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Influence of catalytic system composition on formation of adamantane containing ketones

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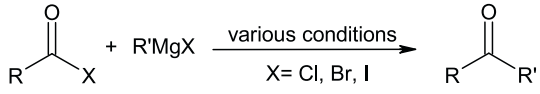
Dedicated to Professor Milan Kratochvíl on his 80th birthday

Abstract—The preparation of non-symmetrical ketones by the reaction of acyl chlorides and the corresponding Grignard reagents in the presence of catalytic amounts of metal halides is described. The composition of catalyst has a great influence on the yield of the required ketone as well as on side product formation. For each catalytic system, the yield of ketone and the number of side products changes with the time of addition of the Grignard reagent. We examined the influence of both factors in our model reaction of adamantane-1-carbonyl chloride with ethylmagnesium bromide and discussed the possible mechanisms from this point of view. We have found $ZnCl_2$, $MnCl_2$, $AlCl_3$ and CuCl to be active catalytic components and developed very efficient, cheap and fast methods for the preparation of alkyl adamantyl ketones. The procedure was also tested for the synthesis of other alkyl aryl ketones.

1. Introduction

One of the most important strategies to obtain a new carbon–carbon bond at a carbonyl group is a nucleophilic substitution of a good leaving group using an organometallic reagent (Scheme 1). Several modifications of the general procedure where an organometallic reagent reacts with acyl chlorides were studied[1–3] or used in synthesis[4,5] recently.



Scheme 1.

Typically, 'soft' organometallic reagents containing copper, zinc, manganese, etc. are used to support substitution of a good leaving group and to avoid the successive addition of an organometallic compound to an unsaturated carbonyl group. It is interesting that good yields of ketones can also be obtained when in situ transmetallation is carried out since this means that the Grignard reagent reacts with the acyl chloride in the presence of a suitable metal halide. This procedure can be improved using only a catalytic amount of the metal halide but in this case the rate of addition of the organomagnesium reagent was found to be important.[6]

2. Results and discussion

A few years ago, Cahiez and Laboue[6] described the preparation of various ketones using acyl chlorides and Grignard reagents in the presence of a catalytic amount of manganese chloride and copper(I) chloride. They optimized the rate of Grignard reagent addition to obtain the best yield of the required ketone. For any other than the optimal rate, the observed yields of the ketone decreased as the amount of tertiary alcohol formed increased. In this work, we carried out a number of experimental conditions for selected catalytic systems to discover the best combination of metals. This study led to the discovery of a new, efficient method for the preparation of adamantyl ketones. Our data from the reaction of Grignard reagents with adamantyl-1-carbonyl chloride (**1**) with similar manganese–copper catalysts are in good agreement with the observation of Cahiez and Laboue[6] (see Table 1, entries 8–13). The best yield (82%) we obtained when the addition took about 56 min. Surprisingly, we did not detect a significant amount of tertiary alcohol **4** anytime[†] and the main

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[†] However, when the structure of Grignard reagent used eliminates the reduction of ketone, the corresponding tertiary alcohol was present.

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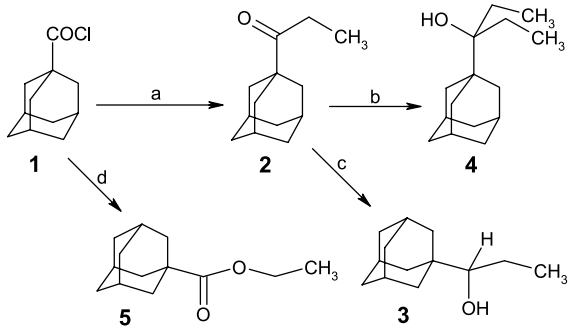
Table 1. Catalyst composition influence on the yield of ketone **2** and side-products distribution

