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COMMUNICATION

Acylation of Grignard reagents mediated by *N*-methylpyrrolidone: A remarkable selectivity for the synthesis of ketones†

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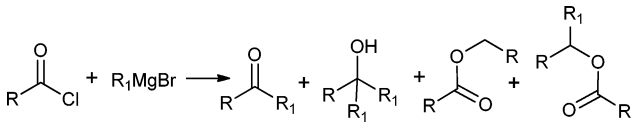
An efficient user-friendly method of acylation of Grignard reagents to selectively synthesize ketones is presented, which is assisted by simple amides such as NMP, or DMF. The present chemoselective method tolerates a variety of functional groups such as ketone, ester, nitrile and other functional groups.

The acylation of organometallic compounds is one of the important methods for the synthesis of ketones.[1] Grignard reagents[2] are widely used organometallic compounds, which are particularly useful in C–C bond formation. Acylation of a Grignard reagent to obtain ketones is a challenging task as ketones readily react with Grignard reagents to produce tertiary alcohols even at lower temperatures.[2,3] In order to address this problem, several strategies have been explored[3] using a variety of organometallic reagents such as organomanganese, organozinc, organocopper, and other methods.[4–9] In recent times, Knochel,[4a] Fürstner,[4b] and others[4] have investigated the acylation of Grignard reagents using acyl halides or acyl cyanides in the presence of an iron catalyst. Acylation of Grignard reagents using a tridentate ligand, bis[2-(*N*,*N*-dimethylamino)ethyl], at −5 to −60 °C to provide aryl ketones[3] was recently reported by Wang and co-workers.[3] In this approach, the nucleophilicity of the Grignard reagent was modulated by complexing it with an organic ligand and reacting with aromatic acid chlorides to furnish ketones. The addition of Weinreb amide to Grignard reagent and similar such variations are also documented.[4d,9,10]

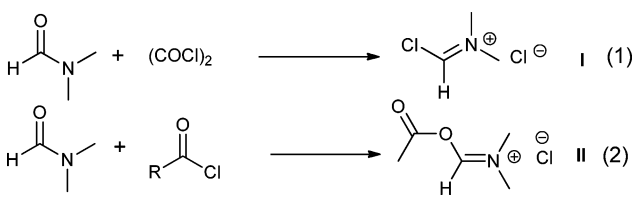
Ketones undergo a facile reaction with Grignard reagent to form tertiary alcohols. Therefore, one of the major challenges associated with the acylation of Grignard reagents is to halt the acylation at ketone stage. To overcome this problem, acylation of Grignard reagent is performed at lower temperature, which generally yields ketones along with other side products including tertiary alcohols (Scheme 1).[3] The successful acylation methods of Grignard reagents to obtain ketones as the major product



Scheme 1 Acylation of Grignard reagents.

have adopted strategies such as increasing the reactivity of acyl group,[4a] or reducing the reactivity of the Grignard reagent by complexing with a tridentate ligand,[3] or selective reaction of a Grignard reagent with Weinreb amide in the presence of ketone.[6c,6g] In Weinreb's approach, the acylating intermediate *N*-methoxy-*N*-methylamides are coupled with the Grignard reagent and the ketone is formed after aqueous work up of the tetrahedral intermediate.

It is known that dimethylformamide (DMF) reacts with oxalyl chloride to form an *N*,*N*-dimethylchloromethylenammonium chloride intermediate which is employed in the preparation of acid chloride (**I**, eq (1), Scheme 2).[10a] Further, DMF is known to react with acid chlorides to form a similar type intermediate **II** (*N*,*N*-dimethyl(acylomethelenium)chloride, (eq (2), Scheme 2),[10] which has been employed in the synthesis of carboxylic anhydrides and esters in the presence of zinc(0).[10d] With this literature precedence, and in light of using tridentate ligands to reduce the nucleophilicity Grignard reagents, we thought that it was reasonable to use simple amides such as DMF or *N*-methylpyrrolidone (NMP) in acylation reactions of Grignard reagents. Therefore, we investigated the acylation of Grignard reagents with *in situ* generated intermediates such as **II** (eq.(2), Scheme 2) and the results are presented in the following section.



Scheme 2 Reaction of DMF with oxalyl chloride and acid chloride.

