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Cu-Catalyzed Alkylation of Grignard Reagents: A New Efficient Procedure

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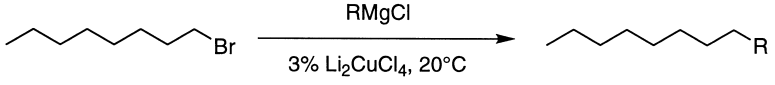
Abstract—The presence of NMP (4–9 equiv.) clearly improves the yield and the chemoselectivity of the Cu-catalyzed alkylation of organomagnesium reagents. Thus, secondary and tertiary alkylmagnesium chlorides were used successfully for the first time in such a reaction and ester, amide, nitrile or keto groups are tolerated. The procedure is cheap, environmentally friendly and very easy to carry out (1–3% Li_2CuCl_4 or CuCl, THF, 20°C). It is an interesting alternative to the classical alkylation of organocuprates reagents. © 2000 Published by Elsevier Science Ltd.

Introduction

The formation of C–C bonds by alkylation of organocopper reagents was extensively studied and it is now a classical tool which is routinely used in organic synthesis.[1] Organocuprates are the most popular reagents to perform this reaction since they lead to high yields and they react very chemoselectively. However, they present some disadvantages, especially for large scale applications. Thus, they are often used in large excess at low temperature. In addition, for industrial applications the presence of a stoichiometric amount (or more) of copper complicates the final work up and makes the waste elimination treatment more expensive. Several improvements have been reported to circumvent these drawbacks (i.e. the use of high order cuprates or mixed cuprates RR′CuLi, R′ being a non transferable group, such as 2-thienyl),[2] however, the more attractive alternative is the Cu-catalyzed alkylation of Grignard reagents.[3] Indeed, this reaction takes place under mild conditions and only involves a catalytic amount of copper salt; unfortunately, it is less chemoselective and leads very often to lower yields. Now, we report a new Cu-catalyzed Grignard reagent procedure which suppresses these limitations.

Results and Discussion

In the course of our studies to search new economical and environmentally friendly cross-coupling reactions (non-expensive or toxic metal and additives, mild reaction conditions…), we have recently shown that NMP (*N*-methyl pyrrolidinone), a cheap and non-toxic solvent, can be successfully used as co-solvent to improve, sometimes considerably, the result of various C–C bond forming reactions.[4] In this communication, we report that this beneficial influence is also observed in the case of the Cu-catalyzed alkylation of Grignard reagents. Thus, the addition of *tert*-butylmagnesium chloride to a solution of octylbromide and 3% Li_2CuCl_4 ($CuCl_2$·2 LiCl) in THF, at 20°C, gave



R = *tert*-Bu
THF : 8%[a]
THF, 4 equiv. NMP : 85%[b]

R = *iso*-Pr
THF : 5%[a]
THF, 4 equiv. NMP : 76%[b]

Scheme 1. (a) GLC yield; (b) yield of distilled product.

Keywords: Grignard reagents; copper-catalyzed alkylation; cross-coupling reaction; solvent effects.
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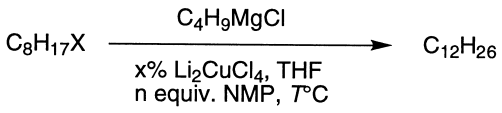
Table 1. Cu-catalyzed alkylation of RMgX in the presence of NMP: influence of various parameters



Entry	NMP (equiv.)	% of Li_2CuCl_4	Temperature (°C)	X	Yield of dodecane[a] (%)
1	0	3	20	Br	32
2	4	–	20	–	86[b]
3	6	–	20	–	84
4	8	–	20	–	80
5	4	1	20	–	85
6	8	3	0	–	80
7	8	3	−30	–	82
8	8	3	−50	–	63
9	4	–	–	I	88
10	–	–	–	$PhSO_3$	65
11	–	3	20	Cl	0

[a] Yield of distilled product.
[b] Similar yield (83%) was obtained by replacing Li_2CuCl_4 by CuCl (introduced as a solution in NMP).

