Chem. Pharm. Bull. **61**(8) 870–872 (2013) Vol. 61, No. 8

The Effect of Indium(III) Triflate in Oxone-Mediated Oxidative Methyl Esterification of Aldehydes

Tomoko Mineno,*[,a] Mai Sakai,[a] Akira Ubukata,[a] Kazuhide Nakahara,[a] Hitoshi Yoshimitsu,[b] and Hisao Kansui*[,c]

[a] *Laboratory of Medicinal Chemistry, Faculty of Pharmacy, Takasaki University of Health and Welfare; 60 Nakaorui, Takasaki, Gunma 370–0033, Japan:* [b] *Laboratory of Natural Medicines, Sojo University; and* [c] *Laboratory of Organic Chemistry, Faculty of Pharmaceutical Sciences, Sojo University; 4–22–1 Ikeda, Kumamoto 860–0082, Japan.*

Received January 24, 2013; accepted June 4, 2013

An oxidative methyl esterification of aldehydes was effectively achieved. The trivalent indium reagent, indium(III) triflate, was revealed to accelerate the reactions in many cases. Aromatic aldehydes with various substituents were subjected to this method, and each produced the corresponding methyl esters in good to excellent yields within a relatively short reaction time.

Key words indium(III) triflate; aldehyde; methyl esterification

Methyl esters of carboxylic acids are one of the most fundamental chemical components. Methyl ester moieties are conveniently utilized as masking units for carboxylates, which, when left in their unmasked free carboxylate forms, may exert an untoward influence on molecules upon implementation of the intended chemical reactions. In the field of chemotherapy, methyl esters often serve as a prodrug in order to improve bioavailability. Methyl esters are generally converted to their active acid form in the body *via* the function of esterase.

Generally, methyl esters can be synthesized by the condensation reaction of carboxylic acids with methanol in the presence of an acid or a base, and there are a number of methods available. We previously reported an efficient method of high-yielding methyl esterification that is catalyzed by a trivalent indium reagent under mild reaction conditions.[1)] Likewise, methyl esters can be practically prepared by treating carboxylic acids in methanol that contains a catalytic amount of trimethylsilyl chloride.[2)]

Meanwhile, the direct oxidative methyl esterification of aldehydes has commanded a great deal of interest in the field of organic synthesis. Although a couple of the esterifying transformations of aldehydes using metal-based reagents have been reported, including iridium,[3–5)] rhenium,[6)] ruthenium,[7)] rhodium,[8)] palladium,[9,10)] manganese,[11)] iron,[12)] copper,[13)] tin,[14)] and pyridinium dichromate (PDC),[15,16)] those heavy/transition metal oxidants might not be sufficiently environmentally benign. As a consequence, esterification methodologies employing H_2O_2 and catalytic amounts of metal-based reagents, such as titanosilicate,[17)] vanadium pentoxide,[18,19)] iron salt, and zinc salt,[20,21)] have been introduced. However, in many cases, the reagents are limited by the use of H_2O_2 with the combination of fourth-row transition elements. Thus, it is worthwhile to develop methodologies that incorporate useful and convenient alternatives for the oxidative methyl esterification of aldehydes.

In recent years, we have studied the usage of trivalent indium reagents,[22,23)] as well as indium metal-based reagents,[24–27)] and reported the catalytic application of indium(III) triflate ($In(OTf)_3$) in the one-step chemical transformations. As part of our ongoing investigations, herein we wish to report the details of our study on the efficient oxidative methyl esterification of aldehydes using $In(OTf)_3$. As the effective oxidant, Oxone® monopersulfate compound (Oxone), a triple salt of potassium composed of potassium peroxymonosulfate, which is a versatile oxidant developed by DuPont, was chosen after a couple of tentative experiments.