The optimal reaction conditions were established after several experimental trials. To a well-stirred cold solution of acid chloride (1.1 equiv) and DMF (1.2 equiv) in toluene was added Grignard

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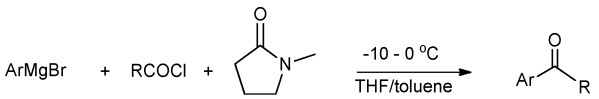
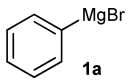
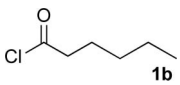
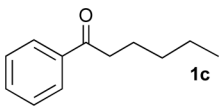
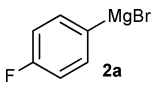
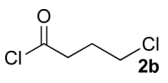
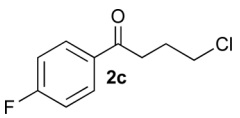
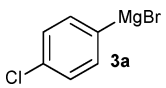
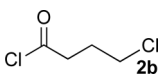
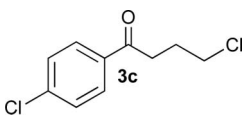
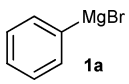
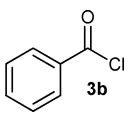
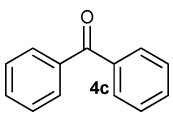
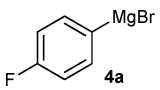
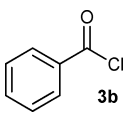
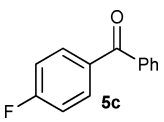
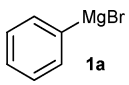
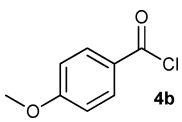
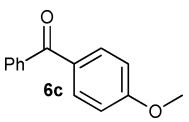
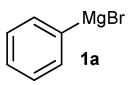
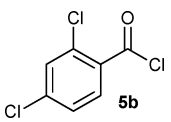
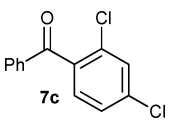
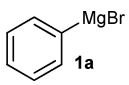
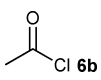
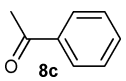
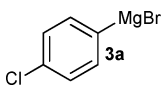
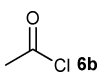
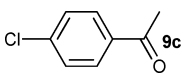
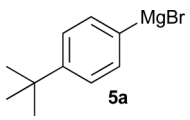
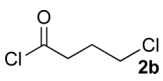
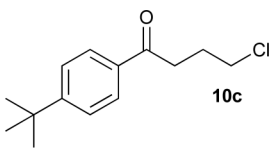
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra for all products. See DOI: 10.1039/c1ob05780d

Table 1 Acylation of Grignard reagents

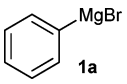
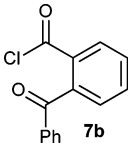
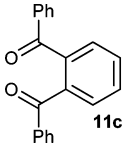
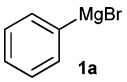
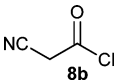
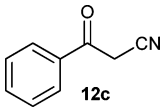
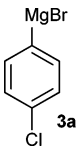
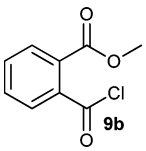
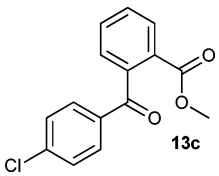
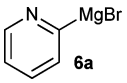
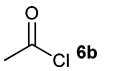
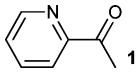
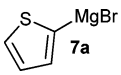
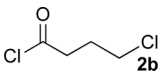
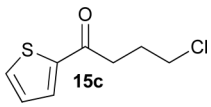
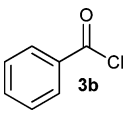
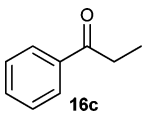
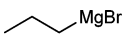
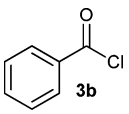
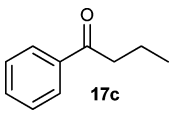
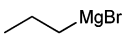
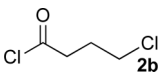
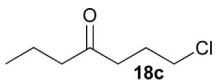


Entry	Grignard reagent	Acid chloride	Product[a]	Yield (%)[b]
1				91 (90)[c]
2				88 (92)[c]
3				90 (86)[c]
4				89 (45)[c]
5				85 (43)[c]
6				80 (40)[c]
7				82
8				84
9				83
10				90

[a] General reaction conditions: RMgX (1 equiv) in THF, acid chloride (1.1 equiv), NMP or DMF in toluene (1.2 equiv). [b] Yield of isolated analytically pure product. [c] Yields in parenthesis indicates the reaction with DMF.

