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A New Entry to 1,5-Keto Esters and Their 4,4-Dideuterio Derivatives via Methylene Chloride as "Methylene Dianion" Equivalents

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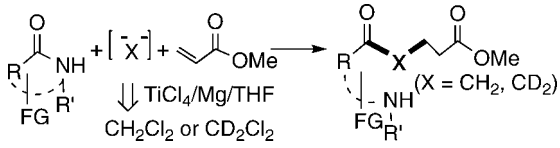


This $TiCl_4-Mg$ promoted multicomponent coupling of various amides with CH_2Cl_2 and methyl acrylate represents an extremely simple and practical synthesis of 1,5-keto esters. The efficiency of this chemistry is illustrated by the very simple preparation of unusual 4,4-dideuterio-1,5-keto esters.

The importance of 1,5-keto esters in and of themselves and as building blocks for further structural elaboration make their availability important. Michael addition of electron-rich alkenes such as metal enolates,[1] enamines,[2] trimethylsily enol ethers/$TiCl_4$,[3] and stannyl ketone enolates/Bu_4NBr[4] to α,β-unsaturated carbonyls constitutes one of the most useful methods for construction of 1,5-dicarbonyl compounds under mild conditions. The major shortcoming of this transformation lies in the preparation or isolation of the ketone- or ester-derived nucleophilic species. In searching for new strategies based upon the concept of multicomponent addition, we turned our attention to the one-pot joining reaction of amides, CH_2Cl_2, and methyl acrylate promoted by $TiCl_4-Mg$ bimetallic species, wherein the titanium−methylene complex[5,6] serves as a synthetic equivalent to methylene dianion as illustrated in Scheme 1. The indication that such a one-pot joining process may occur came as a result of our probing the mechanism of the amide-cyclopropanation promoted by the titanium−methylene complex derived from the $TiCl_4-Mg-CH_2Cl_2$ system,[6a] wherein the intermediate enamine generated in situ can undergo subsequent coupling with methyl acrylate. Herein we wish to record protocols whereby such a novel multicomponent coupling promoted by $TiCl_4-Mg$ can be directed to form either 1,5-keto esters or unusual deuterated keto esters.

SCHEME 1. Retrosynthesis of 1,5-Keto Esters

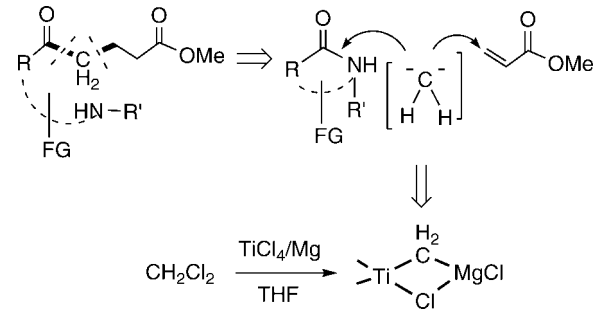
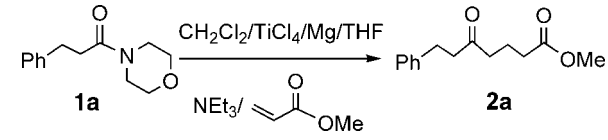


TABLE 1. Reaction Conditions for a Multicomponent Coupling of Amide 1a with CH_2Cl_2 and Methyl Acrylate



entry	rxn. temp (°C)	time (h)	$TiCl_4$/Mg[a] (equiv)	NEt_3 (equiv)	yield (%) of **2a**[b]
1	0	3	1.5/8	0	∼15
2	25	12	1.5/8	0	∼15
3	0	3	1.5/8	3	75
4	25	3	1.5/8	3	74
5	0	3	1.5/8	6	74
6	0	3	2.0/8	3	71
7	0	3	6/35[c]	10	73

[a] The reaction was performed on a 1-mmol scale with 2 mL of THF and 2−3 equiv of methyl acrylate. [b] Isolated yield. [c] 5-mmol scale.

The multicomponent coupling of a simple morpholine amide **1a** with CH_2Cl_2 and methyl acrylate was chosen to test the feasibility of the process (Table 1). Exposing **1a** to magnesium powder (8 equiv, ca. 50 mesh) and $TiCl_4$ (1.5 equiv) in CH_2Cl_2/

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(3) (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.

