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New, General, and Practical Preparation of Methyl Ketones via the Direct Coupling of Amides with CH_2Cl_2 Promoted by $TiCl_4$/Mg

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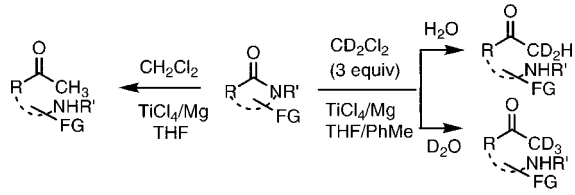
ABSTRACT



The direct coupling of a variety of amides with CH_2Cl_2 or CD_2Cl_2 promoted by $TiCl_4$/Mg/THF provides an extremely simple, practical, selective, and efficient approach for the construction of methyl ketones. The efficiency and practicability of this chemistry is illustrated by the very simple synthesis of deuterated methyl ketones.

The importance of methyl ketones as building blocks for further structural elaboration and the ease of access to carboxylic acid derivatives make the conversion of the latter into the former a useful transformation.[1] Interest in the direct elaboration of carboxylic acid derivatives into methyl ketones continues to generate many exciting organometallic complexes such as Me_3Al/$MeNHCH_2CH_2NHMe$,[2] MeLi,[3] MeMgBr,[4a] MeMgBr/$(Me_2NCH_2CH_2)_2O$,[4b] R_3SnCH_2Li,[5] and Me_2CuLi.[6] However, the direct acylation of methyl-metal reagents is often complicated by accompanying overaddition, leading to the formation of tertiary alcohols, and suffers from one or more experimental drawbacks such as use of expensive or potentially unstable reagents, delicate reaction conditions, and complicated procedures. In searching for a new and practical strategy based upon the concept of simple carbonyl-methylenation,[7,8] we turned our attention to the methylenation of amides since the resultant enamines would be expected to react with water quite readily to give methyl ketones (Scheme 1). Our development of a CH_2Cl_2−$TiCl_4$−Mg system for carbonyl-methylenation led to our consideration of such a system for this process.[8] Effecting such methylenations by use of a highly nucleophilic methylene equivalent derived from the CH_2Cl_2−$TiCl_4$−Mg system may have the advantage of (1) enhancing synthetic

(1) For the acylation of organometallic reagents with carboxylic acid derivatives to form ketones, see:

(2) (a) O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 397−458. (b) Chung, E.-A.; Cho, C.-W.; Ahn, K. H. *J. Org. Chem.* **1998**, *63*, 7590.

(3) (a) Rubottom, G. M.; Kim, C.-W. *J. Org. Chem.* **1983**, *48*, 1550. (b) Cooke, M. P., Jr. *J. Org. Chem.* **1986**, *51*, 951. (c) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.

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(6) (a) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. (b) Fex, T.; Froborg, J.; Magnusson, G.; Thoren, S. *J. Org. Chem.* **1976**, *41*, 3518.

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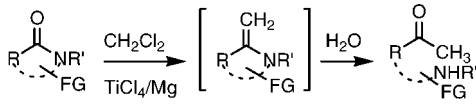
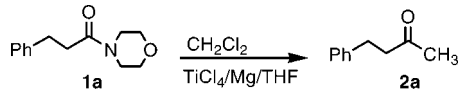
Scheme 1. Synthesis of Methyl Ketones via Direct



efficiency by not requiring expensive or potentially unstable reagents and (2) extending the preparation to deuterated methyl ketones via Ti−Mg-promoted CD_2-transfer reactions of CD_2Cl_2. We wish to report that such a $TiCl_4$/Mg-promoted coupling process may provide a new, general, and practical approach for the construction of methyl ketones, α,α-dideuteriomethyl ketones, and α,α,α-trideuteriomethyl ketones.