Initially, we attempted the use of *para*-tolualdehyde as the starting material for the oxidative chemical transformation, after consulting the previously reported reaction conditions[20,21,28)] (Table 1). Initially, H_2O_2 and ^{t}BuOO^{t}Bu were selected as the oxidants, and the reaction mixtures were stirred in the presence of 10 mol % of $In(OTf)_3$ at room temperature for 40 h in MeOH (Table 1, Entries 1 and 2). However, sterile results were obtained since the reaction did not proceed, and instead, most of the starting material of *para*-tolualdehyde was recovered intact. Seeing the inorganic oxidant in the next vision, Oxone was subsequently tested for its reaction in the presence of 10 mol % of $In(OTf)_3$, as well as other trivalent indium reagents, such as $InCl_3$ and $InBr_3$ (Table 1, Entries 3–5). Surprisingly, despite the identical reaction conditions, at room temperature and for the elongated reaction time of 3 d, only the entry of 10 mol % of $In(OTf)_3$ produced encouraging results in a 52% yield (Table 1, Entry 5). The result prompted us to search for more suitable reaction conditions. The reaction was dramatically improved when the temperature was increased to reflux, and the reaction time was also considerably shortened to a 3 h time of completion (Table 1, Entry 6). For the assurance, the reaction was carried out with 5 mol % of $In(OTf)_3$, which furnished only a 32% yield (Table 1, Entry 7). The reaction was also confirmed using 10 mol % of $Zn(OTf)_2$ and $Mg(OTf)_2$, and the result was moderately diminished yields in both cases (Table 1, Entries 8 and 9). The blank experiment without Lewis acid was then followed, which yielded 56% at reflux and 55% at room temperature based on our reaction method and isolating procedure (Table 1, Entries 10 and 11).

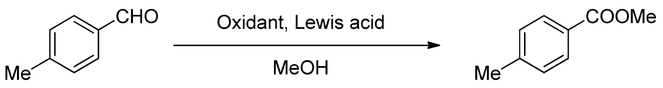
With the optimized reaction conditions in hand, various aromatic aldehydes were subjected to this method of oxidative methyl esterification. Table 2 shows that the reaction proceeded to give the corresponding methyl esters in good to excellent yields. In particular, the entry of the aromatic

---

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: mineno@takasaki-u.ac.jp; kansui@ph.sojo-u.ac.jp

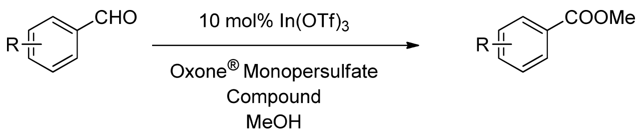
Table 1. Reactions of Several Oxidants in the Search for Optimal Conditions

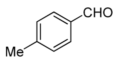
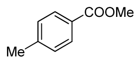
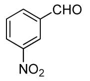
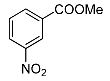
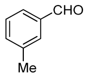
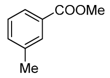
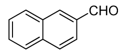
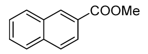
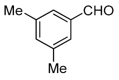
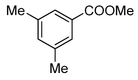
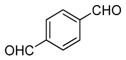
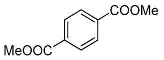
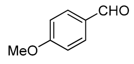
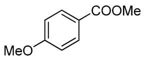
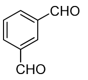
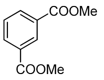
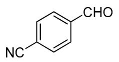
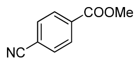
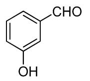
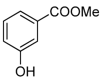
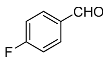
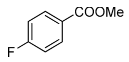
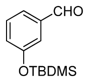
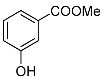
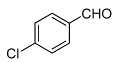
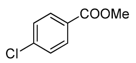
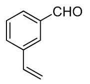
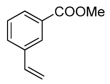
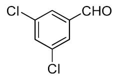
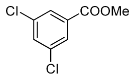
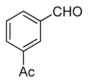
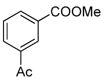
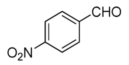
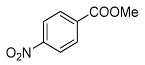
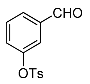
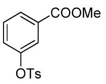


Entry	Oxidant	Oxidant amount	Lewis acid	Lewis acid amount	Temp.	Time	Yield[a] (%)
1	H_2O_2	4.0 eq	$In(OTf)_3$	10 mol %	r.t.	40 h	Trace[b]
2	$^tBuOO^tBu$	1.2 eq	$In(OTf)_3$	10 mol %	r.t.	40 h	N.R.[b]
3	Oxone	1.0 eq	$InCl_3$	10 mol %	r.t.	3 d	Trace[b]
4	Oxone	1.0 eq	$InBr_3$	10 mol %	r.t.	3 d	Trace[b]
5	Oxone	1.0 eq	$In(OTf)_3$	10 mol %	r.t.	3 d	52
6	Oxone	1.0 eq	$In(OTf)_3$	10 mol %	Reflux	3 h	82
7	Oxone	1.0 eq	$In(OTf)_3$	5 mol %	Reflux	3 h	32
8	Oxone	1.0 eq	$Zn(OTf)_2$	10 mol %	Reflux	4 h	74
9	Oxone	1.0 eq	$Mg(OTf)_2$	10 mol %	Reflux	4 h	58
10	Oxone	1.0 eq	None	—	Reflux	3 h	56
11	Oxone	1.0 eq	None	—	r.t.	3 d	55

a) Isolated yields. *b*) Most of the starting material was recovered intact.