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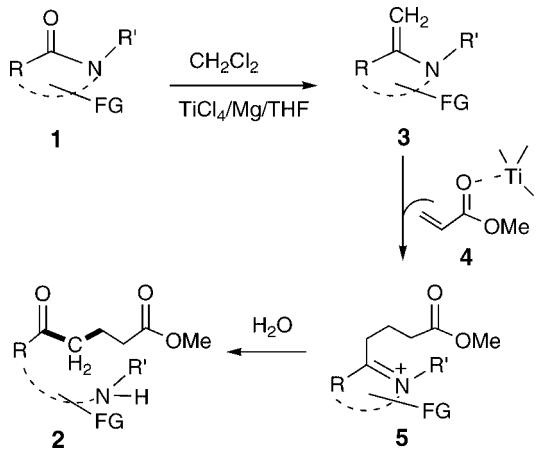
SCHEME 2. Multicomponent Coupling of Amides with CH_2Cl_2 and Methyl Acrylate



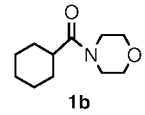
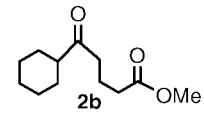
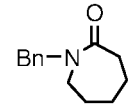
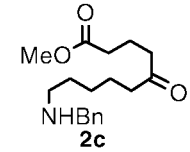
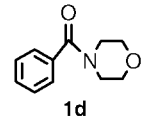
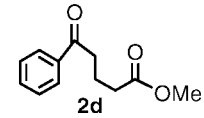
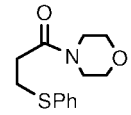
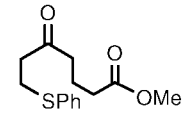
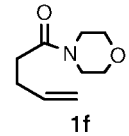
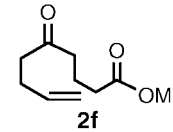
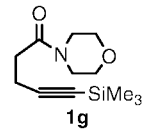
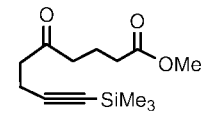
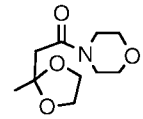
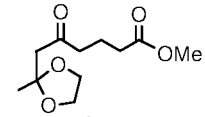
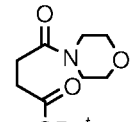
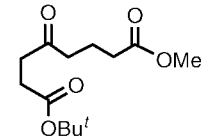
THF at 0 °C for 3 h followed by adding methyl acrylate (2−3 equiv) did indeed produce the desired coupling adduct **2a**[7] but only in less than 15% yield (entry 1), with the remainder largely being methyl ketone derived from methylenation of amide **1a**. Performing the reaction at 25 °C for 12 h failed to improve the yield (entry 2). Remarkably, simply adding a small amount of NEt_3 (~3 equiv) to the original system at 0 °C led to smooth coupling to give a 75% yield of the desired keto ester **2a** (entry 3).[2b,c] Running the reaction at room temperature or increasing the amount of NEt_3 or $TiCl_4$ did not prove beneficial (entries 4−6). Notably, the reaction directly scales up (entry 7); thus, adduct **2a** was obtained in 73% yield on a 5-mmol scale with use of 6 equiv of $TiCl_4$, 35 equiv of Mg, and 12 equiv of methyl acrylate.

The reaction is best envisioned as involving interception of the enamine **3** formed via an amide-methylenation by a presumed electrophilic titanium−acrylate complex **4** to give an alkylated iminium ion **5** (Scheme 2). In contrast to the thermal conjugate-addition of enamine with acrylate, which requires high temperature (refluxing in ethanol, dioxane, acetonitrile, or DMF),[2a] this $TiCl_4$−Mg-promoted mild coupling represents an attractive alternative.

