ORGANIC LETTERS

2012
Vol. 14, No. 22
5788–5791

$InCl_3/Me_3SiCl$-Catalyzed Direct Michael Addition of Enol Acetates to α,β-Unsaturated Ketones

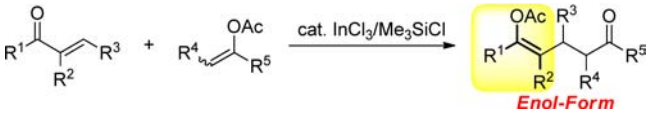
Yoshiharu Onishi, Yuki Yoneda, Yoshihiro Nishimoto, Makoto Yasuda, and Akio Baba*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

baba@chem.eng.osaka-u.ac.jp

Received October 19, 2012

ABSTRACT



The direct Michael addition of enol acetates to α,β-unsaturated ketones was achieved using a combination of Lewis acid catalysts, $InCl_3$ and Me_3SiCl, which furnished stable enol-form products that could be further transformed into functionalized 1,5-diketones by reactions with various electrophiles.

Michael addition of metal enolates to α,β-unsaturated carbonyl compounds is an efficient route to 1,5-dicarbonyl compounds.[1−3] These compounds are obtained after the post-treatment hydrolysis of unstable metal enol-forms of Michael adducts (eq 1, Scheme 1). Despite high potential as a nucleophile, the isolation and utilization of enol-form products have not been sufficiently developed because of instability. Silyl enolate products as Michael adducts have been isolated only by careful treatment[3a,4] and are utilized in total synthesis.[5] Enol acetates are metal-free and stable nucleophiles, which makes them potential reagents, but their direct utilization has been limited to some aldol reactions and oxidative couplings.[6,7] Recently, we have succeeded in the displacement of metal enolates to enol acetates in coupling reactions with either alcohols or their derivatives.[8] Herein, we report Michael additions using enol acetates instead of metal enolates (eq 2, Scheme 1). A catalytic combination of the Lewis acids $InCl_3$ and Me_3SiCl, which specifically activated α,β-unsaturated ketones,

(1) For representative reviews, see: (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. In *Organic Reactions*; Adams, R., Eds.; Wiley: New York, 1959; Vol. 10, pp 179−561. (b) House, H. O. In *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, 1972; pp 595−623.

(2) For pioneering work for the Mukaiyama−Michael reaction, see: (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223–1224. (b) Narasaka, K.; Soai, K.; Aikawa, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779–783.

(3) Selected works of the Mukaiyama−Michael reaction: (a) Wada, M.; Takeichi, E.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 990–994. (b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472–474. (c) Loh, T.-P.; Wei, L.-L. *Tetrahedron* **1998**, *54*, 7615–7624. (d) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178–181. (e) Miura, K.; Nakagawa, T.; Hosomi, A. *Synlett* **2003**, *13*, 2068–2070.

(4) (a) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943–4946. (b) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1986**, 953–956. (c) Inokuchi, T.; Kurokawa, Y.; Kusumoto, M.; Tanigawa, S.; Takagishi, S.; Torii, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3739–3741. (d) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665–4668. (e) Berl, V.; Helmchen, G.; Preston, S. *Tetrahedron Lett.* **1994**, *35*, 233–236.

(5) Selected works: (a) Dratch, S.; Charnikhova, T.; Sarabèr, F. C.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287–4295. (b) Sarabèr, F. C.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; de Groot, A. *Tetrahedron* **2006**, *62*, 1726–1742. (c) Jung, M. E.; Chang, J. J. *Org. Lett.* **2010**, *12*, 2962–2965.

(6) (a) Mukaiyama, T.; Izawa, T.; Saigo, K. *Chem. Lett.* **1974**, 323–326. (b) Masuyama, Y.; Kobayashi, Y.; Yanagi, R.; Kurusu, Y. *Chem. Lett.* **1992**, 2039–2042. (c) Yanagisawa, M.; Shimamura, T.; Iida, D.; Matsuo, J.; Mukaiyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 1838–1840.

