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Dichloromethane as an Unusual Methylene Equivalent. A New Entry of Highly Nucleophilic and Selective Titanium−Methylene Complexes for Ester Methylenation

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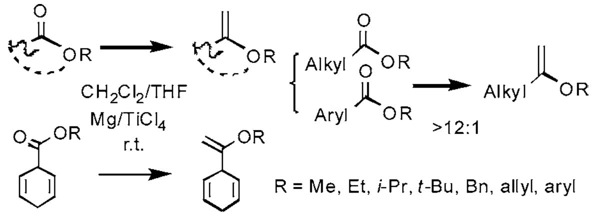
ABSTRACT



The successful application of CH_2Cl_2–Mg–$TiCl_4$-system mediated methylenation of various esters such as *tert*-butyl ester and 2,5-cyclohexadiene-1-carboxylate highlights the extraordinary reactivity, selectivity, and the nonbasic nature of this new methylene–carbenoid, which serves as a practical reagent applicable to large-scale synthesis.

Tebbe-type carbene complexes such as $Cp_2TiCl_2-AlMe_3$,[1] Cp_2TiMe_2,[2] and $TiCl_2-CH_2(ZnI)_2-TMEDA$[3] have been reported to effect methylenation of esters. However, their generation suffers from one or more experimental drawbacks, such as use of expensive or potentially unstable reagents, delicate reaction conditions, and complicated procedures. Therefore, the search for a new entry of titanium methylene complexes, which are highly nucleophilic and available in bulk at a low price, continues to stimulate much thought from a synthetic point of view.[4] Both CH_2Br_2- and CH_2I_2-Zn (cat. lead)$-TiCl_4$ systems have participated in normal methylenation of ketones or aldehydes; however, these processes do not generally extend to esters even in the presence of TMEDA.[3,4a,b,5] The reasons stem from the low nucleophilic nature of the systems. Believing an inorganic Grignard reagent[6] might be more reactive than a titanium−zinc bimetallic species, we turned to $Mg-TiCl_4$ bimetallic complex (intermetallic) promoted methylene-transfer process. Earlier work in our laboratories established that methylenation of sterically hindered ketones such as 2,2-dimethylcy-

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[1] (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahier, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (c) Cannizzo, L. F.; Grubs, R. H. *J. Org. Chem.* **1985**, *50*, 2316. (d) Pine, S. H.; Petti, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

[2] Petasis, N. A.; Bzoweej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

[3] Matsubara, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* **1999**, 825.

[4] For some examples of alkylidenation of ester carbonyl groups, see: (a) Clift, S. M.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 8300. (b) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410. (c) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668. For some examples of ester-methylenation using the Takai protocol, see: Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, 2919. Postema, M. H. D.; Piper, J. L. *Org. Lett.* **2003**, 1721. (d) Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.

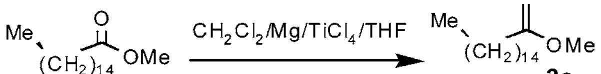
[5] For some other examples of ketone methylenation promoted by metals such as Mo and B, see: (a) Kauffmann, T.; Ennen, B.; Sander, J.; Wieschollek, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 244. (b) Pelter, A.; Singaram, B.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 635.

10.1021/ol047887e CCC: $27.50

clohexanone and fenchone was possible with the CH_2Cl_2–Mg–$TiCl_4$–THF system.[7] We envisioned the feasibility of a direct coupling of esters with CH_2Cl_2 promoted by Mg–Ti–intermetallic. In this paper, we report the critical role that the amount of magnesium relative to titanium chloride plays in enhancing the activity of titanium methylene complexes and the success of this goal which resulted in a practical and selective approach to vinyl ethers.

Initial studies centered on a simple methyl ester **1a** (Table 1). When **1a** and CH_2Cl_2 were treated with magnesium powder (4 equiv) and $TiCl_4$ (1 equiv) at 0–25 °C, **2a** was indeed produced but only in less than 10% conversion after 1 h (entry 1).

