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A general method for the direct transformation of common tertiary amides into ketones and amines by addition of Grignard reagents

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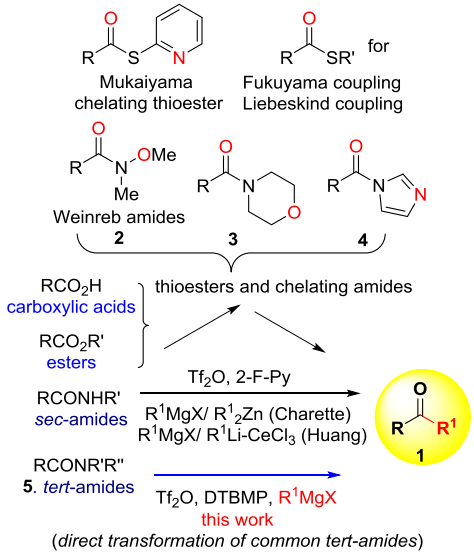
ABSTRACT

The direct transformation of amides into ketones by addition of organometallic reagents has attracted the attention of organic chemists for a long time. However limited methods are reliable for common amides and have found synthetic applications. Here we report a method featuring *in situ* activation of tertiary amides with triflic anhydride (Tf_2O) followed by addition of Grignard reagents. The method displays a good generality in scope for both amides and Grignard reagents, and it can be viewed as the acylation of Grignard reagents using amides as stable and selective acylating agents. Moreover, this deaminative alkylation reaction provides a mild method for the *N*-Deacylation of amides to give free amines.

1. Introduction

Due to their multiple reactivities, ketones (**1**) are perhaps the most versatile class of molecules for C–C bond formation in organic chemistry. The rich chemistry of ketones ranges from enol/enolate-based reactions to electrophilic carbonyl-based reactions. In addition, ketones are found in many bioactive natural products[1] and medicinal agents.[2] Consequently, although numerous methods have been established, the synthesis of ketones still attracts current attention.[3] Among the methods for ketone synthesis, those based on the addition of organometallic reagents to carboxylic acid derivatives are the most popular.[4] However, due to the low reactivity of the carboxylic acid derivatives (except for acid chlorides) compared to ketones, over addition that leads to tertiary alcohols is difficult to be avoided.[5] To tackle this problem, specially designed chelating amides (e.g., **2**,[6] **3**,[7] **4**[8]) and thioesters[9] have been developed as vehicles for the indirect transformation of carboxylic acids and esters into ketones (**1**) (Scheme 1). Among the chelating amides developed so far, the most well-known and reliable one is the *N*-methyl-*N*-methoxyamides **2**, known as Weinreb amides.[6] Recently, by using amide activation strategy, Charette[10a] and our research group[10b,c] have developed independently the direct transformations of secondary amides into ketones by addition of Grignard/organozinc reagents, and organocerium reagents, respectively. However, the development of reliable methods for the direct transformation of common tertiary amides into ketones remains a formidable challenge.



Scheme 1. Representative general methods for the transformation of carboxylic acid derivatives into ketones.

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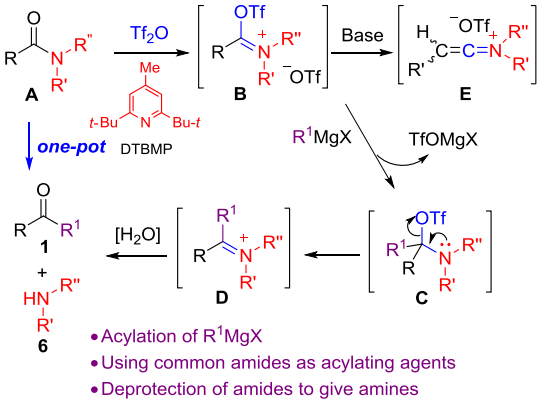
Unactivated[11] common tertiary amides are a class of highly stable and easily available carboxylic acid derivatives.[12] These features make them very useful starting materials and intermediates in organic synthesis.[13] Thus, the deacylation of amides to give amines under mild conditions is an important transformation in the synthesis of alkaloids and *N*-containing pharmaceutics.[13] In addition, tertiary amido groups also serve as powerful directing groups in directed lithiation[14] and C–H functionalization reactions.[15] In this context, after C–H functionalization, the transformation of the directing amido groups into other functional groups such as ketones is imperative.[8c,14b,d,l]

