J|A|C|S
COMMUNICATIONS

Published on Web 02/18/2005

A New Synthetic Method for α-Alkoxycarbonyl Iminium Salt and Its Reaction with Nucleophiles

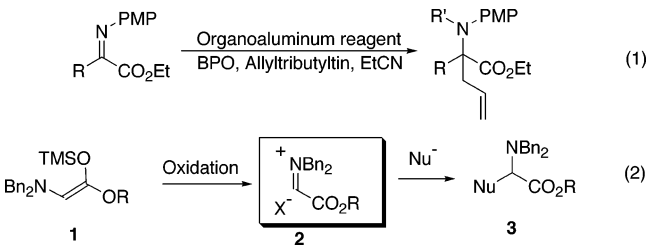
Makoto Shimizu,* Hiroyuki Itou, and Megumi Miura

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Received December 21, 2004; E-mail: mshimizu@chem.mie-u.ac.jp

Iminium salts are very reactive and attractive species in organic synthesis, and therefore, the search for an easy preparation method of these species has received considerable attention.[1] Reported examples using iminium species involve addition of organometallic reagents to the iminium salt for the synthesis of β-amino acids,[2] β-amino ketones, 1,3-amino alcohols,[3] and so on.[4] Use of acyl iminium and related species has been also reported.[5] Control of the reactivity of formaldehyde was successfully accomplished by the use of the Mannich reaction and the Eschenmoser's salt, which have been used extensively for the introduction of an aminomethyl functionality into enolate equivalents.[6]

We have recently reported tandem *N*-alkylation−*C*-allylation reaction of α-imino esters with organoaluminum reagents and allyltributyltin.[7] In this reaction, iminium salts were readily prepared in situ by the oxidation of aluminum enolates, and the subsequent nucleophilic addition proceeded smoothly to afford *N*-alkylation−*C*-allylation products in good yields.[7] During these studies, we focused on the generation of iminium species **2** by oxidizing a readily accessible and stable enol derivative with oxidants. This paper describes a convenient method for the generation of α-alkoxycarbonyl iminium salts **2** from ketene silyl acetals and subsequent reaction with nucleophiles.

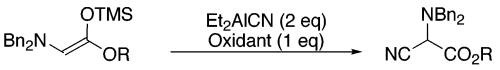


The initial examination into the generation of the iminium salt was carried out using the reaction of amino ketene silyl acetal **1** with oxidizing reagents followed by the reaction with diethylaluminum cyanide, and Table 1 summarizes the results.

As shown in Table 1, among the oxidation reagents used, benzoyl peroxide (BPO), *N*-chlorosuccinimide (NCS), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[8] worked with comparable efficiency in the cases with the methyl derivative **1a**, whereas iodobenzene diacetate and its bis-trifluoroacetate analogue gave slightly decreased amounts of the desired product (entries 1−6). Better yields of the adduct **4** were obtained using the ethyl derivative **1b**, and among the oxidants DDQ recorded good to excellent results (entries 7−10). We next examined the addition of Grignard reagents to the iminium species, and Table 2 summarizes the results.

Under the optimized conditions, we examined the reaction with several Grignard reagents. The reaction was carried out as follows: to a solution of DDQ in DME were added a solution of amino ketene silyl acetal **1b** in CH_2Cl_2 and a solution of Grignard reagent in THF or Et_2O at −50 °C. After the reaction mixture was stirred for 15 h, saturated aqueous $NaHCO_3$ was added. The aliphatic Grignard reagents underwent addition to the iminium salt to give the addition products **5** in moderate to good yields (entries 1−6). The reaction was influenced by the steric bulk of the Grignard reagents, and secondary Grignard reagents depressed the yields (entries 7 and 8). *t*-BuMgBr did not give the addition product; instead, hydrolysis of the ketene silyl acetal occurred to give the parent ester in 36% yield. Functionalized Grignard reagents can also be used for the present reaction. The aromatic Grignard reagents bearing electron-donating and electron-withdrawing groups underwent nucleophilic addition to give the addition products **5** in good

Table 1. Oxidation−Cyanation of Amino Ketene Silyl Acetal **1** under Various Conditions[a]