Table 1. Reaction Conditions for Methylenation of Ester **1a**

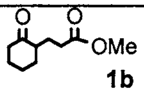
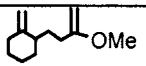
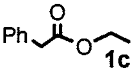
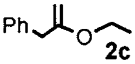
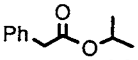
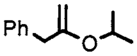
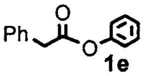
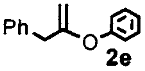
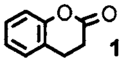
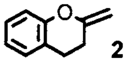
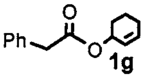
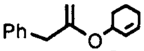
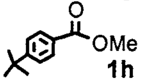
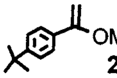
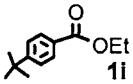
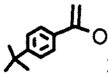
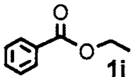
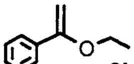
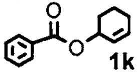
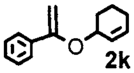
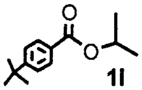
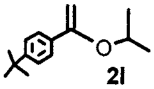
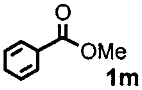
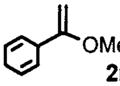
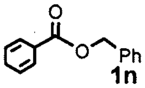
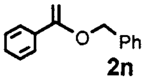
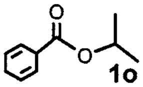
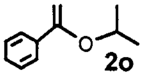
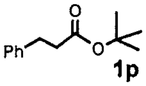
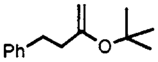


1a **2a**

entry	reaction temp (°C)	$TiCl_4$/Mg (equiv)	isolated yield (%)	
			1a	**2a**
1	0–25	1:4	91	~9
2	25	1:4	78	22
3	0–25	1:6	84	16
4	25	1:6	65	35
5	0–25	1:8	63	37
6	25	1:8	15	85
7	25	2:6	51	49
8	25	2:8	0	94

As the data in Table 1 show, performing the reaction at 25 °C showed more conversion of **1a** to **2a** (entries 1–2, 3–4, and 5–6). Most revealing was the effect of the amount of Mg relative to titanium chloride on this process. Increasing the amount of Mg dramatically improved the vinyl ether formation, the yield varying from 22% to 85% (entries 2 and6). Adopting as a standard ptotocol exposure of a mixture of **1a** (1 equiv) and THF in CH_2Cl_2 to Mg (8 equiv) and $TiCl_4$ (2 equiv) in CH_2Cl_2 at 25 °C, followed by treatment with aqueous K_2CO_3, produced a 94% isolated yield of the desired vinyl ether **2a** (entry 8). The methyl keto ester **1b** gave an analogous result. Use of a 2:8 $TiCl_4$/Mg ratio effects complete methylenation of both ketone and ester carbonyl groups as illustrated in entry 2 wherein the olefin **2b** was obtained in 92% yield (Table 2, entry 1). Variation of alkoxy size was briefly explored. Methylenation onto the ethyl ester **1c** was equally effective (entry 2). Notably, the isopropyl substrate **1d** also gave satisfactory results with CH_2Cl_2–Mg–$TiCl_4$–THF (entry 3). Switching the ester from alkyl to phenyl had little effect (entry 4). The methylenation product **2e** was obtained in 90% yield. Methylenation with dihydrocoumarin **1f** (entry 5) under the standard conditions gave a 40% yield of methylenechroman **2f** in addition to two internal alkenes derived from isomerization of **1f**.[8] Using a 1:1 toluene/THF mixture as solvent, isomerization of *exo*-methylene vinyl ether **2f** was suppressed and **2f** was isolated