However, due to the higher stability of amides compared to esters, the direct transformation of common tertiary amides **5** into ketones by addition of organometallic reagents is more challenging.[16] As a result, although much efforts have been devoted,[7c,17–22] very few examples are reliable for common amides[23] and have found synthetic applications.[24] For example, while the methods based on the addition of RLi are reliable for chelating alkoxy/amino amides[18] and benzamides,[17c] low yields were obtained from aliphatic amides.[17c,f] In addition, for sterically hindered *N*,*N*-diethyl and *N*,*N*-diisopropyl aromatic amides, the most useful directing groups for the directed lithiation,[14] those methods are not efficient due to the competing metalation.[14b,24c,25] Other methods are either restricted to *N*,*N*-dimethylamides and cyclic amine-based amides[21] or limited to the synthesis of methyl ketones.[22] Strangely, Collins' high-yielding method,[20] featuring the use of both alkyl and aryl lanthanum triflates, has only one unsuccessful application[24c] since its publication in 1987. Moreover, while the addition of Grignard reagents to *N*,*N*-dimethylamides has been reported,[17f] no synthetic application can be found, and the reactions failed with *N*,*N*-diethylamides.[14d] Thus, reliable and general methods for the direct transformation of common tertiary amides into ketones by addition of Grignard reagents[26] are highly demanding. As a continuation of our efforts in developing C–C bond-forming methods from amides,[10b,c,27] we report herein a versatile and direct synthesis of ketones from common tertiary amides by addition of Grignard reagents. The application of this deaminative alkylation reaction for the deacylation of amides to give free amines is also demonstrated.

2. Results and discussion

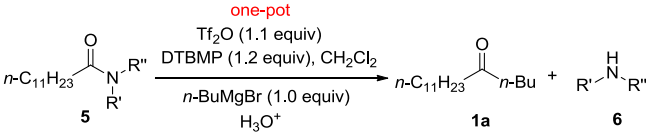
Our approach is based on the tactic of *in situ* activation of "inert" amide to form a highly reactive intermediate. In this context, triflic anhydride (Tf_2O)[28] has been shown to be an advantageous activating reagent allowing the Vilsmeier-Haack-Arnold-type formylation[29a] and isobutanoylation[29b] of soft or stabilized nucleophiles.[29c–f] Our previous work has demonstrated a good compatibility of Tf_2O-based tertiary amide activating system with reactive organometallic reagents.[27] Thus, according to Scheme 2, an amide **A**, when treated with Tf_2O and DTBMP,[28c] will generate the highly electrophilic *O*-triflyl imidate **B**, which can react readily with a Grignard reagent to give *N*,*O*-acetal **C**. The latter can eliminate $^-$OTf to generate iminium ion intermediate **D**. The subsequent acidic hydrolysis of **D** will release ketone **1** and amine **6**. Among the three possible intermediates **B**, **C**, and **D**, imidoyl triflate **B** is the most reactive, which lays the foundation of a chemoselective and controlled reaction. Noteworthy is that the keteniminium intermediate **E** could also be generated from the intermediate **B** as demonstrated by the Ghosez [2+2] keteniminium-olefin cycloaddition reaction.[30] Thus milder conditions should be used to avoid its formation.

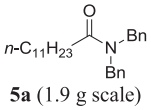
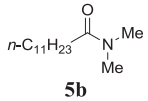
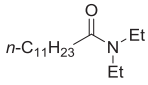
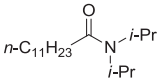
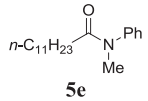
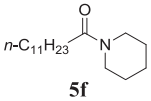
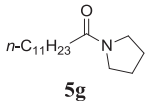
On the basis of these precedents and considerations, we set out to explore the deaminative alkylation of common tertiary amides with Grignard reagents. At the outset of our investigation, the reaction of *n*-butyl Grignard reagent with amide **5a** was selected as a prototype reaction, and the optimal reaction conditions were defined as: treatment of amide **5a** (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (1.2 equiv) in dichloromethane with Tf_2O (1.1 equiv) at −78 to 0 °C (2 h), followed by addition of *n*-BuMgBr (1.0 equiv) at −78 °C and stirred for 2 h (−78 to 0 °C). The mixture was warmed up and subjected to acidic hydrolysis to give ketone **1a** in 89% yield (Table 1, entry 1). Notably, the reaction could



Scheme 2. Strategy for the direct transformation of amides into ketones and amines under mild conditions.

Table 1
Effects of *N*-substituents on the deaminative alkylation of tertiary amides



Entry	Amide	Product (% Yield)[a]
1	 **5a** (1.9 g scale)	**1a** (89) **6a** (86) (R′=R″=Bn)
2	 **5b**	73
3	 **5c**	69
4	 **5d**	53
5	 **5e**	80
6	 **5f**	72
7	 **5g**	70

[a] Isolated yield.