A	B	Time (min)	C[a] **2**	Composition of crude product[b]			
				2	**5**	**3**	**4**
0	1	4.4	53	74.1	2.0	23.1	0.8
	2	17.0	59	90.6	5.8	3.4	0.2
	3	30.9	59	88.6	9.3	2.0	0.1
	4	39.9	60	84.3	13.9	1.6	0.2
	5	65.2	61	82.8	16.0	1.1	0.1
	6	91.5	57	78.3	20.9	0.7	0.1
	7	173.5	60	69.6	28.2	1.7	0.5
$MnCl_2 \cdot CuCl$	8	2.8	38	74.8	0.3	24.9	0.0
	9	18.5	49	84.6	0.6	14.8	0.0
	10	37.4	73	94.7	5.0	0.3	0.0
	11	55.8	82	97.8	1.3	0.9	0.0
	12	75.5	77	88.0	12.0	0.0	0.0
	13	100.0	55	87.6	12.4	0.0	0.0
$AlCl_3 \cdot CuCl$	14	0.25	95	>99.5	0.0	0.0	0.0
	15	12.2	73	91.6	8.4	0.0	0.0
	16	35.3	53	87.0	13.0	0.0	0.0
	17	47.9	52	86.0	14.0	0.0	0.0
	18	58.7	57	85.0	15.0	0.0	0.0
	19	66.3	59	84.0	16.0	0.0	0.0
	20	90.0	53	81.0	19.0	0.0	0.0
	21	105.4	51	78.0	22.0	0.0	0.0
$ZnCl_2 \cdot CuCl$	22	4.5	82	98.4	0.8	0.7	0.1
	23	15.8	80	98.3	1.2	0.5	0.0
	24	29.6	79	97.4	2.0	0.5	0.1
	25	44.8	80	96.2	3.3	0.4	0.0
	26	66.9	81	95.1	4.5	0.4	0.0
	27	82.9	76	93.9	5.8	0.3	0.0
	28	105.9	74	93.2	6.5	0.3	0.0
$AlCl_3$	29	0.3	49	97.0	1.9	0.0	1.1
	30	10.4	55	90.6	8.5	0.0	0.9
	31	19.1	57	89.5	9.6	0.0	0.7
	32	31.7	56	86.6	13.4	0.0	0.0
	33	47.1	53	85.6	14.4	0.0	0.0
	34	67.8	47	77.0	22.8	0.0	0.2
	35	87.0	50	75.4	24.5	0.0	1.0
	36	119.4	41	68.7	30.8	0.0	0.5
CuCl	37	0.3	77	95.5	0.3	2.9	0.0
	38	8.4	82	98.5	1.3	0.2	0.0
	39	15.1	80	98.0	1.5	0.5	0.0
	40	31.2	78	97.9	1.5	0.6	0.0
	41	42.9	82	94.1	5.5	0.4	0.0
	42	60.7	81	92.2	7.7	0.1	0.0
	43	93.5	74	92.9	6.9	0.3	0.0
$MnCl_2 \cdot AlCl_3$	45	4.15	68	94.9	0.3	4.3	0.4
	46	14.0	71	97.5	0.6	1.8	0.1
	47	31.4	67	96.7	1.4	1.7	0.2
	48	58.6	64	91.7	7.5	0.9	0.0
	49	70.1	56	89.5	9.9	0.6	0.0
	50	132.6	46	78.7	20.9	0.3	0.0

A=catalyst, B=entry number, C=yield.
[a] Determined by GC with cyclohexanone as an internal standard.
[b] Determined by GC (relative %).

side product at high addition rate was the secondary alcohol **3** arisen from reduction of ketone **2**. Furthermore, at a low addition rate we detected the ethyl adamantane-1-carboxylate **5** as the main side product. There are two possible routes to ester **5**. The first one is reaction between the acyl chloride and the corresponding alcoholate coming from impurities in the starting material (ethyl bromide) for Grignard reagent preparation. This pathway is proved by reactions where several different Grignard reagents were used and always the relevant ester was detected as well as the ketone. Nevertheless, this possibility cannot explain the increasing amount of ester with a prolonged time of addition. Thus, another pathway based on acylative cleavage of diethyl ether[7–11] is unambiguously present. The reaction pathways



Scheme 2. Supposed reaction pathways leading to main components of crude products. (a) Ethylmagnesium bromide substitution of chlorine, (b) Grignard reagent addition to carbonyl, (c) reduction of carbonyl group by Grignard reagent, (d) acylative cleavage of diethyl ether.

leading to the most important side products are shown in Scheme 2.