2,2-dimethyldecane in only 8% yield (GLC) whereas 85% of isolated product was obtained in the presence of 4 equiv. of NMP (Scheme 1). A similar improvement was observed when the reaction was performed from *iso*-propylmagnesium chloride and octylbromide (76% instead of 5%).

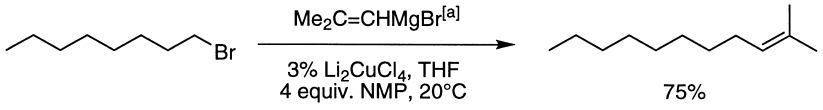
As shown in Table 1, we have studied the influence of various parameters on the reaction of butylmagnesium chloride with octylbromide. Interestingly, the best yield was obtained by using only 4–6 equiv. of NMP based on RMgX (entries 1–4) and 1% of catalyst was enough to achieve the reaction (entry 5). It should be noted that similar yields were obtained by using CuCl (as a solution in NMP) instead of Li_2CuCl_4 as catalyst (respectively 86 and 83%, see note b) The alkylation can be performed indifferently between room temperature and −30°C (entries 4, 5 and 7), whereas below −40°C the reaction rate is slower since the reaction mixture becomes heterogeneous (entry 8). As expected, octyliodide and bromide led to similar results (entries 2 and 9); on the other hand, the corresponding benzenesulfonate gave a lower yield and the less reactive chloride did not react (entries 10 and 11).

As exemplified herein, primary (Table 1) and even secondary or tertiary alkyl Grignard (Scheme 1) which generally give lower yields owing to the competitive β-elimination decomposition process[5] were used successfully. Alkenylmagnesium halides also led to the cross-coupling product, a slight excess of organometallic (1.4 equiv.) was required to drive the reaction to completion (Scheme 2).

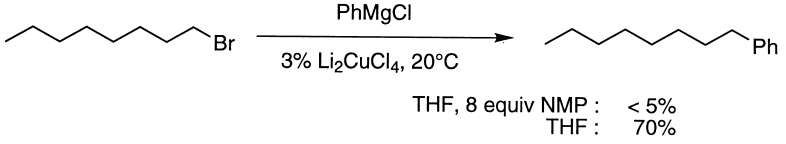
It should be noted that with an aromatic Grignard, it is better to perform the reaction in THF alone (Scheme 3). It should be recalled that such an unexpected negative influence of NMP has already been observed with arylmanganese chloride.[4a]

Unfortunately, the addition of NMP has no influence in the case of secondary or tertiary alkyl halides, thus octylmagnesium chloride reacted with *iso*-propylbromide to afford the alkylated product in only 6% yield.

As a rule, the chemoselectivity of the Cu-catalyzed alkylation of Grignard reagents is not excellent. In the presence of NMP the reaction is much more rapid; therefore, it was likely to be more selective and we have decided to perform some competitive test experiments (Table 2). The results show that a ketone, an ester, a nitrile (entries 1–3) or an amide (NMP) is tolerated under our conditions as well as a carboxylic acid or an alcohol (entries 5 and 6). However, with the latter two groups, two equivalents of butylmagnesium chloride must be added since the corresponding magnesium carboxylate or alcoholate is formed at first. No selectivity was observed by using a 1:1 mixture of

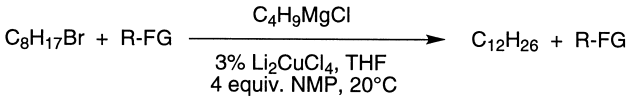


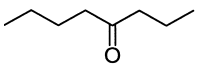
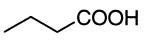
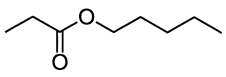
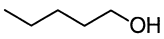
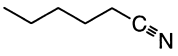
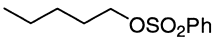
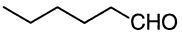
Scheme 2. (a) 1.4 equiv. $Me_2C{=}CHMgBr$ were used.