Table 1. Reaction Conditions for Elaboration of Morpholine-Derived Amide **1a** into Methyl Ketone **2a**



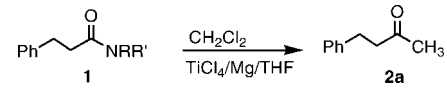
entry	reaction temp (°C)	$TiCl_4$/Mg[a] (equiv)	yield (%) of **2a**[b]
1	0	1/4	15
2	25	1/4	14
3	0	1/8	75
4	0	2/8	80
5	0	1.2/8	82
6	0	1.5/8	85
7	0	5/30[c]	83

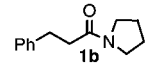
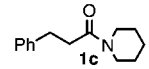
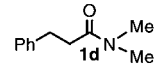
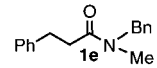
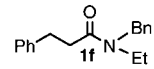
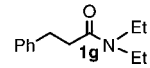
[a] The reaction was performed on a 1 mmol scale using 2 mL of THF. [b] Isolated yield. [c] 5 mmol scale.

The reaction of a simple morpholine amide **1a** with CH_2Cl_2 was chosen to test the feasibility of the process (Table 1). After treatment of **1a** with CH_2Cl_2, magnesium powder (4 equiv) and $TiCl_4$ (1 equiv) at 0 °C for 1 h followed by quenching with aqueous K_2CO_3, the desired methyl ketone **2a**[9] was indeed produced but only in less than 15% completion after 1 h (entry 1), with starting material remaining. Running the reaction at 25 °C failed to improve the conversion (entry 2). As shown in Table 1, increasing the amount of Mg and $TiCl_4$ dramatically improved the methyl ketone formation; the yield varying from 75% to 85% (entries 3−6). More gratifyingly, the reaction directly scales up; thus, **2a** was obtained in 83% yield on a 5-mmol scale using a 5 equiv of $TiCl_4$ and 30 equiv of Mg (entry 7). Adopting as a standard protocol exposure of a mixture of **1a** (1 equiv) and THF in CH_2Cl_2 to Mg (8 equiv) and $TiCl_4$ (1.5 equiv) in CH_2Cl_2 at 0 °C followed by treatment with aqueous K_2CO_3 produced an 85% isolated yield of the desired adduct **2a**.

With conditions established to give excellent yield, we explored the effect of the alkyl groups on nitrogen (Table 2). Methylenation onto the pyrrolidine amide **1b** was equally effective (entry 1). Using the piperidine-derived amide **1c** also gave satisfactory results with CH_2Cl_2−Mg−$TiCl_4$−THF (entry 2). Switching from the heterocyclic amine-derived amide to the acyclic amine-derived analogue **1d** or **1e** led to equally gratifying results (entries 3 and 4) with formation of methyl ketone **2a**. In the case of sterically more bulky amides **1f** and **1g**, applying the standard reaction conditions led to coupling adduct **2a** in less than 20% yield. Interestingly, increasing the amount of THF dramatically improved the methyl ketone formation, leading to smooth coupling to give the desired ketone **2a** in good yields (Table 2, entries 5 and 6).

Table 2. Results and Conditions of the Coupling of Various Amine-Derived Cinnamamides with $TiCl_4$−Mg-CH_2Cl_2



entry	substrate	$TiCl_4$:Mg (mmol)[a] CH_2Cl_2/THF (mL)	yield[b] (%)
1	 **1b**	1.5:8 5/2	85
2	 **1c**	1.5:8 5/2	83
3	 **1d**	1.5:8 5/2	82
4	 **1e**	1.5:8 5/2	78
5	 **1f**	1.5:8 3/8	80
6	 **1g**	1.5:8 3/12	78

[a] The reaction was performed on a 1 mmol scale. [b] Isolated yield.

Extension of these observations to other amides confirms their generality. Variation of acyl structure was briefly explored. Elaboration of the less reactive aromatic amide **3** into methyl ketone was equally effective (Table 3, entry 1). Under the above conditions, Mg−$TiCl_4$-promoted coupling of **3** with CH_2Cl_2 gave acetophenone[3a,10a] in 71% yield. More delightfully, this highly nucleophilic system also reacted efficiently with either sterically demanding amide **4** or cyclic amide **5**. Thus, when 3:12 CH_2Cl_2/THF was used, either **4** or **5** reacted efficiently with CH_2Cl_2−Mg−$TiCl_4$ to afford the desired cyclohexyl methyl ketone[4a,10b] (75% yield) and aminoheptanone **5a**[10c] (82% yield), respectively (entries 2 and 3). To further demonstrate the scope of this methyl ketone-forming methodology, the utility of this protocol was

(9) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.

