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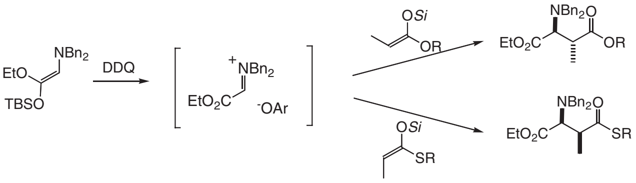
Efficient Mannich Reaction Using Iminium Salts Generated from Glycine Derivatives

Makoto Shimizu,* Toshiki Kusunoki, Mari Yoshida, Koichi Kondo, and Isao Mizota
Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507

(Received December 27, 2010; CL-101094; E-mail: mshimizu@chem.mie-u.ac.jp)

Iminium salts generated by the oxidation of amino ketene silyl acetals underwent a facile Mannich reaction with another ketene silyl acetal to give aspartic acid derivatives in good yields. The diastereoselectivities were controlled to some extent by using an appropriate isomer of ketene silyl (thio)acetals.



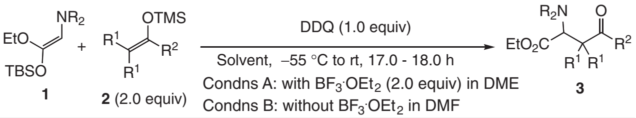
Scheme 1. The present strategy.

Increasing interest in controlling the reactivity of imino derivatives involving iminium salts[1] coupled with the need to construct amino diacid skeletons such as aspartic acid[2] in an efficient manner prompted us to report our recent approach to this class of compounds using iminium salts generated by the oxidation of glycine derivatives. We have recently disclosed a simple and useful approach to alkoxycarbonyl iminium salts[3] using the oxidation of the ketene silyl acetals derived from *N*,*N*-dibenzylglycinate with DDQ[4] or BPO (benzoyl peroxide). The alkoxycarbonyl iminium salts are excellent acceptors of electrophiles such as alkylaluminums, Grignard reagents, allylmetals, and metal cyanides. For the preparation of amino esters and amino ketones, the Mannich reaction offers one of the most straightforward methods. To the best of our knowledge, little is known about the diastereoselectivity of the Mannich reaction (addition to iminium salts), although stereocontrol in the addition reactions to imines has been achieved using several promoters.[5]

We have now found that the alkoxycarbonyl iminium salts prepared as above work in an efficient manner in the Mannich reaction to give aspartic acid derivatives and α-amino-γ-ketoesters in good yields with good diastereoselectivities (Scheme 1). Table 1 summarizes the reaction of the iminium salts with a variety of ketene silyl (thio)acetals and silyl enol ethers.

The reactions were carried out either in the presence of BF$_3$•Et$_2$O in DME (conditions A) or in its absence in DMF (conditions B). In general, although better product yields were obtained under conditions A, use of silyl enol ethers recorded comparable results under both conditions (Entries 23–26). Regarding the alkoxy group of the ketene silyl acetal **2**, only slight differences in the product yields were observed among the methoxy, ethoxy, and *tert*-butoxy derivatives (Entries 1–6). On the other hand, use of their ethylsulfanyl counterpart resulted in an enhanced product yield (Entry 7), although a prominent effect was not observed under conditions B (Entry 8). Among the substituents at the nitrogen, the dibenzyl and morpholino derivatives gave better results (Entries 3 and 17). In terms of further functional group transformations, dibenzyl or diallyl derivative appeared to be the substrate of choice. Under similar conditions, diastereoselectivity was next examined using trisubstituted ketene silyl acetals.

Table 1. Addition of TMS-enolates[a]

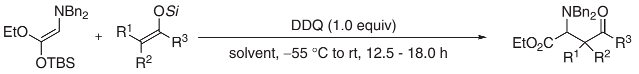


Entry	R, R	R^1	R^2	Conditions	**3**/%[b]
1	Bn, Bn	Me	OMe	A	68
2	Bn, Bn	Me	OMe	B	59
3	Bn, Bn	Me	OEt	A	81
4	Bn, Bn	Me	OEt	B	59
5	Bn, Bn	Me	O^{t}Bu	A	66
6	Bn, Bn	Me	O^{t}Bu	B	54
7	Bn, Bn	Me	SEt	A	81
8	Bn, Bn	Me	SEt	B	60
9	Me, Me	Me	OEt	A	57
10	Me, Me	Me	OEt	B	55
11	Allyl, Allyl	Me	OEt	A	69
12	Allyl, Allyl	Me	OEt	B	52
13	–(CH$_2$)$_4$–	Me	OEt	A	46
14	–(CH$_2$)$_4$–	Me	OEt	B	50
15	–(CH$_2$)$_5$–	Me	OEt	A	70
16	–(CH$_2$)$_5$–	Me	OEt	B	64
17	–(CH$_2$)$_2$O(CH$_2$)$_2$–	Me	OEt	A	78
18	–(CH$_2$)$_2$O(CH$_2$)$_2$–	Me	OEt	B	49
19	Bn, Bn	H	OEt	A	66
20	Bn, Bn	H	OEt	B	50
21	Bn, Bn	H	SEt	A	71
22	Bn, Bn	H	SEt	B	56
23	Bn, Bn	H	^{t}Bu	A	70
24	Bn, Bn	H	^{t}Bu	B	74
25	Bn, Bn	H	Ph	A	67
26	Bn, Bn	H	Ph	B	65