Scheme 3.

Table 2. Cu-catalyzed alkylation of RMgX in the presence of NMP: chemoselectivity



Entry	R-FG	Yield of $C_{12}H_{26}$ (%)	Entry	R-FG	Yield of $C_{12}H_{26}$ (%)
1		88	**5**		87[a]
2		90	**6**		89[a]
3		88	**7**		55[b]
4		27[c]	**8**	Cyclohexenone	33[d]

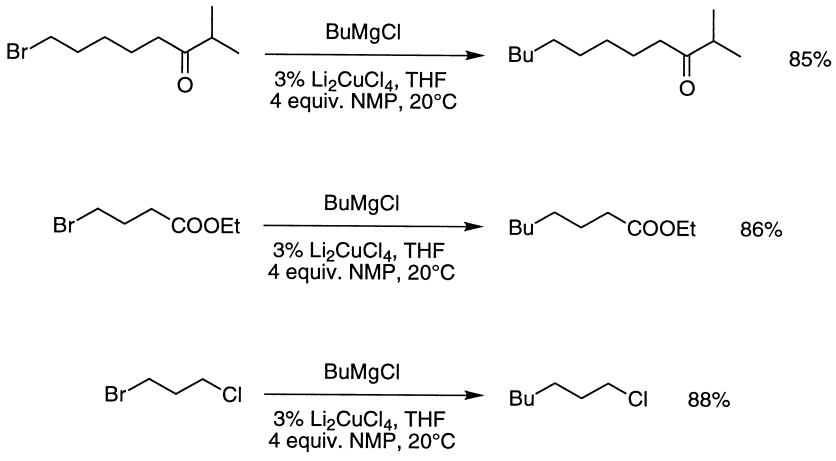
[a] 2 equiv. of BuMgCl were used.
[b] The alkylation product derived from the sulfonate was obtained in 43% yield.
[c] GLC yield, the reaction mainly led to the 1,2 addition product.
[d] GLC yield, the reaction mainly led to the 1,4 addition product.

octylbromide and heptylbenzene sulfonate, and the reaction resulted in a 55:43 mixture of the two alkylated products (entry 7). Finally, in the presence of the very reactive hexanal or cyclohexenone we have mainly obtained, respectively, the 1,2 and the 1,4-addition product (entries 4 and 8).

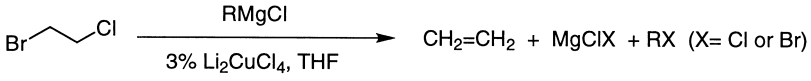
The chemoselectivity evidenced above is well demonstrated by the selective alkylation of the bromoketone, the bromoester and the bromochloroalkane depicted below (Scheme 4).

We have also tried to alkylate selectively 1-bromoalkanes bearing a leaving group in the β-position such as 1-bromo-2-chloroethane or 1-bromo-2-acyloxyethane. Indeed, it is well known that such compounds are very poor substrates for alkylation reactions since, with Cu-catalyzed Grignard reagents as well as with organocuprates, they mainly undergo an elimination reaction leading to ethylene (Scheme 5).[6]

Interestingly, the presence of NMP dramatically changes the course of the reaction.[7] Thus, the 1-bromo-2-chloroethane

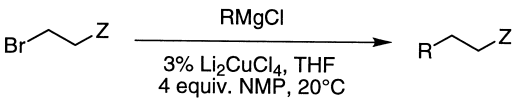


Scheme 4.



Scheme 5.

Table 3. Cu-catalyzed alkylation of $BrCH_2CH_2Z$ in the presence of NMP



Entry	R	Z	Yield (%)[a]
1	Oct	Cl	56[b]
2	Oct	BuCOO	88
3	Bu	EtOCOO	92

[a] Yield of isolated product.
[b] 0% yield in the absence of NMP.

reacted with octylmagnesium bromide to afford 56% of 1-chlorododecane (Table 3, entry 1). This yield is very satisfactory regarding the nature of the substrate. Under similar reaction conditions, two esters of 2-bromoethanol were selectively converted to the expected cross-coupling products in high yields (entries 2 and 3).