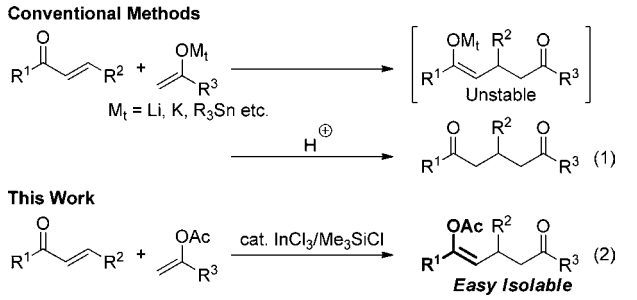
(7) (a) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002–6004. (b) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069–3072.

(8) (a) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9131–9134. (b) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2011**, *13*, 2762–2765. (c) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Chem. Lett.* **2011**, *40*, 1223–1225.

(9) "Indirect" Michael reactions, in which tin enolates derived from enol esters were employed as enol nucleophiles, have been reported; see: (a) Hashimoto, Y.; Sugumi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1695–1698. (b) Yanagisawa, A.; Izumi, Y.; Arai, T. *Chem. Lett.* **2008**, *37*, 1092–1093.

10.1021/ol302888k
Published on Web 11/06/2012

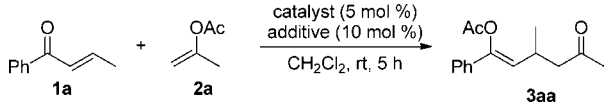
Scheme 1



led to this achievement. To the best of our knowledge, this is the first report of the direct use of enol acetates in Michael additions.[9] In addition, it is noteworthy that Michael adducts were readily isolated as a pure enol-form because they are considerably more stable than the corresponding metal enolates.

First, the screening of Lewis acid catalysts was carried out in the model reaction of (*E*)-1-phenyl-2-buten-1-one (**1a**) with isopropenyl acetate **2a** (Table 1). While neither $InCl_3$ nor Me_3SiCl had catalytic ability, their combination provided the enol-form product **3aa** in a 69% yield (entries 1−3).[8a−c,10] Other combinations using $InBr_3$ or InI_3 also gave a level of yields similar to that of $InCl_3$ (entries 4 and 5). Representative Lewis acids such as $TiCl_4$, $AlCl_3$, and $BF_3{\cdot}OEt_2$ did not promote the desired reaction (entries 6−8), and the result was not improved by a combination with Me_3SiCl (entry 9). $Sc(OTf)_3$ and $BiCl_3$, which are reported to be effective catalysts for Michael additions using silyl enolates,[3a,b] produced only low yields of **3aa** (entries 10 and 11). In toluene, the desired reaction proceeded sufficiently (entry 12), while coordinative solvents considerably deactivated the catalyst, and, in particular, THF completely disturbed the reaction (entries 13 and 14). Five equivalents of **2a** increased the yield of **3aa** to

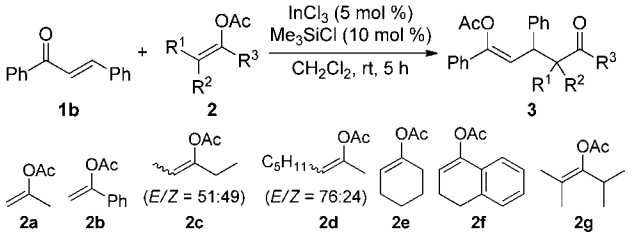
Table 1. Screening of Catalysts[a]



entry	catalyst	additive	yield[b] (%)
1[c]	$InCl_3$		6
2[e]		Me_3SiCl	0
3	$InCl_3$	Me_3SiCl	69
4	$InBr_3$	Me_3SiCl	53
5	InI_3	Me_3SiCl	72
6[e]	$TiCl_4$		0
7[e]	$AlCl_3$		0
8[e]	$BF_3{\cdot}OEt_2$		8
9[e]	$BF_3{\cdot}OEt_2$	Me_3SiCl	0
10[e]	$Sc(OTf)_3$		9
11[e]	$BiCl_3$		0
12[d]	$InCl_3$	Me_3SiCl	62
13[e]	$InCl_3$	Me_3SiCl	48
14[e,f]	$InCl_3$	Me_3SiCl	0
15[g]	$InCl_3$	Me_3SiCl	90

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), catalyst (0.05 mmol), additive (0.1 mmol), CH_2Cl_2 (1 mL), rt, 5 h. [b] Yield by ^1H NMR analysis. [c] **1a** was considerably recovered. [d] Toluene (1 mL) was used instead of CH_2Cl_2. [e] MeCN (1 mL) was used instead of CH_2Cl_2. [f] THF (1 mL) was used instead of CH_2Cl_2. [g] **2a** (5 mmol).