Table 2. Methylenation of Esters with CH_2Cl_2/$TiCl_4$/Mg/THF

Entry	Ester Compound.	$TiCl_4$/Mg (equiv)	Methylene Product	Yield[a] %
1	 **1b**	2 : 8	 **2b**	92
2	 **1c**	2 : 8	 **2c**	90
3	 **1d**	2 : 8	 **2d**	91
4	 **1e**	2 : 8	 **2e**	90
5	 **1f**	2 : 8	 **2f**	40[b] 82[c]
6	 **1g**	2 : 8	 **2g**	75
7	 **1h**	2 : 8	 **2h**	70[d]
8	 **1i**	2 : 8	 **2i**	85
9	 **1j** (10 mmol)	15 : 60[e]	 **2j**	87
10	 **1k**	2 : 8	 **2k**	78
11	 **1l**	2 : 8 1.2 : 8	 **2l**	10 66
12	 **1m**	2 : 8	 **2m**	88
13	 **1n**	2 : 8	 **2n**	90
14	 **1o**	2 : 8	 **2o**	87
15	 **1p**	2 : 8 1 : 12~16	 **2p**	0 50[f]

[a] Isolated yield. [b] Plus ~45% olefin isomerization products derived from **2f**. [c] Yield obtained by performing reaction in toluene/THF. [d] Plus ~20% hydrolysis product derived from **2h**. [e] 10 mmol scale. [f] Plus recovered starting ester **1o** (40%) and 4-phenyl-2-butanone (10%) derived from hydrolysis of **2o**.

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(6) For some examples of novel inorganic Grignard reagents, see: (a) Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones S. Liao, D. J.; Michalowicz, A.; Roziere, J.; Schott, A. *J. Organomet. Chem.* **1993**, *459*, 87. (b) Kornowski, A.; Giersig, M.; Vogel, R.; Chemseddine, A.; Weller, H. *Adv. Matter*. **1993**, *5*, 634. (c) Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. J. *J. Org. Chem.* **1982**, *47*, 248. (d) Sobota, P.; Jezowska-Trzebiatowska, B. *Coord. Chem. Rev.* **1978**, *26*, 71.

(7) Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004**, *6*, 4961.

(8) In the case of benzyl formate as substrate, the desired benzyl viny ether was found to be admixed with significant amounts (>75%) of benzyl alcohol derived from viny ether hydrolysis.

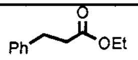
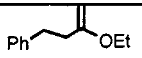
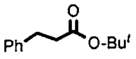
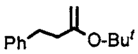
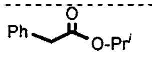
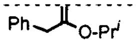
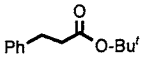
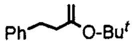
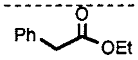
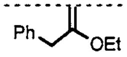
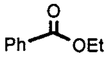
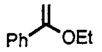
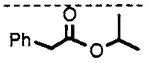
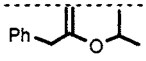
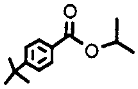
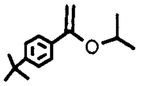
in 82% yield. The utility of allyl vinyl ethers as easy precursors of γ,δ-unsaturated carbonyl compounds led to our examination of 2-cyclohexenyl ester **1g** (entry 6), which participated equally well, giving the desired allyl vinyl ether **2g** in 75% yield. With an eye to extending these observations to other less reactive carboxylic esters, we explored the methylenation of aromatic ester with CH_2Cl_2. Fortunately, exposing methyl *p*-*tert*-butylbenzoate **1h** (entry 7) to the CH_2Cl_2−Mg−$TiCl_4$−THF system led to smooth methylenation to give the desired vinyl ether **2h** in 70% isolated yield.

Methylenation onto ethyl benzoate was equally effective (entry 8). The methylenation product **2i** was obtained in 85% yield. More gratifyingly, the reaction directly scales up; thus, ethyl vinyl ether **2j** (entry 9) was obtained in 87% yield on a 10-mmol scale using a 15 equiv of $TiCl_4$ and 60 equiv of Mg. Notably, decreasimg the amount of Mg led to incomplete methylenation of **1j**—presumably the collapse of titanium−methylene complex to its precursor is competitive with its methylene transfer to the ester carbonyl group. On the other hand, using the 2-cyclohexenyl benzoate **1k** also gave satisfactory results (entry 10) wherein the allyl vinyl ether **2k** was obtained in 78% yield. Surprisingly, applying the standard reaction condition to sterically more bulky isopropyl benzoate **1l** led to methylenation product in only 10% yield (entry 11). Interestingly, decreasing the amount of $TiCl_4$ to 1.2 equiv significantly increased the yield to 66%.

A dramatic illustration of the utility of this protocol was the methylenation of 2,5-cyclohexadiene-1-carboxylate **1m** (entry 12), which by virtue of the sensitivity of the polyunsaturation within a small molecular framework demands very mild methods. Most delightfully, performing the methylenation at ambient temperature led to complete consumption of starting material within 2 h to give the desired vinyl ether **2m** in excellent yield. None of the olefin isomerization product could be detected by 400 MHz ^1H NMR. Changing the ester to benzyl ester **1n** or isopropyl ester **1o** led to equally gratifying result (entries 13 and 14) with formation of vinyl ethers **2n** and **2o**.[9] The ability to effect such a methylenation even in the presence of an active methine hydrogen highlights the nonbasic nature of this new titanium methylene complex. On the other hand, steric hindrance does play a role. Thus, *tert*-butyl ester **1p** fails to react under the standard conditions. Remarkably, increasing the amount of Mg by going from 8 to 12 equiv dramatically enhances the nucleophilicity of this new titanium methylene complex. Thus, using a 1:12 $TiCl_4$/Mg ratio proves most satisfactory, giving a 50% yield of vinyl ether **2p** (entry 15) with starting material remaining (82% yield based upon recovered starting material). It should be noted that there is an optimum equiv of Mg above which no further improvement pertains. While further mechanistic work is clearly required, such steric factors may provide good chemoselectivity with diesters.

The chemoselectivity was briefly explored with a series of esters as summarized in Table 3. As expected, exposure of a mixture of ethyl ester **1q** and *tert*-butyl ester **1p** to a 1 equiv of $TiCl_4$ and 8 equiv of Mg in CH_2Cl_2/THF produced exclusively the ethyl vinyl ether **2q** (Table 3, entry 1). The isopropyl substrate gave an analogous result in the presence of *tert*-butyl ester, as in the methylenation of a mixture of **1d** and **1p** (entry 2). A particularly interesting example illustrating the chemoselectivity of this process is the methylenation of a mixture of aliphatic and aromatic esters (entries 3 and 4). The preference (>12:1) for methylenation of an aliphatic ester highlihgts the chemoselectivity of the process.

Table 3. Selectivity in CH_2Cl_2−$TiCl_4$−Mg System Mediated Methylenation of Diesters at 0−25 °C

Entry	Ester Mixture		$TiCl_4$/Mg	Products		yield (%)[a]
1		**1q**	1 : 8		**1q**	96
		**1p**			**1p**	0
2		**1d**	1 : 8		**2d**	89
		**1p**			**2p**	<5
3		**1c**	1 : 8		**2c**	86
		**1j**			**2j**	~7
4		**1d**	1 : 8		**2d**	84
		**1l**			**2l**	<5

[a] Isolated yields; ratios determined by 400 MHz ^1H NMR.

The successful application of the Mg−$TiCl_4$-promoted CH_2 transfer to a variety of ester carbonyl groups illustrates the extraordinary reactivity of this new titanium methylene complex. Not only is this CH_2Cl_2−Mg−$TiCl_4$ system highly nucleophilic but it also seems highly selective and might become a practical methylenation reagent applicable to large-scale synthesis. This method constitutes the first report that CH_2Cl_2 can be directed to serve as a highly nucleophilic methylene equivalent in methylenation of esters. 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 spectra data for **2b**,**e**−**g**,**k**,**n**,**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] New compounds have been characterized spectroscopically.