[a] See a typical procedure in the Supporting Information (SI).[9]
[b] Isolated yields.

As can be seen from Table 2, better diastereoselectivities were observed with (*Z*)-ketene silyl acetals (Entries 9–18), whereas use of their (*E*)-counterparts usually gave almost 1:1 mixtures of diastereomers (Entries 1, 2, 4, and 7). However, the use of ketene silyl thioacetal with BF$_3$•Et$_2$O in CH$_2$Cl$_2$ recorded good diastereoselectivity, where noteworthy is the fact that CH$_2$Cl$_2$ appears to be the solvent of choice for *syn*-selectivity (Entry 8). Regarding the ester group in the ketene silyl acetal **2**, use of the methyl propionate derivative gave a better result

Table 2. Diastereoselective Mannich reaction using **1a**[a]



1a **2** (2.0 equiv) **3**

Conditions A: with $BF_3•OEt_2$ (2.0 equiv) in DME
Conditions B: without $BF_3•OEt_2$ in DMF
Conditions C: with Et_2AlCl (2.0 equiv) in DME
Conditions D: with $BF_3•OEt_2$ (2.0 equiv) in CH_2Cl_2
Conditions E: without $BF_3•OEt_2$ in DME

Entry	R^1	R^2	R^3	*Si*	Conditions	**3**/%[b]	*anti*:*syn*[c]
1	H	Me	OEt	TBS	A	57	56:44
2	H	Me	OEt	TBS	B	47	51:49
3	H	Me	OEt	TMS	A	40	39:61
4	H	Me	OEt	TMS	B	55	46:54
5	H	Me	OMe	TMS	A	28	40:60
6	H	Me	OMe	TMS	D	23	28:72
7	H	Me	SEt	TMS	A	68	50:50
8	H	Me	SEt	TMS	D	74	30:70
9	Me	H	OEt	TBS	A	50	81:19
10	Me	H	OEt	TBS	B	51	75:25
11	Me	H	OMe	TBS	A	36	88:12
12	Me	H	OMe	TBS	B	38	77:23
13	Me	H	OMe	TBS	C	48	84:16
14	BnO	H	OMe	TMS	A	61	82:18
15	BnO	H	OMe	TMS	B	35	79:21
16	BnO	H	OMe	TBS	C	66	85:15
17	BnO	H	OEt	TBS	A	43	90:10
18	BnO	H	OEt	TBS	C	52	83:17
19	Me	H	Ph	DMS	A	40	49:51
20	Me	H	Ph	TMS	A	57	47:53
21	Me	H	Ph	TBS	A	58	42:58
22	Me	H	Ph	TIPS	A	60	14:86
23	Me	H	Ph	DMS	E	57	27:73
24	Me	H	Ph	TMS	E	37	47:53
25	Me	H	Ph	TBS	E	18	39:61
26	Me	H	Ph	TIPS	E	13	8:92

[a]See a typical procedure in SI.[9] [b]Isolated yields. [c]Determined by HPLC and/or ^1H NMR (ref. 6).

(Entry 11), whereas its ethyl counterpart recorded the best selectivity of 90:10 in the case with a glycolate derivative (Entry 17). Interestingly, the use of the TIPS enol ether gave the adduct with good *syn*-selectivity (Entry 22).

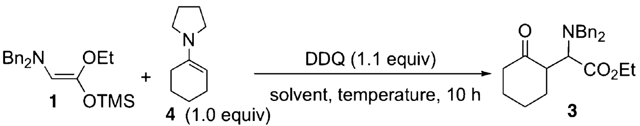
Use of enamines as nucleophiles was next examined (Tables 3 and 4). The addition of enamines was sensitive to the reaction solvents and temperatures, and among the reaction conditions screened, the reaction in propionitrile at 0 °C to rt gave the best result (Entry 8, Table 3).

Under these conditions the enamines screened here gave the Mannich adducts in good yields where use of 1 equiv of the enamine effected completion of the addition reaction, although the diastereoselectivity was not high (Table 4).