In case when no catalyst was used, the ketone **2** yield does not change significantly and for all the rates of the Grignard reagent addition varies around 60%. The distribution of products after reaction using $MnCl_2$/CuCl catalyst is very similar to that without any catalyst. The amount of ester **5** in the non-catalyzed reaction is even higher than that in the reaction catalyzed by manganese (compare entries 6 and 13). Use of aluminium trichloride with copper chloride (entries 14–21) led to a completely different situation. The highest ketone **2** yield (95%) was observed for the shortest addition time (entry 14) and for any lower rate of addition the yields were rapidly decreased.

Good yields (about 80%) were obtained when $ZnCl_2$ was used together with CuCl. They are nearly independent of the time of addition (entries 22–26). A small decrease of ketone **2** yield (caused by ester formation) was observed only for longer times of addition (entries 27 and 28).

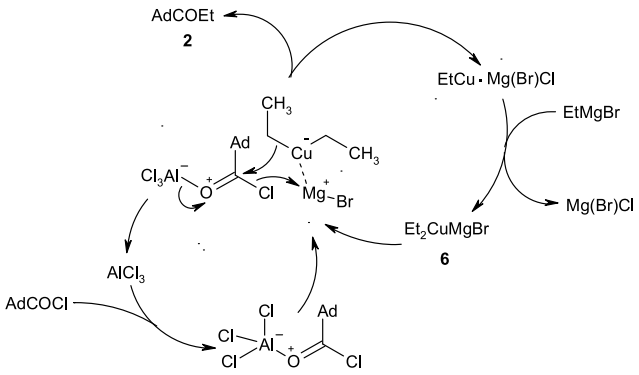
Sets of experiments where $AlCl_3$ (entries 29–36) and CuCl (entries 37–43) were used separately show that the influence of addition time with the $AlCl_3$ catalyst has no significant influence on the yield. However, the presence of CuCl increases ketone **2** yield for all rates by about 20% in comparison with the non-catalyzed reactions.

In the case of $AlCl_3$ catalyst, no significant amount of alcohols was detected in the product although the yield of ketone **2** was not higher than 60%. Appropriate unreacted starting material was recovered after hydrolysis and identified as adamantane-1-carboxylic acid. Finally, manganese chloride instead of copper chloride was used (entries 45–50) but the reactions were less successful. The best yield (71%) of ketone **2** in this case was obtained for 14 min lasting addition.

We can conclude, that the best result was observed when the strongest Lewis acid was used together with the most efficient organometallic reagent (formed in situ via transmetallation). This assertion is in good agreement with the trends indicated in Table 1. $AlCl_3$ as well as CuCl used separately decrease the amount of secondary alcohol, which is formed when excessive amount of Grignard reagent is present and that reacts not only with acyl chloride but consequently also with the already formed ketone **2**. When $AlCl_3$ and CuCl are used together, the absence of secondary alcohol **3** at all addition rates implies the presence of a mechanism that consumes Grignard reagent very rapidly, and so undesirable reductions or additions can not occur.