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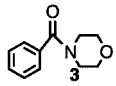
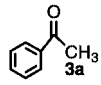
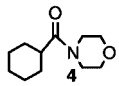
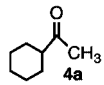
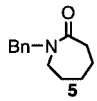
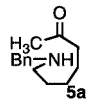
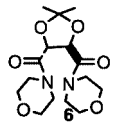
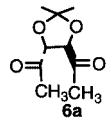
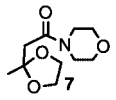
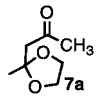
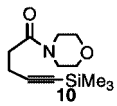
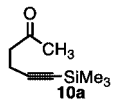
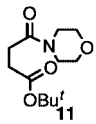
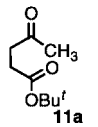
Table 3. $TiCl_4$−Mg-CH_2Cl_2 System for Elaboration of Various Amides into Methyl Ketones

entry	substrate	CH_2Cl_2/THF (mL)[a]	product	yield (%)[b]
1	 **3**	5/2	 **3a**	71
2	 **4**	3/12	 **4a**	75
3	 **5**	3/12	 **5a**	82
4	 **6**	5/2[c]	 **6a**	81
5	 **7**	5/2	 **7a**	79
6	 **8**	5/2	 **8a**	82
7	 **9**	5/2	 **9a**	80
8	 **10**	5/2	 **10a**	76
9	 **11**	5/2	 **11a**	82

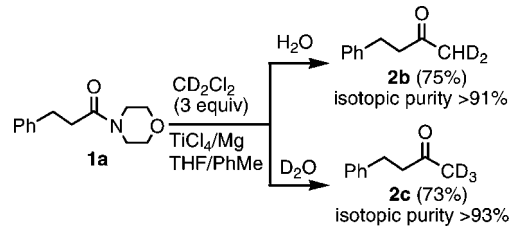
[a] Coupling reaction was performed on a 1 mmol scale using 1.5 mmol of $TiCl_4$ and 8 mmol of Mg. [b] Isolated yield. [c] Coupling reaction was performed with 0.5 mmol of substrate.

examined in the elaboration of chiral diamide **6** into diketone. Reacting tartaric acid-derived diamide **6** with CH_2Cl_2−Mg−$TiCl_4$ complex proceeded smoothly, resulting in a 81% yield of the desired diketone[6a11] without danger of racemizations (entry 4).

The chemoselectivity was explored with a series of amides as summarized in Table 3, entries 5−9. As expected, acetal, sulfide, alkene, and alkyne have no effect (entries 5−8). A particularly interesting example illustrating the chemoselectivity of this process is the coupling of dicarbonyl compound **11** with CH_2Cl_2. Surprisingly, CH_2Cl_2−Mg−$TiCl_4$ system can discriminate between carbamoyl and *t*ert-butoxycarbonyl

(11) Prasad, K.; Chandrakumar, A. *Synthesis* **2006**, 2159.
(12) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912.

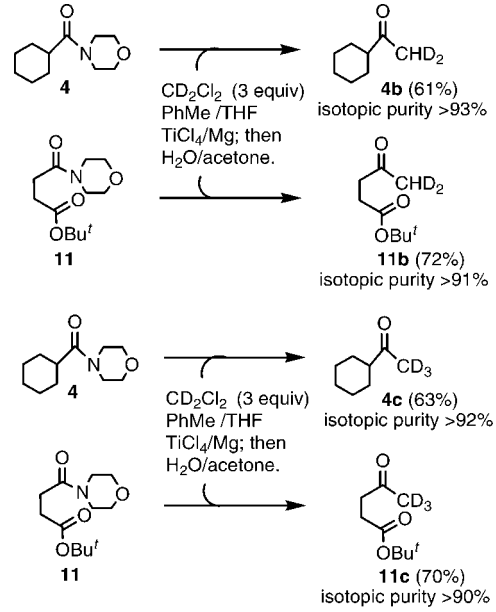
Scheme 2. Conversion of Amides into Deuterated Methyl Ketone



group in **11**, effecting selective elaboration of the less electrophilic carbamoyl group into acetyl group (entry 9). Thus, exposing morpholine amide **11** to 1.5 equiv of $TiCl_4$ and 8 equiv of Mg produced the keto ester **11a**[12] in 82% isolated yield.