Conclusion

In conclusion, we have shown that the presence of NMP dramatically improves the yield and the chemoselectivity of the Cu-catalyzed alkylation of organomagnesium reagents by alkyl bromides or iodides. The procedure described above is an interesting alternative to the classical cuprate alkylation reaction, especially for large scale preparative organic chemistry since the yields are similar or even better (Scheme 6) and it is more environmentally friendly, cheaper and easier to carry out (catalytic amount of copper, one equivalent of organometallic, no expensive or toxic additive, mild reaction conditions).

Experimental

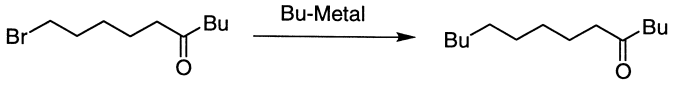
All reactions were performed on a 50 mmol scale under a nitrogen atmosphere. THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere and NMP was distilled before use. All products were isolated by distillation and their purity (≥98%) has been controlled by GC analysis; Fisons GC 8000, capillary column SGE 25QC5/BP1 (25 m×0.53 mm, 0.5 mm film thickness). All the alkylation products were compared to commercial products or to authentic samples (2-methyldecane and 2-methyl-2-undecene),[4a] except those described below (elemental analyses: C: ±0.2%, H: ±0.3%). ^{1}H and ^{13}C NMR spectra ($CDCl_3$, δ ppm, ^{1}H ±0.01, ^{13}C ±0.05, internal standard TMS, J values in Hz ±0.3) were recorded on a JEOL JNM-EX 270 (270 MHz for 1H) spectrometer. IR spectra (neat, ν cm^{-1}) were recorded on a Nicolet Impact 400 (OMNIC software FT spectrometer).

Typical procedure: preparation of 2,2-dimethyldecane (Scheme 1)

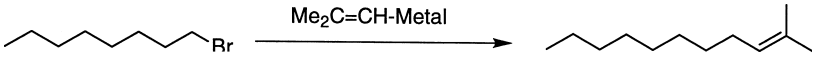
To a solution of octyl bromide (9.6 g, 50 mmol), $CuCl_2$ (1.5 mmol, 201 mg) and anhydrous LiCl (1.5 mmol, 63 mg) in a mixture of THF (75 mL) and NMP (*N*-methylpyrrolidinone, 19 mL) were added dropwise, at 20°C, 1.05 equiv. of *tert*-butylmagnesium chloride (1.2 M solution in THF, 55 mmol, 45.8 mL). Stirring was continued for 1 h and the reaction mixture was cooled at −10°C then quenched with an aqueous hydrochloric acid solution (1N, 100 mL). After decantation, the aqueous layer was extracted twice with pentane (2×70 mL) then the combined organic layers were washed with an aqueous hydrochloric acid solution (1N, 30 mL) and with water (2×70 mL). After drying over magnesium sulfate, the solvents were eliminated under vacuum and the product was isolated by distillation (bp: 80°C/7 Torr) in 85% yield (7.24 g). ^{1}H NMR: δ=0.88 (t and s, 12H, CH_3, J=6.3 Hz), 1.26 (s br, 14H, CH_2); ^{13}C NMR: δ=14.15 (CH_3), 22.70 (CH_2), 24.60 (CH_2), 29.70 (CH_2), 30.00 (4C, CH_2 and CH_3), 30.20 (C), 30.60 (CH_2), 31.90 (CH_2), 44.00 (CH_2).