Table 2. Michael Additions of Various Enol Acetates **2** to Chalcone **1b**[a]



entry	2	3	yield/ %[b]
1	**2a**	**3ba**	96 (81)
2	**2b**	**3bb**	90 (78)
3[c]	**2c**	**3bc**	72[d] (41)
4[c]	**2d**	**3bd**	95[e] (66)
5[f]	**2e**	**3be**	50[g] (32)
6	**2f**	**3bf**	76[h] (83)
7	**2g**	**3bg**	0

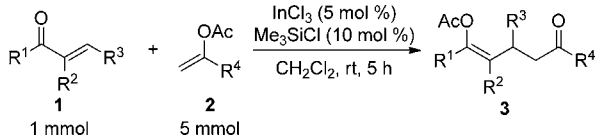
[a] Reaction conditions: **1b** (1 mmol), **2** (1.5 mmol), $InCl_3$ (0.05 mmol), Me_3SiCl (0.1 mmol), CH_2Cl_2 (1 mL), rt, 5 h. [b] Yield by ^1H NMR analysis. Values in parentheses are isolated yields. [c] $InCl_3$ (0.15 mmol), Me_3SiCl (0.3 mmol). [d] dr = 51:49. [e] dr = 65:35. [f] $InCl_3$ (0.1 mmol), Me_3SiCl (0.2 mmol), **2e** (5 mmol). [g] dr = 62:38. [h] dr = 51:49.

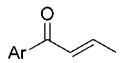
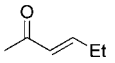
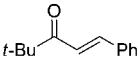
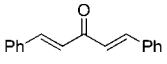
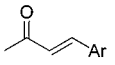
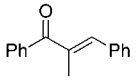
(10) (a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578–1581. (b) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737–1739. (c) Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516–8522. (d) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, *72*, 8588–8590.

(11) Other combinations of indium halides and silyl halides were investigated, and the results are shown in the Supporting Information.

(12) The employment of $InCl_3$ was the combination of choice due to the moisture sensitivity of $InBr_3$ and InI_3.

Table 3. Michael Additions Using Diverse α,β-Unsaturated Ketones[a]



entry	1		2	3	yield/ %[b]
					
1[c]	Ar = 4-MeOC$_6$H$_4$	**1c**	**2a**	**3ca**	61 (33)
2[d]	= 4-ClC$_6$H$_4$	**1d**	**2a**	**3da**	91 (62)
3		**1e**	 **2b**	**3eb**	0
4		**1f**	**2b**	**3fb**	99 (70)
5[e]		**1g**	**2b**	**3gb**	85 (57)
6[e]		**1h**	**2b**	**3hb**	89 (58)
					
7[e]	Ar = C_6H_5	**1i**	**2b**	**3ib**	80[f] (68)
8[g]	= 4-MeC$_6$H$_4$	**1j**	**2b**	**3jb**	94[h] (58)
9	= 4-MeOC$_6$H$_4$	**1k**	**2b**	**3kb**	94[i] (70)
10	= 4-ClC$_6$H$_4$	**1l**	**2b**	**3lb**	90[j] (72)
11[e]		**1 m**	**2b**	**3mb**	15 (12)
12[k]		**1n**	**2b**	**3nb**	56 (32)