With conditions established to give high yields, we explored the effect of amide structure (Table 2). Applying the standard reaction condition to sterically more bulky cyclohexanecarbonylmorpholine **1b** or cyclic amide **1c** led to coupling adduct in only ~20% yield. Interestingly, increasing the amount of THF dramatically enhances the multicomponent coupling. Thus, using a 3:12 CH_2Cl_2:THF mixture as solvent led to equally gratifying results with formation of keto ester **2b**[8] (72%) and **2c** (60%) (entries 1 and 2). Changing the amide to aromatic amide **1d** also led to smooth coupling to afford the desired keto ester **2d**[9a] (entry 3).

The reaction exhibits good chemoselectivity. As expected, acetal, sulfide, alkene, and alkyne have no effect (entries 4−7). Remarkably, the CH_2Cl_2−Mg−$TiCl_4$ system can also discriminate between carbamoyl and the *tert*-butoxycarbonyl group in a dicarbonyl compound, effecting selective elaboration of the less sterically hindered amide into 1,5-keto ester. Thus, exposing carbamoylester **1i** to 1.5 equiv of $TiCl_4$ and 8 equiv of Mg produced the keto ester **2i** in 68% isolated yield (entry 8).[10]

TABLE 2. Multicomponent Coupling of Amides with CH_2Cl_2 and Methyl Acrylate[a,b,c]

entry	substrate	$TiCl_4$: Mg	product	yield (%)[b]
1[c]	 **1b**	1.5 : 8	 **2b**	74[c]
2	 **1c**	1.5 : 8	 **2c**	60[c]
3[c]	 **1d**	1.5 : 8	 **2d**	61
4	 **1e**	1.5 : 8	 **2e**	65
5	 **1f**	1.5 : 8	 **2f**	71
6	 **1g**	1.5 : 8	 **2g**	64
7	 **1h**	1.5 : 8	 **2h**	56
8	 **1i**	1.5 : 8	 **2i**	68

[a] Reactions were run on a 1-mmol scale with 2 mL of THF and 2−3 equiv of methyl acrylate in CH_2Cl_2 (5 mL)/THF (2 mL) at 0−25 °C unless noted otherwise. [b] Isolated yield. [c] Reactions were run in CH_2Cl_2 (3 mL)/THF (12 mL).

This $TiCl_4$−Mg-promoted multicomponent coupling opens a convenient entry into the deuterium-labeled compounds, which serve as a major avenue to probing the course of the reaction.[11,12] To further demonstrate the efficiency and practicability of this chemistry, a very simple synthesis of

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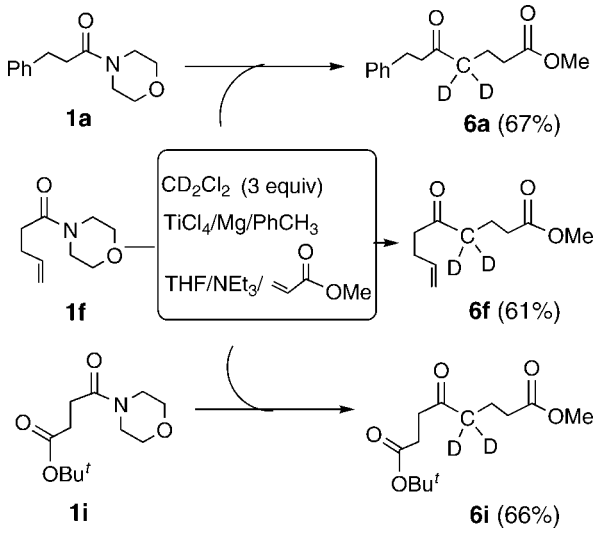
(8) Babudri, F.; Finadanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513.
(9) (a) Jo, E.-A.; Jun, C.-H. *Eur. J. Org. Chem.* **2006**, *11*, 2504. (b) Compound **2f** was previously prepared by a different route: Paul, M.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047–1051.
(10) All new compounds have been satisfactorily characterized spectroscopically.