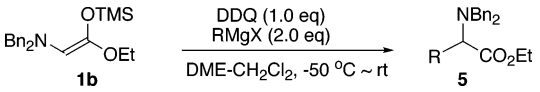


1a: R = Me, **1b:** R = Et

entry	R	solvent	oxidant	temp (°C)	time (h)	4 (%)[b]
1	Me	Et_2O	BPO	−78 to rt	12.0	45
2	Me	DME	BPO	−78 to rt	11.0	36
3	Me	DME	DDQ	−50 to rt	11.0	44
4	Me	DME	NCS	−50 to rt	12.0	44
5	Me	DME	$PhI(OAc)_2$	−78 to rt	11.0	32
6	Me	DME	$PhI(OTFA)_2$	−78 to rt	11.0	35
7	Et	Et_2O	BPO	−78 to rt	12.0	53
8	Et	DME	NCS	−50 to rt	17.5	58
9	Et	DME	DDQ	−50 to rt	11.5	71
10	Et	DME	DDQ[c]	−78 to rt	17.5	80

[a] See typical procedure. [b] Isolated yields. [c] DDQ (0.7 equiv) was used.

Table 2. Oxidation−Alkylation of Amino Ketene Silyl Acetal **1b**[a]

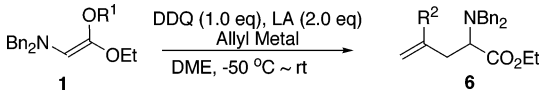


entry	RMgX	product	yield (%)[b]
1	MeMgBr	**5a**	51
2	EtMgBr	**5b**	66
3	EtMgBr[c]	**5b**	69
4	*n*-PrMgBr	**5c**	67
5	$PhCH_2MgCl$	**5d**	51
6	$PhCH_2CH_2MgCl$	**5e**	60
7	*i*-PrMgBr	**5f**	47
8	*cyclo*-Hex	**5g**	24
9	*t*-Bu	**5h**	0
10	Ph	**5i**	70
11	p-$CH_3C_6H_4MgBr$	**5j**	75
12	p-ClC_6H_4MgBr	**5k**	60
13	p-$CH_3OC_6H_4MgBr$	**5l**	68
14	*cyclo*-PrMgBr	**5m**	41
15	$TMSCH_2MgCl$	**5n**	60
16	CH_2═$CHCH_2CH_2MgBr$	**5o**	73
17	p-$CH_3OC_6H_4O(CH_2)_6MgBr$	**5p**	55

[a] See typical procedure. [b] Isolated yields. [c] EtMgBr in DME was used.

10.1021/ja042330f CCC: $30.25

Table 3. Oxidation−Allylation of Amino Ketene Silyl Acetal **1**[a]



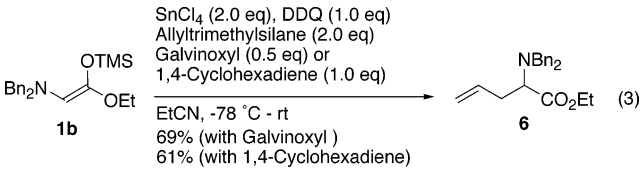
entry	R^1	allyl metal (equiv)	Lewis acid	R^2	time (h)	**6** (%)[b]
1	TMS	(methallyl)$_4$Sn(0.5)	Et_2AlCl	Me	11.5	68
2	TBS	(methallyl)$_4$Sn(0.5)	Et_2AlCl	Me	18.0	72
3	TMS	(allyl)$_4$Sn(0.5)	Et_2AlCl	H	12.0	65
4	TMS	allylSn(^{n}Bu)$_3$(1.0)	Et_2AlCl	H	12.0	69
5	TBS	allylSn(^{n}Bu)$_3$(1.0)	Et_2AlCl	H	18.0	64
6	TBS	allylSiMe$_3$(2.0)	$SnCl_4$[c]	H	18.5	82

[a] See typical procedure. [b] Isolated yields. [c] In EtCN.

yields (entries 11−13). Cyclopropylmagnesium bromide and trimethylsilylmethyl-magnesium bromide gave the addition products **5** in moderate to good yields (entries 14 and 15). Grignard reagents bearing an olefin or an ether group were also employable (entries 16 and 17). It should be noted that products arising from the addition of Grignard reagents to DDQ were not obtained in every case. For further elaboration of these species, we next examined use of allylation reagents. Table 3 summarizes the results.

Tetraallyl- and tetramethallyltin reagents effected allylation reaction to give the adducts in moderate yields (entries 1−3), while allyltributyltin could also be used with comparable efficiency under the influence of diethylaluminum chloride as a Lewis acid (entries 4 and 5). Regarding the substituents at the silicon atom, TMS and TBS derivatives recorded essentially the same range of product yields. A better result was obtained using allyltrimethylsilane, and in this case the reaction of the TBS derivative in propionitrile in the presence of tin(IV) chloride was proved to be superior (entry 6).

