

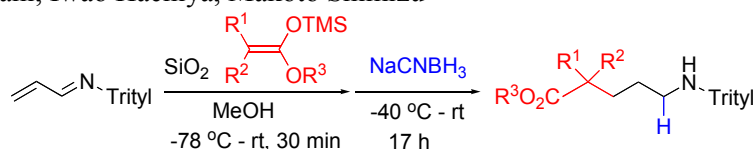
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Leave this area blank for abstract info.

Reductive aminopropylation of ketene silyl (thio)acetals leading to the synthesis of δ -amino esters

Isao Mizota, Shun Agatani, Iwao Hachiya, Makoto Shimizu





Reductive aminopropylation of ketene silyl (thio)acetals leading to the synthesis of δ -amino esters

Isao Mizota, Shun Agatani, Iwao Hachiya, Makoto Shimizu*

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

ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Aminopropylation
ketene silyl acetal
ketene silyl thioacetal
 α,β -unsaturated aldimine
 δ -amino esters

ABSTRACT

In the presence of silica gel or titanium tetrachloride, ketene silyl acetals or ketene silyl thioacetals underwent 1,4-addition with α,β -unsaturated aldimines which possess a large triphenylmethyl group at the imino nitrogens followed by reduction with sodium cyanoborohydride to give aminopropylated products, δ -amino esters, in good yields.

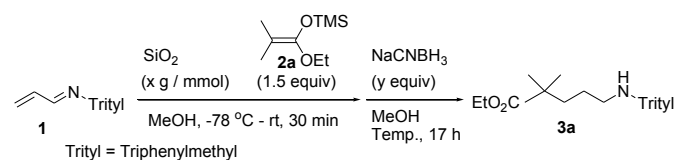
2009 Elsevier Ltd. All rights reserved.

In connection with unusual helix types in oligomers of δ -amino acids (δ -peptides) and their stabilities, δ -amino acids have received considerable attention from the standpoints of dipeptide isosteres and reversal of turn mimetics.¹ Although we have already reported new synthetic methods for δ -amino esters of type **A** using double nucleophilic addition to α,β -unsaturated aldimines,² there still remains an important problem for the selective synthesis of δ -amino esters of type **B** using the double addition tactic, in other words, reductive aminopropylation (Scheme 1). This kind of transformation is not trivial due to the instability of an intermediary enamino or imino compound against hydrolysis or isomerization.³ The ready second 1,2-addition of the same 1,4-nucleophiles has also been found to be quite problematic.⁴ We would like to describe herein

an easy access to δ -amino esters of type **B** by reductive aminopropylation of ketene silyl (thio)acetals, in which use of α,β -unsaturated aldimines having a large trityl group at the imino nitrogens is crucial.

The initial examination was carried out using aminopropylation of the ketene silyl acetal **2a** derived from ethyl isobutyrate with allylideneamine **1**, and results are summarized in Table 1.

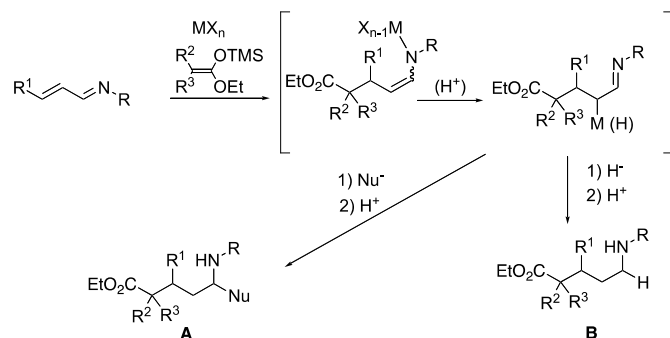
Table 1. Reductive aminopropylation of ketene silyl acetal-comparison of reaction conditions.^a



Entry	SiO ₂ (g/mmol)	NaCNBH ₃ (equiv)	Temp (°C)	Yield of 3a (%) ^b
1	2.50	4.0	-78 to rt	41
2	2.50	4.0	-78 to rt	49
3	2.50	1.0	-78 to rt	33
4	1.25	4.0	-78 to rt	22
5	5.00	4.0	-78 to rt	68
6	6.25	4.0	-78 to rt	52
7	5.00	4.0	0 to rt	66
8	5.00	4.0	-20 to rt	71
9	5.00	4.0	-40 to rt	75

^aThe reaction was carried out according to the typical procedure.

^bIsolated yield.