A reasonable explanation of our results leads to the formulation of a mechanism based on two joint cycles (Scheme 3). In the first cycle, aluminium trichloride reacts with acyl chloride to produce an acyl chloride–trichloro-aluminium complex.[12,13]

This activated alkyl carbonyl then interacts with organo-copper compound **6** to produce the expected ketone **2**, $EtCu{\cdot}MgX_2$ and regenerated aluminium trichloride. In the second joint cycle $EtCu{\cdot}MgX_2$ is alkylated by another molecule of Grignard reagent and the reactive



Scheme 3. Proposed mechanism of ketone **2** formation based on Lewis acid activated acyl chloride reaction with organocuprate.

organocuprate **6** is regenerated. Such a system can operate efficiently only when conversion of alkylcopper into **6** by action of Grignard reagent is sufficiently fast and when **6** reacts again very quickly with the activated acyl chloride rather than with other electrophiles present in the reaction mixture. The second assumption is acceptable because activated acyl chloride seems to be the most electrophilic species in the mixture.

Finally, we tested our new method in the synthesis of several ketones to eliminate the possible specific influence of the bulky adamantane moiety. These results are summarized in Table 2. In all the cases we obtained the expected ketones in good or excellent yields. It should be mentioned tertiary or secondary alcohols were not detected in any cases and the corresponding amounts of unreacted carboxylic acids were recovered (except acetic, propionic and pivalic acid).

3. Conclusion

A new, efficient, cheap and fast method for the synthesis of non-symmetrical ketones has been developed. In comparison with other methods, this one involves easily accessible reagents and provides very good yields. Ketones are obtained within 10 min at 10 °C and no special conditions or work-up procedures are required. In addition, no undesirable alcohols were present in crude product. Non-substituted ketones are produced very efficiently but the full scope of our reaction procedure remains a question for further research.

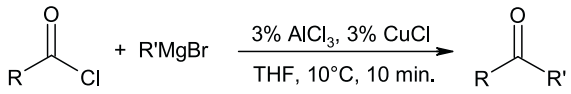
4. Experimental

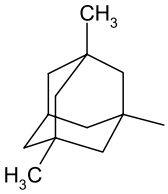
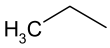
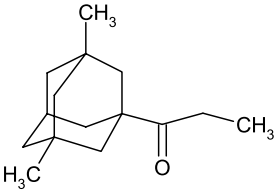
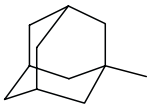
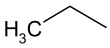
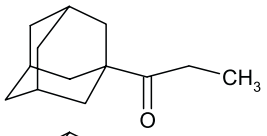
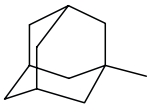
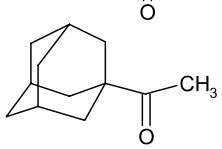
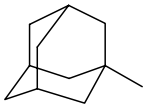
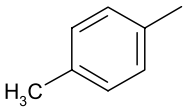
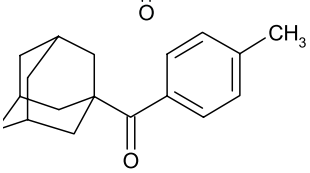
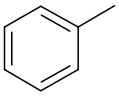
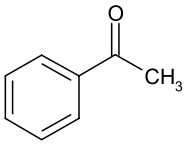
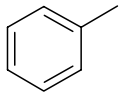
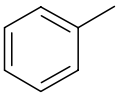
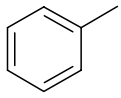
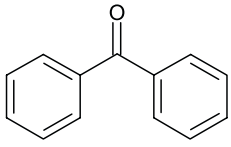
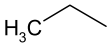
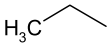
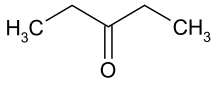
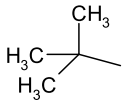
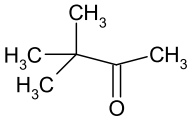
4.1. General data

All reactions were carried out under an argon atmosphere. Solvents were dried by the standard methods and were freshly distilled before use. LiCl, $MnCl_2$, $ZnCl_2$ were purchased from Fluka Co. and were dried before use under vacuum at 160 °C for 2 h. $AlCl_3$ was obtained from Merck.[‡] CuCl was prepared from $CuSO_4$ via reduction by $K_2S_2O_5$ in the presence of NaCl and was dried in the same way as

[‡] We used freshly crushed pale yellow coarse-grained crystals. White powder available from other sources was not suitable for our purpose (poor solubility).