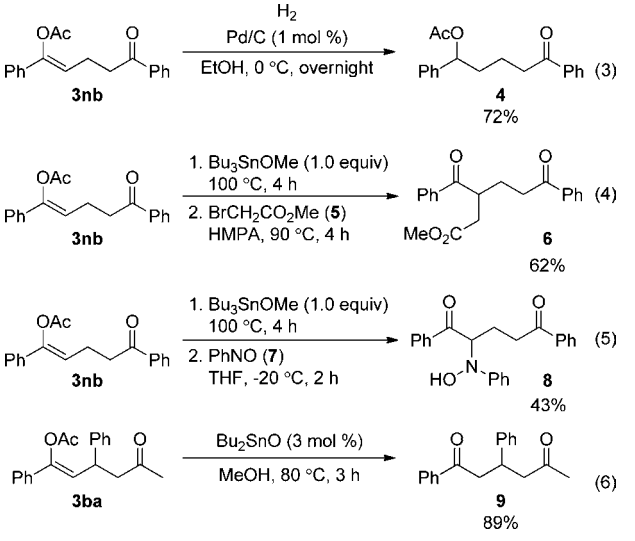
[a] Reaction conditions: **1** (1 mmol), **2** (5 mmol), $InCl_3$ (0.05 mmol), Me_3SiCl (0.1 mmol), CH_2Cl_2 (1 mL), rt, 5 h. [b] Yield by ^1H NMR analysis. Values in parentheses are isolated yields. [c] 0 °C. [d] $InCl_3$ (0.1 mmol), Me_3SiCl (0.2 mmol). [e] **2b** (1.5 mmol). [f] E/Z = 17:83. [g] **2b** (1.5 mmol), $InCl_3$ (0.1 mmol), Me_3SiCl (0.2 mmol). [h] E/Z = 11:89. [i] E/Z = 19:81. [j] E/Z = 15:85. [k] In toluene solvent, careful treatment was required (see the Supporting Information).

90% (entry 15), but we found that the conditions employed in entry 3 were the ones that were practical and optimal.[11,12]

The scope of enol acetates was investigated by reactions using chalcone **1b** (Table 2). Enol acetates **2a** and **2b** were derived from aliphatic and aromatic ketones, respectively, and effectively gave Michael adducts **3** as an enol acetate form (entries 1 and 2). Enol acetates **2c** and **2d**, which bear a substituent at the vinyl terminus, also provided the corresponding products in 72 and 95% yields, respectively (entries 3 and 4). Reactions using cyclohexanone-derived cyclic enol acetate **2e** and α-tetralone-derived **2f** proceeded smoothly to give the desired product in moderate to high yield (entries 5 and 6). Unfortunately, sterically hindered enol acetate **2g** furnished no Michael adduct (entry 7). We confirmed that all of the obtained enol acetates **3** had the *Z*-configuration in their olefin moieties.[13]

Table 3 shows that diverse α,β-unsaturated ketones were applicable to this reaction. (*E*)-1-(4-Methoxyphenyl)-2-buten-1-one (**1c**) gave a lower yield than 4-chlorophenyl-substituted derivative **1d** (entries 1 and 2). These results indicate that the electronic factor on the phenyl ring apparently affects the reactivity of α,β-unsaturated ketones. Acyclic aliphatic unsaturated ketone **1e** gave no adduct, but cyclic **1f** produced the *E*-form of **3fb** in excellent yield (entries 3 and 4). Enol acetate **2b** reacted with *tert*-butyl ketone derivative **1g** to provide Michael adduct **3gb** in an 85% yield (entry 5). In the reaction of dibenzylideneacetone **1h**, the desired product **3hb** was obtained in 89% yield (entry 6). In contrast to entries 1 and 2, benzalacetone **1i** and its analogues **1j**–**l** furnished Michael adducts in high yields, regardless of the electronic factor on the phenyl ring. In addition, mixtures of *E* and *Z* isomers were produced unexpectedly (entries 7–10). The introduction of a methyl group at the vinylic α-position of the carbonyl group dramatically lowered the yield of adduct **3mb** to only 15% (entry 11). The reaction using phenyl vinyl ketone **1n**, which was easily polymerized, was also successful by the following treatment in a toluene solution to give Michael adduct **3nb** in a 56% yield.