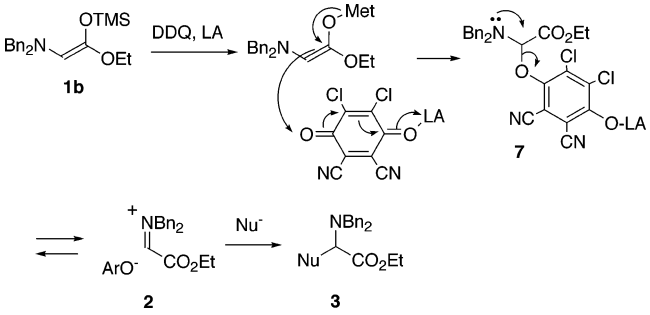
Close examination of the ^{1}H and ^{13}C NMR spectra of the reaction mixture revealed a possible formation of the iminium species **2**. Upon treatment of the ketene silyl acetal **1b** with DDQ in CD_3CN at −40 °C and gradual warming of the mixture to room temperature during 12 h, new signals appeared at 9.27 and 193.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, which actually indicated the formation of the iminium species **2** (see Supporting Information).[9] Furthermore, to check a possibility of the involvement of a radical mechanism, the reaction was carried out in the presence of galvinoxyl or 1,4-cyclohexadiene as a radical scavenger (eq 3). However, the yields did not considerably decrease, indicating that an ionic mechanism might be involved.



(3)

On the basis of these results, a possible mechanism of the present iminium formation and nucleophilic addition reaction is shown in Scheme 3. First, DDQ reacts with the ketene silyl acetal **1b** to give the *N*,*O*-acetal **7**, which collapses to the iminium salt **2**. The subsequent nucleophilic attack gives an addition product **3**.[10]

Scheme 1. A Possible Mechanism of Nucleophilic Addition to the Iminiumu Salt Prepared from Amino Ketene Silyl Acetal



In conclusion, we found that the iminium salt was easily prepared using the oxidation of amino ketene silyl acetal with DDQ, and that subsequent nucleophilic addition to this iminium species proceeded efficiently to afford the amino esters in good yields.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture, and Technology, Japan.

Supporting Information Available: Experimental procedures and product characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Isolation of iminium salts. See for example: Schroth, W.; Jahn, U.; Andersch, J. *Synthesis* **1997**, 573.
(2) (a) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627. (b) Mooiweer, H. H.; Roots, E. C.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6769.
(3) Okuda, M.; Hioki, H.; Miyagi, W.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 6131.
(4) (a) Yoshida, J.; Suga, S.; Okajima, M. *Tetrahedron Lett.* **2001**, *42*, 2173. (b) Yoshida, J.; Suga, S.; Watanabe, M. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (c) Knochel, P.; Millot, N.; Piazza, C.; Avolio, S. *Synthesis* **2000**, 941. (d) Bieber, L. W.; Estevam, I. H. S. *Tetrahedron Lett.* **2003**, *44*, 667. (e) Suginoue, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* **2004**, *6*, 1167. (f) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (g) Suginome, M.; Uehlin, L.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 13196.
(5) (a) Quintard, J. P.; Chevallier, F.; Beaudet, I.; Grignec, F. L.; Toupet, L. *Tetrahedron Lett.* **2004**, *45*, 761. (b) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1994**, *59*, 3530. (c) Fisher, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (d) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. (e) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 1413.
(6) See for example, Yun, H. *Synlett* **2004**, 1321 and references therein.
(7) (a) Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720. See, for related reactions: (b) Niwa, Y.; Takayama, K.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1819. (c) Niwa, Y.; Takayama, K.; Shimizu, M. *Tetrahedron Lett.* **2001**, *42*, 5473.
(8) Oxidation of alkyl benzyl ethers with DDQ was recently used for the C−C bond formation. See: Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523.
(9) For the ^{1}H and ^{13}C NMR spectra of iminium salts, see ref 4g and earlier references therein.
(10) It was reported that the reaction of *O*-trimethylsilyl imidate with DDQ gave *C*-alkylation products. See: (a) Williams, J. M.; Marchesini, G.; Reamer, R. A.; Dolling, R. U.-H.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 5337. (b) Bhattacharya, A.; DiMichele, L. M.; Dolling, R. U.-H.; Douglas, A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.

JA042330F