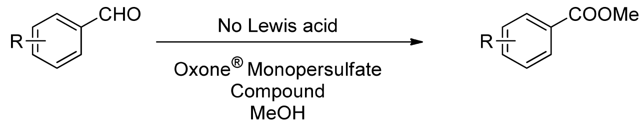
Table 2. Reactions Using Optimized Conditions[a]

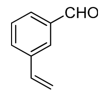
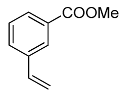
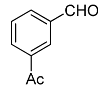
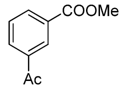
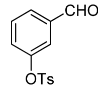
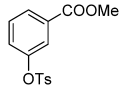


Entry	Starting substrate	Product	Time (h)	Yield[b] (%)	Entry	Starting substrate	Product	Time (h)	Yield[b] (%)
1			3	82	10			3	70
2			3	79	11			1	81
3			3	89	12			1.5	55
4			3	82	13			1.5	92
5			5	94	14			2	91
6			3	80	15			2	88
7			3	73	16			3	74
8			2.5	78	17			3	53
9			3	70	18			3	80

a) All the reactions were conducted at reflux using 1.0 eq of Oxone and 10 mol % of $In(OTf)_3$ in MeOH. *b*) Isolated yields.

Table 3. Reactions without Lewis Acid[a]



Entry	Starting substrate	Product	Time (h)	Yield[b] (%)
1			5	50
2			7	51
3			3	89

a) All the reactions were conducted at reflux using 1.0 eq of Oxone without Lewis acid in MeOH. *b*) Isolated yields.

aldehyde with electron-donating methoxy group smoothly furnished the desired product in a good yield (Table 2, Entry 4). Although the cyano derivative required a 5 h reaction time, the resultant yield was very high at 94% (Table 2, Entry 5). Among the electron-withdrawing substituents, the compounds possessing nitro groups were converted into the corresponding methyl esters with reduced yields (Table 2, Entries 9 and 10). In the case of 2-naphthaldehyde, terephthalaldehyde, and isophthalaldehyde as the starting substrates, the reaction also led to the desired methyl esters in good to acceptable yields (Table 2, Entries 11–13). We then attempted the reactions in order to confirm the tolerance of some of the substituents. Both reactions with vinyl- and acetyl-possessing aromatics furnished moderate yields (Table 2, Entries 16 and 17). As for the protecting groups, the base labile tosyl group (Table 2, Entry 18) was inert and generated a good yield. On the other hand, the acid labile *tert*-butyldimethylsilyl (TBDMS) group was removed giving a free hydroxyl form of the product in an 88% yield (Table 2, Entry 15), which could have been due to the sulfate component of Oxone. Consequently, the blank reaction with substrates having vinyl, acetyl, and tosyl groups was conducted. Although the reaction with vinyl- and acetyl-possessing substrates proceeded in the absence of Lewis acid, the reaction time took longer and the yields became shortened (Table 3, Entries 1 and 2). Compared with the above result in Table 2, it is suggestive that $In(OTf)_3$ as Lewis acid positively promote this esterification. On the other hand, the reaction with tosyl-possessing substrate also gave a good yield even without Lewis acid (Table 3, Entry 3). Therefore, the positively promoting function of Lewis acid can be performed in the substrate-dependent manner.

In summary, an oxidative methyl esterification of aldehydes was effectively achieved. A couple of Lewis acid and oxidant combinations were investigated. The trivalent indium reagent, $In(OTf)_3$, was revealed to accelerate the reactions in many cases. Aromatic aldehydes with various substituents were subjected to this method, and each produced the desired corresponding methyl esters in good to excellent yields within relatively short reaction times. A tolerance of the substituents, such as vinyl, acetyl, and tosyl groups, was also revealed. It is indicated that $In(OTf)_3$ as Lewis acid positively promote this esterification in the substrate-dependent manner. The further investigation on mechanistic insight, as well as the elucidation of the role and scope of Lewis acid, is ongoing.