2-Methyl-3-dodecanone: Bp: 130°C/7 Torr; IR ν=1740 (C=O); ^{1}H NMR: δ=0.87 (t, 3H, CH_3, J=6.9 Hz), 1.06 (d, 6H, CH_3, J=7.9 Hz),1.26 (m, 12H, CH_2), 1.62 (m, 2H, CH_2), 2.43 (t, 2H, COCH_2, J=7.3 Hz), 2.60 (hept, 1H, CH, J=6.9 Hz); ^{13}C NMR: δ=13.90 (CH_3), 18.30 (2C, CH_3), 22.50 (CH_2), 23.60 (CH_2), 29.15 (CH_2), 29.20 (CH_2), 29,30 (2C, CH_2), 31.75 (CH_2), 40.20 (CH_2), 40.60 (CH), 214.70 (C=O).

Octyl pentanoate: Bp 87°C/10 Torr; IR: ν=1735, 1170; ^{1}H NMR: δ=0.88 (t, 3H, CH_3, J=6.8 Hz), 0.92 (t, 3H, CH_3, J=7.3 Hz), 1.33 (m, 8H, CH_2), 1.63 (m, 4H, CH_2), 2.30 (t, 2H, CH_2C=O, J=7.6 Hz), 4.06 (t, 2H, O–CH_2, J=6.6 Hz); ^{13}C NMR: δ=13.70 (CH_3), 13.95 (CH_3), 22.40 (CH_2), 22.65



BuMgCl, 3% Li_2CuCl_4, 8 eq. NMP, THF, 20°C : 84%
Bu_2CuLi, THF, -78°C to 0°C : ≤ 5%[7]



1.4 eq. Me_2CH=CHMgCl, 3% Li_2CuCl_4, 4 eq. NMP, THF, 20°C : 84%
$(Me_2CH=CH)_2CuLi$, THF, -78°C to 0°C : traces

Scheme 6.

(CH_2), 25.75 (CH_2), 27.25 (CH_2), 28.85 (CH_2), 31.60 (CH_2), 34.15 (CH_2), 65.40 (CH_2), 173.75 (C═O),

1-(Ethoxycarbonyloxy)hexane: Bp: 87°C/10 Torr; IR: ν=1740, 1280, 1220; ^{1}H NMR: δ=0.89 (t, 3H, CH_3, J=6.6 Hz), 1.30 (t, 3H, CH_3, J=7.2 Hz), 1.32 (m, 6H, CH_2), 1.66 (tt, 2H, CH_2, J=6.6 and 6.6 Hz), 4.12 (t, 2H, CH_2, J=6.6 Hz), 4.19 (q, 2H, CH_2, J=7.2 Hz); ^{13}C NMR: δ=14.00 (CH_3), 14.35 (CH_3), 22.65 (CH_2), 25.55 (CH_2), 28.85 (CH_2), 31.60 (CH_2), 38.00 (CH_2), 63.75 (CH_2), 155.40 (C═O).

5-Tetradecanone: Bp: 92°C/5 Torr; IR: ν=1707; ^{1}H NMR: δ=0.80 (t, 3H, CH_3, J=3 Hz), 0.83 (t, 3H, CH_3, J=7.2 Hz) 1.20 (m, 14H, CH_2), 1.50 (m, 4H, CH_2), 2.31 (t, 2H, CH_2C═O, J=7.5 Hz), 2.32 (t, 2H, CH_2C═O, J=7.5 Hz); ^{13}C NMR: δ=13.80 (CH_3), 14.05 (CH_3), 22.30 (CH_2), 22.60 (CH_2), 23.85 (CH_2), 25.95 (CH_2), 29.20 (CH_2),29.40 (2C, CH_2), 31.80 (2C, CH_2), 42.45 (CH_2), 42.80 (CH_2), 211.70 (C═O).

Acknowledgements

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7. The main reaction was the 1,2-addition to the ketone. Two products were isolated; the tertiary alcohol **I** (yield: 31.5%) and the tetrahydropyran **II** (yield: 38.5%) resulting from the in situ cyclization of the bromoalcoholate.