Scheme 2. Further Application of Enol-Form Michael Adducts **3**



Synthetic applications of the easily isolated enol form of Michael adducts **3** are shown in Scheme 2. Pd/C-catalyzed

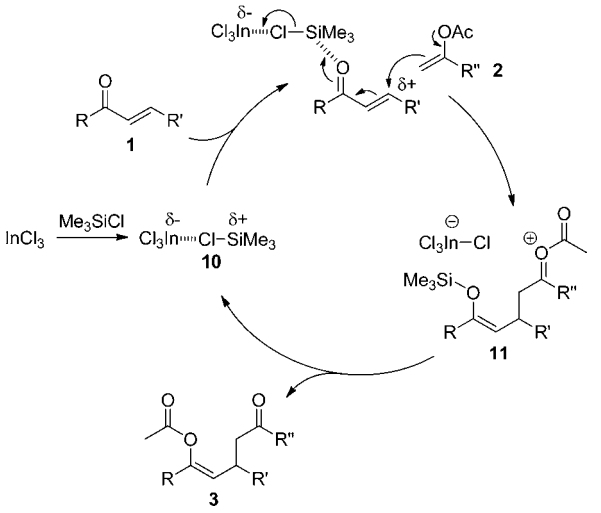


Figure 1. Tentative mechanism.

hydrogenation selectively promoted the C−C double bond reduction to produce alkyl acetate **4** in a 72% yield (eq 3). These results indicate the great advantage of utilizing enol acetates **3**, because the preparation of **4** from the corresponding 1,5-diketone is quite burdensome. The tin enolate generated from Michael adduct **3nb** and Bu_3SnOMe in situ occurred in a successive radical coupling with methyl α-bromoacetate **5** to furnish tricarbonyl compound **6** in a 62% yield (eq 4).[14] A nitroso aldol reaction was also successful to produce α-hydroxyamino ketone **8** in a moderate yield (eq 5).[15] Furthermore, when the 1,5-diketone corresponding to Michel adduct **3** was sought, Bu_2SnO-catalyzed transesterification was effectively employed (eq 6).[16]

Figure 1 shows a plausible reaction mechanism. The Lewis acidity of Me_3SiCl is enhanced by the combination with $InCl_3$, and the silicon center activates enone **1**. Then, the succesive nucleophilic attack of enol acetate **2** forms silyl enolate **11**. Finally, an intramoleculer acyl migration produces the desired adduct **3** along with the regeneration of combined Lewis acid **10**. According to this mechanism, only the *Z*-isomer of **3** may be obtained. But only the reactions using benzalacetone **1i** and its analogues **1j**–**l** (entries 7−10, Table 3) were accompanied by the *E*-isomer as a minor product. The involvement of the *s-trans* form of α,β-unsaturated ketones **1** may give *E*-isomers in the addition step with **2**. It is also conceivable that keto−enol tautomerization of **11** takes place, but as yet there is no proof of that assertion.[17] We confirmed that no tautomerization of obtained *E*-isomer **3ib** took place under the reaction conditions.

In summary, we have achieved the first successful direct Michael addition using enol acetates as enol nucleophiles. The combination of the Lewis acids $InCl_3$ and Me_3SiCl was the turning point in this reaction system. It is noteworthy that Michael adducts can be easily isolated as an enol-form.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (Nos. 24750090, 24350047, and 243500680) and for Scientific Research on Innovative Areas (No. 24106725, "Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances", and No. 23105525, "Molecular Activation Directed toward Straightforward Synthesis") and Challenging Exploratory Research (No. 23655083 and No. 24655030) from the Ministry of Education, Culture, Sports, Science and Technology (Japan). Y.O. thanks JSPS Research Fellowships for Young Scientists.

Supporting Information Available. Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) The geometry of the olefin moiety in enol acetates **3bb**, **3ca**, **3gb**, **3ib**, **3jb**, **3hb**, **3lb**, and **3nb** was assigned as the *Z*-configuration by NOESY.

(14) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591–2594.

(15) Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579–3582.

(16) Poller, R. C.; Retout, S. P. *J. Organomet. Chem.* **1979**, *173*, C7–C8.

(17) To the best of our knowledge, there are no reports for keto−enol tautomerization of silyl enolates.

The authors declare no competing financial interest.