Since the formation of the iminium species **6** was observed by the ^1H and ^{13}C NMR spectra of the reaction mixture; i.e., the signals appeared at 9.27 and 193.6 ppm in the ^1H and ^{13}C NMR spectra, respectively,[7] a possible reaction mechanism is shown in Scheme 2.

First, DDQ reacts with the ketene silyl acetal **1a** either via a one-electron transfer or an ionic intermediate[4] to give the *N*,*O*-acetal **5**, which collapses to the iminium salt **6**. The subsequent nucleophilic attack with ketene silyl acetals gives an addition

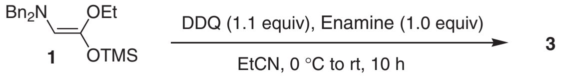
Table 3. Addition of enamines: comparison of reaction conditions

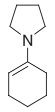
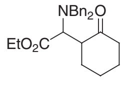
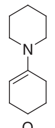
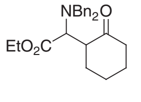
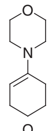
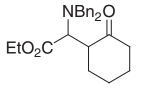
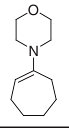
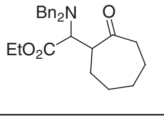


Entry	Solvent	Temp	Yield/%	Dr[a]
1	CH_2Cl_2	rt	23	38:62
2	Toluene	rt	25	45:55
3	MeCN	rt	30	45:55
4	EtCN	rt	31	43:57
5	DME	rt	15	45:55
6	DMF	rt	29	58:42
7	EtCN	−78 °C to rt	53	40:60
8	EtCN	0 °C to rt	72	37:63
9	EtCN	reflux	0	—

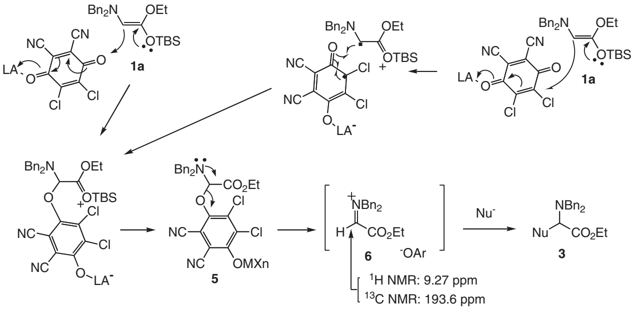
[a]Diastereomer ratio: determined on the basis of isolated products on TLC.

Table 4. Addition of various enamines

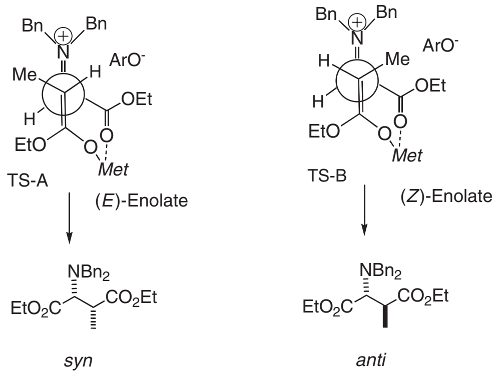


Entry	Enamine	Product	Yield/%	Dr[a]
1			72	37:63
2			36[b]	45:55
3			42[c]	38:62
4			83	36:64
5			63	38:62
6			76	33:67

[a]Diastereomer ratio: determined on the basis of isolated products on TLC. [b]In the presence of $BF_3•Et_2O$ (1.0 equiv). [c]In the presence of $AlCl_3$ (1.0 equiv).



Scheme 2. A possible reaction mechanism.



Scheme 3. Possible transition states for diastereoselectivity.

product **3**. Regarding the diastereoselectivity, although there is much room to define appropriate transition state models, we explain the present diastereoselectivity using the following models (Scheme 3).

Addition reactions of both (*E*)- and (*Z*)-ketene silyl acetals would proceed via the chelated intermediates in anti-periplaner fashions (**TS-A** and **TS-B**). Although the chelation would be weak when the silicon–metal exchange reaction would not be facile,[8] these intermediates may lead to one of the explanations.

In conclusion, we have found that iminium salts generated by the oxidation of amino ketene silyl acetals undergo a facile Mannich reaction with another ketene silyl acetal to give aspartic acid derivatives in good yields. The diastereoselectivity studied here shows the first example where the diastereoselectivities in the addition reaction to the iminium salts is controlled to some extent by using the appropriate geometry of ketene silyl (thio)acetals. In addition, enamines also act as good nucleophiles in the present Mannich addition. This study opens a new entry into the use of iminium salts for the diastereoselective approach to this important class of amino esters and ketones.

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9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.