General Experimental Procedure The starting aldehyde materials (1 mmol) were dissolved in MeOH (5 mL), and Oxone (1 mmol) and 10 mol % of $In(OTf)_3$ were added at room temperature. The reaction mixture was heated at reflux, and was monitored for completion by TLC. After the reaction mixture was filtered, the filtrate was condensed using a rotary evaporator. Flash column chromatography on silica gel furnished the corresponding products, which were confirmed by spectroscopy.

Acknowledgment This study was partially supported by a Grant from the Naito Foundation.

References

1) Mineno T., Kansui H., *Chem. Pharm. Bull.*, **54**, 918–919 (2006).
2) Mineno T., Miller M. J., *J. Org. Chem.*, **68**, 6591–6596 (2003).
3) Yamamoto N., Obora Y., Ishii Y., *J. Org. Chem.*, **76**, 2937–2941 (2011).
4) Kiyooka S., Wada Y., Ueno M., Yokoyama T., Yokoyama R., *Tetrahedron*, **63**, 12695–12701 (2007).
5) Kiyooka S., Ueno M., Ishii E., *Tetrahedron Lett.*, **46**, 4639–4642 (2005).
6) Espenson J. H., Zhu Z., Zauche T. H., *J. Org. Chem.*, **64**, 1191–1196 (1999).
7) Murahashi S., Naota T., Ito K., Maeda Y., Taki H., *J. Org. Chem.*, **52**, 4319–4327 (1987).
8) Grigg R., Mitchell T. R. B., *Tetrahedron*, **37**, 4313–4319 (1981).
9) Lerebours R., Wolf C., *J. Am. Chem. Soc.*, **128**, 13052–13053 (2006).
10) Wei L.-L., Wei L.-M., Pan W.-B., Wu M.-J., *Synlett*, **2004**, 1497–1502 (2004).
11) Sharma R. K., Sharma C., *J. Macromol. Sci.*, *Pure Appl. Chem.*, **48**, 155–163 (2011).
12) Reddy R. S., Rosa J. N., Veiros L. F., Caddick S., Gois P. M. P., *Org. Biomol. Chem.*, **9**, 3126–3129 (2011).
13) Yoo W.-J., Li C.-J., *Tetrahedron Lett.*, **48**, 1033–1035 (2007).
14) Qian G., Zhao R., Ji D., Lu G., Qi Y., Suo J., *Chem. Lett.*, **33**, 834–835 (2004).
15) Garegg P. J., Olsson L., Oscarson S., *J. Org. Chem.*, **60**, 2200–2204 (1995).
16) O'Connor B., Just G., *Tetrahedron Lett.*, **28**, 3235–3236 (1987).
17) Chavan S. P., Dantale S. W., Govande C. A., Venkatraman M. S., Praveen C., *Synlett*, **2002**, 267–268 (2002).
18) Gopinath R., Patel B. K., *Org. Lett.*, **2**, 577–579 (2000).
19) Gopinath R., Barkakaty B., Talukdar B., Patel B. K., *J. Org. Chem.*, **68**, 2944–2947 (2003).
20) Wu X.-F., Darcel C., *Eur. J. Org. Chem.*, **2009**, 1144–1147 (2009).
21) Wu X.-F., *Tetrahedron Lett.*, **53**, 3397–3399 (2012).
22) Mineno T., *Tetrahedron Lett.*, **43**, 7975–7978 (2002).
23) Mineno T., Nikaido N., Kansui H., *Chem. Pharm. Bull.*, **57**, 1167–1170 (2009).
24) Mineno T., Hirayama H., Nakahara K., Yamashita M., Kansui H., Moriwaki H., *Tetrahedron Lett.*, **51**, 6045–6048 (2010).
25) Mineno T., Kansui H., Kunieda T., *Tetrahedron Lett.*, **48**, 5027–5030 (2007).
26) Mineno T., Choi S.-R., Avery M. A., *Synlett*, **2002**, 883–886 (2002).
27) Valluri M., Mineno T., Hindupur R. M., Avery M. A., *Tetrahedron Lett.*, **42**, 7153–7154 (2001).
28) Travis B. R., Sivakumar M., Hollist G. O., Borhan B., *Org. Lett.*, **5**, 1031–1034 (2003).