reagent (1 equiv) in THF at 0–5 °C and stirred at –5 °C for 4 h to produce the corresponding ketones in good yields (entries 1–3, Table 1). However, the same reaction of arylmagnesium chlorides **1a** and **4a** with aromatic acid chlorides (**3b** and **4b**) in DMF produced lower yields of the ketones **4c**, **5c**, and **6c** respectively (40–45%, entries 4–6, Table 1, yields in parenthesis). We contemplated that the decrease in the yield of the ketones was due to the presence of a formyl proton in DMF. Therefore to avoid a formyl proton in the reaction, we decided to use NMP instead of DMF. Therefore, PhMgBr (**1a**) was acylated with hexanoyl chloride (**1b**) in the

Table 2 Chemoselective acylation of Grignard reagents

Entry	Grignard reagent[a]	Acid chloride	Product	Yield (%)[b]
1	 **1a**	 **7b**	 **11c**	83
2	 **1a**	 **8b**	 **12c**	73
3	 **3a**	 **9b**	 **13c**	86
4[c]	 **6a**	 **6b**	 **14c**	79
5[c]	 **7a**	 **2b**	 **15c**	89
6	 **8a**	 **3b**	 **16c**	54
7	 **9a**	 **3b**	 **17c**	55
8	 **9a**	 **2b**	 **18c**	75[d]

[a] General reaction conditions: RMgX (1 equiv) in THF, acid chloride (1.1 equiv), NMP in toluene (1.2 equiv). [b] Yield of isolated analytically pure product. [c] Grignard reagent obtained by the exchange reaction with isopropyl magnesium bromide. [d] GC Yield.

presence of NMP. Quite pleasingly, replacing DMF by NMP has produced the most satisfying results as several arylmagnesium halides as well as aliphatic magnesium halides reacted successfully with a variety of acid chlorides (aromatic as well as aliphatic acid chlorides) to produce their corresponding ketones in good to excellent yields (Tables 1 and 2). In a typical reaction, acid chloride was added to NMP at 0 °C during 15 min, followed by the addition of RMgBr at –5 to –10 °C over 15 min. Then the reaction mixture was stirred for 4 h at –5 to –10 °C and worked up to furnish the ketone in good yields (Tables 1 and 2).

As seen in Table 1, the acylation of Grignard reagents with a variety of acid chlorides in NMP was successfully performed and the reaction appears to be general and also selective. A variety of arylmagnesium bromides reacted well with acid chlorides (aliphatic as well as aromatic acid chlorides) to furnish the corresponding ketones in excellent yields (entries 1–10,Table 1).

Interestingly, acylation of Grignard reagent in the presence of NMP turned out to be a good chemoselective reaction as several functional groups, which are readily susceptible for Grignard reaction such as ketone, nitrile, and ester were unaffected during the reaction conditions. Hence, substrates **7b**, **8b**, and **9b** reacted well with arylmagnesium bromide to yield the corresponding ketone **11c**, **12c**, and **13c** in good yields (entries 1–3, Table 2). These examples indicate that functional groups such as ketone, nitrile, and ester functionalities are unaffected during acylation.

Reaction of heterocyclic Grignard reagents such as 2-pyridylmagnesium bromide (**6a**) and 2-thiophenylmagnesium bromide (**7a**), which were obtained by the exchange reaction with isobutyl magnesium chloride, reacted with acetyl chloride (**6b**) to produce the corresponding ketones **14c** and **15c** in 79% and 89% respectively (entries 4 and 5, Table 2). Our attempts to employ aliphatic Grignard reagents under the same reaction

conditions furnished moderate yields of ketones. Ethylmagnesium bromide (**8a**) reacted with benzoyl chloride (**3b**) to furnish the propiophenone **16c** in moderate yield (54%, entry 6, Table 2). Similarly, Grignard reaction of propylmagnesium bromide **9a** with benzoyl chloride **3b** resulted in the formation of butyrophenone **17c** in 55% yield. Grignard reaction of an aliphatic Grignard reagent with an alphatic acid chloride is illustrated in the example 8 of Table 2. In this reaction, propylmagnesium chloride (**9a**) reacted with 4-chlorobutyrol chloride (**2b**) to furnish the corresponding ketone, 1-chlorohept-4-one (**18c**) in 75%. Our attempt to resolve the mechanism did not yield fruitful results. Further work is under way to find out the reaction mechanism for the above reaction.

In summary, we have developed a method for the acylation of Grignard reagents mediated by NMP or DMF in easily attainable reaction conditions to furnish ketones in excellent yields. The highlights of the present protocol are that it is chemoselective, and the reaction tolerates a variety of functional groups such as keto, ester, cyano and other functional groups. Importantly, the acylation can be carried out with ease with aromatic or aliphatic acid chlorides and with aromatic as well as aliphatic Grignard reagents. Application of the present protocol of modulating the reactivity of the acid chloride is under way in our laboratory.

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