The widespread utility of deuterium-labeled compounds in research[13,14] make their easy availability by synthesis important. To further demonstrate the synthetic utility of this protocol, a synthesis of deuterated methyl ketones **2b**,**c** was carried out (Scheme 2).

Scheme 3. Synthesis of Dideuteriomethyl and Trideuteriomethyl Ketones via Coupling of Amides with CD_2Cl_2



Performing the Ti−Mg-promoted CD_2-transfer reaction of CD_2Cl_2 in toluene to maintain homogeneity allowed the use of 3 equiv of CD_2Cl_2. Thus, direct coupling of amide **1a** with CD_2Cl_2 at 0 °C followed by the normal hydrolysis with

(13) For reviews, see:(a) Junk, T.; Catallo, W. J. *Chem. Soc. Rev.* **1997**, *26*, 401. (b) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S.; Koike, Y *Chem. Soc. Rev.* **2000**, *29*, 239.
(14) (a) Lienhard, G. E.; Wang, T.-C *J. Am. Chem. Soc.* **1969**, *91*, 1146. (b) Furuta, T.; Takahashi, H.; Kasuya, Y *J. Am. Chem. Soc.* **1990**, *112*, 3633. (c) Gardner, K. H.; Kay, L. E. *J. Am. Chem. Soc.* **1997**, *119*, 7599.

H_2O produced a 75% yield of a mixture of α,α-dideuterio ketone,[2b] monodeuterio ketone, and **2a** in a 91.2:8.3:0.5 ratio as determined by ^1H NMR spectroscopy. Similarly, quenching the coupling adducts with D_2O afforded a 74% yield of a >93:7 ratio of α,α,α-trideuterio ketone **2c** to α,α-dideuterio ketone **2b**. Scheme 3 provides further examples of the selective elaboration of amides **4** and **11** into dideuteriomethyl ketones and trideuteriomethyl ketones.

(15) The following procedure for the synthesis of 4-phenyl-2-butanone **2a** is illustrative. To a 0 °C suspension consisting of Mg (192 mg, 8 mmol) and $TiCl_4$ (1.5 mmol, 1 M in CH_2Cl_2, 1.5 mL) in CH_2Cl_2 (4 mL) was added over a 2 min period a solution of amide **1a** (219 mg, 1 mmol) in CH_2Cl_2 (5 mL) and THF (2 mL). After being stirred for 1 min at 0 °C, the resulting green-black mixture was stirred for an additional 1 h at 0 °C. Saturated potassium carbonate solution (10 mL) was added, and the mixture was diluted with CH_2Cl_2 (25 mL). The organic layer was separated, dried, evaporated, and purified by flash chromatography on silica gel (elution with 1:15 ethyl acetate−hexane) to give **2a** (126 mg, 85% yield) as a colorless oil. See the Supporting Information for characterization. In the case of aromatic amide **3**, treatment under the above conditions gives the desired acetophenone **3a** as well as the intermediate enamine (olefinic signals at δ 4.31 and 4.17). For **3**, a standard operating procedure which involved adding H_2O or potassium carbonate solution to the green-black mixture followed by stirring at 0−25 °C for 2−3 h was adopted.

This $TiCl_4$/Mg-promoted coupling of amides with CH_2Cl_2 or CD_2Cl_2 represents an extremely practical, and general approach for the construction of methyl ketones.[15] Not only is this titanium methylene complex highly nucleophilic, but it also seems highly selective and might become a practical methylenation reagent applicable to large-scale synthesis. The efficiency and practicability of this chemistry is illustrated by the very simple synthesis of deuterated methyl ketone. The novel nucleophilicity involved suggested several intriguing directions which are currently under active investigation.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support.

Supporting Information Available: Experimental procedures and spectral data, including copies of ^1H and ^{13}C NMR spectra for **2b**,**c**, **4b**,**c**, and **11b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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