SCHEME 3. One-Step Conversion of Amides into 4,4-Dideuterio-1,5-keto Esters



unusual deuterated keto esters was carried out (Scheme 3). Thus, reacting amides **1a** and **1f** with CD_2Cl_2 under the same conditions but replacing dichloromethane with toluene led to smooth coupling to give the desired 4,4-dideuterioketo esters **6a** (67%) and **6f** (61%), respectively. Analysis by ^{1}H NMR indicated that about 10% of unlabeled keto ester was present. Notably, performing the multicomponent coupling in toluene to maintain homogeneity allowed the use of 3 equiv of CD_2Cl_2. A dramatic illustration of the utility of this protocol was the elaboration of amide **1i** into the unusual 4,4-dideuterioketo diester **6i** (66%) (contaminated by less than 5% of unlabeled keto ester).

This $TiCl_4$−Mg-promoted multicomponent coupling of various amides with CH_2Cl_2 and acrylate represents an extremely simple and practical synthesis of 1,5-keto esters. The efficiency of this chemistry is illustrated by the very simple preparation of unusual deuterated 1,5-keto esters.

Experimental Section

General Procedure for $TiCl_4$−Mg-Promoted Multicomponent Coupling of Amides with CH_2Cl_2 and Methyl Acrylate with 2a as an Example. Methyl 5-Oxo-7-phenylheptanoate, 2a. 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 the solution was stirred for 1 h at 0 °C, NEt_3 (0.4 mL) was added and stirring continued for 30 min.. The green-black mixture was quenched with methyl acrylate (0.2 mL, 3 mmol) and stirred for an additional 2 h at 0−25 °C. Saturated potassium carbonate solution (10 mL) was added and the mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was separated, dried, evaporated, and purified by flash chromatography on silica gel (elution with 1:10 ethyl acetate−hexane, R_f 0.3) to give **2a** (176 mg, 75% yield) as a colorless oil: IR (neat) 3062, 2951, 1736, 1706, 1600, 1499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.09 (m, 5 H), 3.58 (s, 3 H), 2.82 (t, J = 7.6 Hz, 2 H), 2.65 (t, J = 7.6 Hz, 2 H), 2.38 (t, J = 7.2 Hz, 2 H), 2.26 (t, J = 7.2 Hz, 2 H), 1.80 (tt, J = 7.2 Hz, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 173.5, 141.0, 128.4, 128.3, 126.1, 51.5, 44.2, 41.7, 33.0, 29.7, 18.8; high-resolution MS (EI) *m/e* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1258.

General Procedure for the One-Step Conversion of Amides into 4,4-Dideuterio-1,5-keto Esters with 6a as an Example. Methyl 4,4-Dideuterio-5-oxo-7-phenylheptanoate, 6a. To a 0 °C suspension consisting of Mg (192 mg, 8 mmol) and $TiCl_4$ (1.5 mmol, 1 M in toluene, 1.5 mL) was added over a 2-min period a solution of amide **1a** (219 mg, 1 mmol) in $PhCH_3$ (2 mL), CD_2Cl_2 (0.3 mL), and THF (2 mL). After the solution was stirred for 1 h at 0 °C, NEt_3 (0.4 mL) was added and stirring continued for 30 min. The green-black mixture was quenched with methyl acrylate (0.2 mL, 3 mmol) and stirred for an additional 2 h at 0−25 °C. Saturated potassium carbonate solution (10 mL) was added and the mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was separated, dried, evaporated, and purified by flash chromatography on silica gel (elution with 1:10 ethyl acetate−hexane, R_f 0.3) to give **6a** (158 mg, 67% yield) as a colorless oil: IR (neat) 3062, 2951, 1734, 1702, 1599, 1497 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.14 (m, 5 H), 3.64 (s, 3 H), 2.87 (t, J = 7.6 Hz, 2 H), 2.71 (t, J = 7.6 Hz, 2 H), 2.41 (t, J = 7.2 Hz, ∼0.24 H), 2.29 (t, J = 7.2 Hz, 2 H), 1.85 (t, J = 7.2 Hz, ∼1.95 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 173.4, 140.9, 128.4, 128.2, 126.0, 51.4, 44.1, 41.3 (quintet, J = 19.1 Hz), 32.8, 29.6, 18.6; high-resolution MS (EI) *m/e* calcd for $C_{14}H_{16}D_2O_3$ 236.1381, found 236.1384.

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 ^{1}H and ^{13}C NMR spectra for **2c**, **2e**, **2g**, **2h**, **2i**, **6a**, **6f**, and **6i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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