Table 2. Summarized results of acyl chlorides reaction with organomagnesium compounds catalyzed by $AlCl_3 \cdot CuCl$



R	R′	Product	Yield (%)
			91[a]
			94[b]
			89[a]
			77[a]
			87[a]
			80[a]
			96[a]
			67[b]
			87[a]

[a] Isolated yields of purified product.
[b] Determined by GC.

the other chlorides. The white powder obtained can be stored under an argon atmosphere for several months.[§] Melting points are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75.5 (^{13}C) MHz (Bruker AM-300) or 500 (^{1}H) and 125.8 (^{13}C) MHz (Bruker DRX-500) respectively, using solvent as an internal standard. The IR spectra were recorded with FT-IR instrument Genesis ATI. GC analyses were run on a Shimadzu GC-17A instrument.

Ethylmagnesium bromide was prepared by refluxing ethyl bromide (10.90 g, 0.1 mol) with an excess of magnesium turnings (3.16 g, 0.13 mol) in diethyl ether.[14] The concentration of clear solution was determined by acid/base titration[15] before use.

[§] Commercial CuCl purchased from Fluka containing traces of $CuCl_2$ (colored light green) was not suitable for our experiments. It is not completely soluble in THF and caused low reproducibility and increasing amount of secondary alcohols.

4.2. General procedure for ketone preparation

Into a dry three-necked flask equipped with a magnetic stirring bar, thermometer and rubber septum, lithium chloride (5 mL of 0.03 M solution in THF) was transferred and the corresponding metal halide (0.075 mmol) was added and dissolved. Into the obtained clear solution, adamantane-1-carbonylchloride (**1**) (0.5 g, 2.5 mmol) was added and solution was stirred for 5 min. Then, Grignard reagent (2.5 mmol, 2 mL in ether) was added for the required time period using a syringe pump. After complete addition, the reaction mixture was quenched with hydrochloric acid (10 mL, 1 M solution). The water layer was extracted three times with 10 mL of diethyl ether. The collected organic layers were washed twice with potassium carbonate solution (10 mL, 1 M), once with ammonium chloride solution (10 mL, 3 M) and dried over sodium sulfate overnight. The solution was filtered from Na_2SO_4 and diluted to 50 mL with diethyl ether. The yield of ketone **2** and the composition of the crude product were then determined by gas chromatography. Cyclohexanone was used as an internal standard.

4.2.1. Adamantane-1-carbonyl chloride (1). Into a suspension of adamantane-1-carboxylic acid (25.0 g, 0.126 mol) in toluene (32 mL) at 70 °C, $SOCl_2$ (19.6 g, 0.164 mol) was added dropwise. The reaction mixture was stirred at this temperature for 8 h. Then dry toluene (30 mL) was added, the mixture was heated up and the $SOCl_2$/toluene azeotrope (30 mL) was distilled out. This procedure was repeated three times. Finally, 20 mL of solvent was distilled out, the residue was cooled down and allowed to crystallize at −15 °C. Pale yellow needles obtained were filtered and dried in a stream of an inert gas (yield 22.3 g, 89%, mp 47–48 °C, lit.[16] mp 49–51 °C). NMR data correspond with literature.[16]

4.2.2. 1-Adamantyl ethyl ketone (2). Used as a standard sample was prepared by the way described above scaled up to 25 mmol of starting acyl chloride **1**. $AlCl_3$ and CuCl were used as catalysts. Colorless flat crystals were obtained after crystallization from ethanol/water (4.3 g, 89%, mp 31–33 °C, lit.[17] 31–32 °C). NMR data correspond with literature.[18]