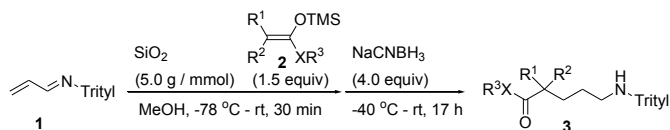
Scheme 1. Double nucleophilic addition to α,β -unsaturated aldimine

*Corresponding author. Tel. & fax: +81 59 231 9413

E-mail address: mshimizu@chem.mie-u.ac.jp

As shown in Table 1, the addition reaction of the ketene silyl acetal **2a** in the presence of SiO₂ (5.00 g/mmol) as previously reported⁵ gave an intermediary 1,4-addition product which in turn was reduced with NaCNBH₃ (4.0 equiv) at -40 °C to rt to afford the desired aminopropylated product **3a** in 75% yield (entry 9). Under the optimum conditions a variety of ketene silyl (thio)acetals **2** were subjected to the aminopropylation reaction, and Table 2 summarizes the results.⁶

Table 2. Reductive aminopropylation of ketene silyl (thio)acetals^a



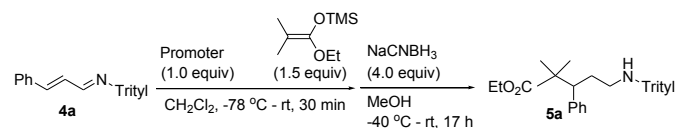
Entry	$\begin{matrix} R^2 \\ \text{OTMS} \\ R^1 \end{matrix}$ $\begin{matrix} \text{XR}^3 \end{matrix}$	Yield of 3 (%) ^b	Entry	$\begin{matrix} R^2 \\ \text{OTMS} \\ R^1 \end{matrix}$ $\begin{matrix} \text{XR}^3 \end{matrix}$	Yield of 3 (%) ^b
1	2b	3b , 54	8	2h	3h , 60
2	2c	3c , 70	9	2i	3i , 49
3	2a	3a , 75	10	2j	3j , 46
4	2d	3d , 78	11	2k	3k , 31
5	2e	3e , 38	12	2l	3l , 42
6	2f	3f , 51	13	2m	3m , 52
7	2g	3g , 33			

^aThe reaction was carried out according to the typical procedure.

^bIsolated yield.

As shown in Table 2, tetra-substituted ketene silyl acetals underwent aminopropylation reaction to give the products **3** in good yields in which methoxy derivative gave the best result (entries 1-8). Although tri-substituted ketene silyl acetals did not give the adducts in good yields, their sulfur analogues gave the aminopropionated products in moderate yields (entries 9-11), in which cyclohexylthio derivative recorded the best result (entry 9). In the cases with di-substituted ketene silyl acetals, the reaction did not give the desired product, either, where only the hydrolysis of ketene silyl acetals was observed. However, use of ketene silyl thioacetals gave the aminopropylated products in moderate yields (entries 12 and 13). We next examined use of β -phenyl α,β -unsaturated aldimine **4a**, and Table 3 summarizes the results.

Table 3. Reductive aminoalkylation of ketene silyl acetal-comparison of reaction conditions^a



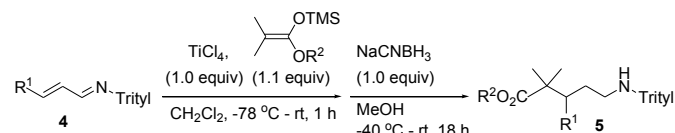
Entry	Promoter	Yield of 5a (%) ^b
1	SiO ₂ ^c	-
2	SnCl ₂	27
3	SnCl ₄	61
4	AlCl ₃	52
5	TiCl ₄	72
6	TiCl ₄ ^d	77

^aThe reaction was carried out according to the typical procedure.

^bIsolated yield. ^cSiO₂ (5.0 g/mmol) was used. ^dThe initial 1,4-addition was conducted for 1 h.

