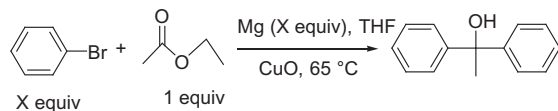
Entry	Catalyst	Ligand	T (°C)	Yield ^b (%)
1	FeCl ₃	None	65	Trace
2	NiCl ₂	None	65	Trace
3	ZnCl ₂	None	65	9
4	CuI	None	65	58
5	CuBr ₂	None	65	61
6	CuO	None	65	93
7	Cu ₂ O	None	65	85
8	CuS	None	65	78
9	CuSe	None	65	21
10	CuO	TMEDA	65	86
11	CuO	TEA	65	33
12	CuO	BPY	65	Trace
13	CuO	PMDETA	65	85
14	CuO	BDMAEE	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

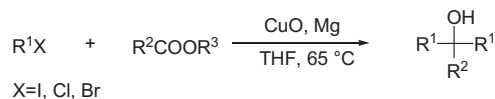
^a Reaction conditions: PhBr (X mmol), Mg (X mmol), AcOEt (2.5 mmol), CuO (15 mol %), 15 mL of THF at 65 °C for 4 h.

^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 compounds^a



X=I, Cl, Br

Entry	R ¹ X	R ² COOR ³	Products	Yield ^b (%)
1	R ¹ = Ph X = I	R ² = CH ₃ R ³ = C ₂ H ₅	3a	95
2	R ¹ = Ph X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3a	93
3	R ¹ = Ph X = Cl	R ² = CH ₃ R ³ = C ₂ H ₅	3a	Trace
4	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3b	90
5	R ¹ = 4-MeOC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3c	86
6	R ¹ = 2-MeC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3d	81
7	R ¹ = 2-MeOC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3e	75
8	R ¹ = 2,4-dimethylbenzyl X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3f	67
9	R ¹ = 3-FC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3g^c	83
10	R ¹ = 4-ClC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3h	85
11	R ¹ = 2-thienyl X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3i	74
12	R ¹ = 1-naphthyl X = Br	R ² = CH ₃ R ³ = C ₂ H ₅	3j	68
13	R ¹ = Ph X = Br	R ² = CH ₃ R ³ = n-C ₄ H ₉	3k	89
14	R ¹ = Ph X = Br	R ² = n-C ₃ H ₇ R ³ = n-C ₄ H ₉	3l	87
15	R ¹ = Ph X = Br	R ² = i-C ₃ H ₇ R ³ = C ₂ H ₅	3m	85
16	R ¹ = Ph X = Br	R ² = c-C ₃ H ₅ R ³ = C ₂ H ₅	3n	84
17	R ¹ = Ph X = Br	R ² = PhCH ₂ R ³ = C ₂ H ₅	3o	86
18	R ¹ = Ph X = Br	R ² = C ₂ H ₅ OC ₂ H ₄ R ³ = C ₂ H ₅	3p^c	83
19	R ¹ = Ph X = Br	R ² = ClC ₂ H ₄ R ³ = C ₂ H ₅	3q	81
20	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = CH ₃ R ³ = n-C ₄ H ₉	3r	88
21	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = n-C ₃ H ₇ R ³ = n-C ₄ H ₉	3s	83
22	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = i-C ₃ H ₇ R ³ = C ₂ H ₅	3t	81
23	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = c-C ₃ H ₅ R ³ = C ₂ H ₅	3u	78
24	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = PhCH ₂ R ³ = C ₂ H ₅	3v	79
25	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = C ₂ H ₅ OC ₂ H ₄ R ³ = C ₂ H ₅	3w^c	77
26	R ¹ = 4-MeC ₆ H ₄ X = Br	R ² = ClC ₂ H ₄ R ³ = C ₂ H ₅	3x	72

^a Reaction conditions: R¹X (7.5 mmol), Mg (7.5 mmol), R²COOR³ (2.5 mmol), CuO (15 mol %), 15 mL of THF at 65 °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

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