4.2.3. 1-(1-Adamantyl)propan-1-ol (3). Ketone **2** (1.32 g, 7 mmol) was treated with $LiAlH_4$ (0.2 g, 5 mmol) in 20 mL of dry diethyl ether at room temperature for 24 h according to literature procedure.[19] The reaction mixture was quenched by addition of 30% aq. KOH solution (20 mL). The resulting white suspension was filtered and washed with diethyl ether. The combined organic phases were washed with water and dried over Na_2SO_4. The solvent was removed and colorless needles were obtained in amount of 1.2 g (92%), mp 84–86 °C, lit.[20] mp 85–86 °C). NMR data correspond with literature.[20]

4.2.4. 3-(1-Adamantyl)pentan-3-ol (4). Into a solution of ethylmagnesium bromide (18.5 mL of 2.8 M diethyl ether solution), ketone **2** (10 mL of 1.04 M in THF) was dropwise added at 0 °C. The reaction mixture was well stirred for 20 h at 0–20 °C. After this period, the excess of Grignard reagent was destroyed by diluted hydrochloric acid. Organic layer was washed twice with solution of K_2CO_3 (20 mL, 1 M solution) and with brine (20 mL) and dried over Na_2SO_4. Colorless crystals obtained after solvent removing were crystallized from hexane to yield 2.03 g of alcohol **4** (88%), mp 67–69 °C, lit.[21] 68–69 °C. NMR data correspond with literature.[21]

4.2.5. Ethyl adamantane-1-carboxylate (5). The above title compound was prepared according to literature procedure[22] from adamantane-1-carboxylic acid (2.5 g, 0.014 mol). It was refluxed for 2 h in ethanol (20 mL, 0.343 mol) in the presence of catalytic amount of H_2SO_4. Crude product was purified by column chromatography (silica gel, chloroform) to yield 2.5 g of ester (86%) as a colorless liquid. Spectral data correspond with literature.[23]

4.2.6. 3,5-Dimethyladamantane-1-yl ethyl ketone. The above title compound was prepared by the same procedure like the ketone **2**. Colorless liquid was obtained after purification of the crude product by column chromatography (silica gel, 11% ethyl acetate/hexane); [Found: C, 81.8; H, 11.1. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%]; ν_{max}(KBr) 2944–2844 (br), 1701, 1455, 1375, 1357, 1333, 1260, 1208, 1159, 1126, 1094, 1027, 895, 842, 804, 700, 514 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.39 (2H, q, J=7.2 Hz, $COCH_2CH_3$); 2.04–2.07 (1H, m, Ad); 1.57 (2H, m, Ad); 1.31–1.39 (4H, m, Ad); 1.28 (4H, m, Ad); 1.05–1.12 (2H, m, Ad); 0.94 (3H, t, J=7.2 Hz, $COCH_2CH_3$); 0.78 (6H, s, Ad-*Me*,); δ_C (75.5 MHz, $CDCl_3$) 216.2, 51.0, 48.5, 44.8, 43.1, 37.3, 31.1, 30.8, 29.6, 29.5, 8.1.

4.2.7. 1-Adamantyl 4-methylphenyl ketone. The above title compound was prepared by the same procedure like the ketone **2**. Colorless crystals were obtained after purification of the crude product by crystallization from methanol, mp 61–63 °C; [Found: C, 85.0; H, 8.8. $C_{18}H_{22}O$ requires C, 84.99; H, 8.72%]; ν_{max}(KBr) 2943–2846(br), 1657, 1606, 1452, 1342, 1271, 1238, 1176, 1103, 991, 928, 833, 812, 737, 607 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.53 (2H, m, Ph); 7.19 (2H, m, Ph); 2.39 (3H, m, Ad); 2.04–2.08 (9H, m, Ph-CH_3, Ad); 1.77 (6H, m, Ad); δ_C (75.5 MHz, $CDCl_3$) 209.5, 140.9, 136.8, 128.8, 127.8, 47.1, 39.5, 36.8, 28.5, 21.6.

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