In contrast to allylideneamine **1** the initial addition reaction did not proceed with β -phenyl α,β -unsaturated aldimine **4a** in the presence of silica gel (entry 1), whereas other Lewis acids examined here promoted the reductive aminoalkylation reaction to give the adduct **5a** in moderate to good yields. Among the Lewis acids screened titanium tetrachloride promoted the desired transformation most efficiently to give the product **5a** in 77% yield (entry 6). Under these conditions a series of β -substituted α,β -unsaturated aldimine **4** were used for the present aminoalkylation reaction and Table 4 summarizes the results.⁷

Table 4. Reductive Aminoalkylation of Ketene Silyl Acetals^a



Entry	R ¹	R ²	Yield of 5 (%) ^b
1	4a : Ph	2a , Et	5a , 77
2	4a : Ph	2d , Me	5d , 71
3	4a : Ph	2b , ⁿ Pr	5b , 66
4	4a : Ph	2c , ⁱ Pr	5c , 63
5	4b : Me	2a , Et	5e , 59
6	4c : Et	2a , Et	5f , 60
7	4d : ⁿ Pr	2a , Et	5g , 55
8	4e : ⁿ Bu	2a , Et	5h , 59
9	4f : Cy	2a , Et	5i , 46

^aThe reaction was carried out according to the typical procedure.

^bIsolated yield.

Regarding the alkoxy part of the ketene silyl acetal, ethoxy derivative **2a** recorded the best result (entries 1-4). Other β -substituted α,β -unsaturated aldimines **4** besides the cinnamylidene derivative **4a** could also be used for the present aminoalkylation reaction to give the adducts **5** in moderate to good yields (entries 5-9). However, at present time use of tri- and di-substituted ketene silyl acetals or their thio analogues did not give satisfactory yields of the aminoalkylated products

presumably due to the competing hydrolysis of the ketene silyl (thio)acetals and/or intermediary imines or enamines under the present reaction conditions.⁸

In conclusion, the present reductive aminoalkylation of ketene silyl (thio)acetals provides an easy access to δ -amino esters which are useful molecules in drug discovery as well as for new functional materials. Although some limitation of the nucleophiles is involved in the cases with β -substituted α,β -unsaturated aldimines, use of a large trityl group at the imino nitrogen has provided new environment for the control of the double nucleophilic addition reaction to use only small second nucleophiles for the 1,2-addition.

Acknowledgments

This work was supported by Grant-in-Aids for Scientific Research (B) and on Innovative Areas "Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances" from JSPS and MEXT.

References and notes

- (a) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687-1690; (b) Trabocchi, A.; Menchi, G.; Danieli, E.; Guarna, A. *Amino Acids* **2008**, *35*, 37-44; (c) Baldauf, C.; Günther, R.; Hofmann, H.-J., *J. Org. Chem.* **2004**, *69*, 6214-6220.
- (a) Shimizu, M.; Kawanishi, M.; Mizota, I.; Hachiya, I. *Org. Lett.* **2010**, *12*, 3571-3573. (b) Takahashi, A.; Kawai, S.; Hachiya, I.; Shimizu, M. *Eur. J. Org. Chem.* **2010**, 191-200. (c) Mizota, I.; Matsuda, Y.; Hachiya, I.; Shimizu, M. *Eur. J. Org. Chem.* **2009**, 4073-4084. (d) Mizota, I.; Matsuda, Y.; Hachiya, I.; Shimizu, M. *Org. Lett.* **2008**, *10*, 3977-3980. (e) Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585-3587. (f) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2005**, *34*, 1456-1457. (g) Shimizu, M.; Kurokawa, H.; Takahashi, A. *Lett. Org. Chem.* **2004**, *1*, 353-356. (h) Shimizu, M.; Yamauchi, C.; Ogawa, T. *Chem. Lett.* **2004**, *33*, 606-607. (i) Shimizu, M.; Kamiya, M.; Hachiya, I. *Chem. Lett.* **2003**, *32*, 606-607. (j) Shimizu, M.; Nishi, T. *Chem. Lett.* **2002**, 46-47. (k) Shimizu, M.; Ogawa, T.; Nishi, T. *Tetrahedron Lett.* **2001**, *42*, 5463-5466. (l) Shimizu, M.; Morita, A.; Kaga, T. *Tetrahedron Lett.* **1999**, *40*, 8401-8405.
- It has been reported that several imines are readily hydrolyzed to the parent carbonyl compounds. See, (a) Saggiomo, V.; Lüning, U. *Tetrahedron Lett.* **2009**, *50*, 4663-4665. (b) Godoy-Alcántar, C.; Yatsimirsky, A. K.; Lehn, J.-M. *J. Phys. Org. Chem.* **2005**, *18*, 979-985. (c) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141-142. (d) Dash, A. C.; Dash, B.; Panda, D. *J. Org. Chem.* **1985**, *50*, 2905-2910.
- For a review, see: Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Commun.* **2009**, 874-889.
- Shimizu, M.; Kawanishi, M.; