Methylenation of Esters with Bis(iodozincio)methane-$TiCl_2$-TMEDA System

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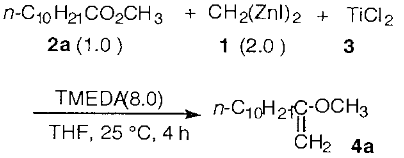
Methylenation of ester carbonyl group with bis(iodozincio)-methane was examined: a use of $TiCl_2$ and amine as mediators facilitated the reaction to give vinyl ethers in good yields.

Methylenation of carbonyl group of esters are still challenging problem. Although the methylenation of ketones or aldehydes has been performed by many types of reagents, such as Wittig-type reagents,[1] *gem*-dimetallic reagents,[2] and nucleophilic metallocarbenes,[3] only a few reagents were effective for methylenation of esters:[4] Tebbe reagent and titanocene methylidene complex showed high performance for the methylenation of esters. Some other titanium mediated reagents offered a useful alkylidenation of esters, but did not work well for methylenation of esters.[5] Recently, we showed an effective preparation of bis(iodozincio)methane (1)[6] and its use for methylenation of aldehydes and ketones under the mediation with $TiCl_2$.[6] We considered a modification of this reaction system would be appliable for a methylenation of esters as a novel method. This paper discloses a novel method for the effective methylenation of ester carbonyl group.

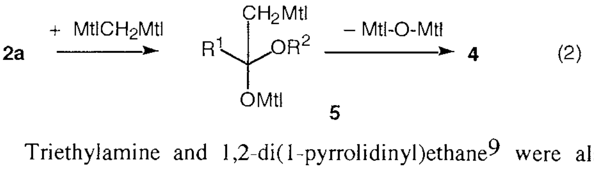
In previous paper,[5a] alkylidenation of ester was performed by Zn–$RCHBr_2$–$TiCl_4$–TMEDA system. Analogously, a reagent consist of **1**–$TiCl_2$–TMEDA was examined for the methylenation of methyl *n*-undecanoate (**2a**) as shown in eq 1. The reaction condition using 2.0 eq of **1**, 4.0 eq of $TiCl_2$, and 8.0 eq of TMEDA to ester, gave the best result. The detailed procedure was as follows: To a suspension of $TiCl_2$ (4.0 mmol)[7] in THF (10 ml), **1** (2.0 mmol, 0.4 M in THF) and TMEDA (8.0 mmol) were added at 25 °C. The mixture was stirred for 3 min and become a deep reddish brown solution. A solution of **2a** in THF (1.0 ml) was added and the whole was stirred for 4 h. The resulting mixture was diluted with ethyl acetate (20 ml) and hexane (20 ml), and passed through a short celite and alumina column (ICN Alumina B, Grade III). Concentration *in vacuo* gave **4a** in 86% yield.[8]



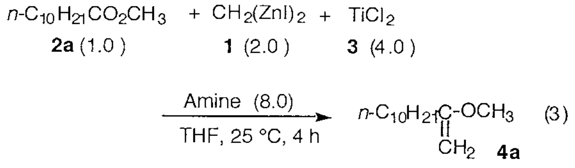
$$\underset{\mathbf{2a}\,(1.0)}{n\text{-}C_{10}H_{21}CO_2CH_3} + \underset{\mathbf{1}\,(2.0)}{CH_2(ZnI)_2} + \underset{\mathbf{3}}{TiCl_2} \xrightarrow[\text{THF, 25 °C, 4 h}]{\text{TMEDA(8.0)}} \underset{\mathbf{4a}}{n\text{-}C_{10}H_{21}\overset{}{C}(=CH_2)\text{-}OCH_3} \qquad (1)$$

$TiCl_2$	**4a**
-	<1%
2.0	54
3.0	85
4.0	86
5.0	73

A reaction of **2a** (1.0 mmol) with **1** (2.0 mmol) and $TiCl_2$ in the absence of TMEDA did not afford **4a**, although the starting material was completely consumed. A treatment of the reaction mixture with 1M HClaq instead of the non-aqueous work-up described above afforded 2-dodecanone in 68% yield. This fact may imply the reaction proceeds stepwise as shown in eq 2. An elimination of metal oxide from the adduct **5** will lead to the formation of **4**. In the absence of TMEDA, the elimination may be slow and a hydrolysis of **5** gave methyl ketone. TMEDA may plays a role for acceleration of the elimination of metal oxide. Although the structural information of the reactive species formed by **1** and $TiCl_2$ has not been clear, we suppose transmetallation from **1** to titanium plays an important role.[6] The possibility of the formation of titanium carbene complex from **1**–$TiCl_2$–TMEDA cannot be denied.



Triethylamine and 1,2-di(1-pyrrolidinyl)ethane[9] were also examined instead of TMEDA. Bidentate amine gave the better result. A reaction of methyl undecanoate **2a** (1.0 mmol) with **1** (2.0 mmol) and $TiCl_2$ (4.0 mmol) resulted in a quantitative recovery of starting material. An addition of amine, however, enforced the methylenation reaction. The amount of $TiCl_2$ was varied to improve the yield of the product as shown in eq 1.

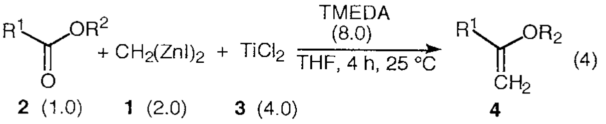


$$\underset{\mathbf{2a}\,(1.0)}{n\text{-}C_{10}H_{21}CO_2CH_3} + \underset{\mathbf{1}\,(2.0)}{CH_2(ZnI)_2} + \underset{\mathbf{3}\,(4.0)}{TiCl_2} \xrightarrow[\text{THF, 25 °C, 4 h}]{\text{Amine (8.0)}} \underset{\mathbf{4a}}{n\text{-}C_{10}H_{21}C(=CH_2)\text{-}OCH_3} \qquad (3)$$

Amine	Yield of **4a**
TMEDA:	86%
Et_3N:	20
1,2-di(1-pyrrolidinyl)ethane:	54

By the procedure described above, various esters were examined for methylenation (Table 1). The reaction proceeded with ethyl, isopropyl, and *t*-butyl alkanoate (entries 1-3). An easily enolizable ester, methyl phenylacetate was also methylenated with the reagent system (entry 6).

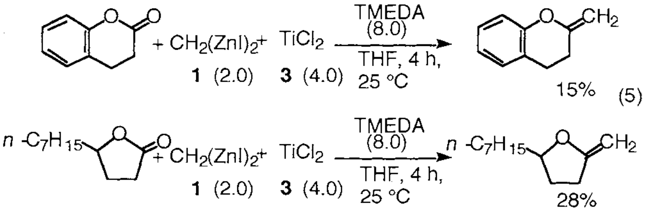
Table 1. Methylenation of carboxylic acid esters



entry	R^1	R^2	$TiCl_2$	4^a
1	n-C_7H_{15}	C_2H_5	4.0	75
2	n-C_9H_{19}	$CH(CH_3)_2$	4.0	90
3	n-C_7H_{15}	$C(CH_3)_3$	4.0	46
4			4.0	34[b]
5	Ph	CH_3	4.0	89
6	$PhCH_2$	CH_3	4.0	51

[a]Isolated yields. [b]The mixture was stirred for 24 h.

The methylenation of lactones were also examined as shown in eq 5. As shown in eq 5, γ- and δ-lactones were able to be transformed into vinyl ether via methylenation; the reaction condition has not been well optimized.



A study for the reactive species which was formed with **1** and $TiCl_2$ in the presence of TMEDA is now under progress.

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8 A use of $TiCl_4$ (4.0 mmol) instead of $TiCl_2$ with **1** (6.0 mmol), and TMEDA (8.0 mmol) gave **4a** in 15% yield. See also Ref 5a.

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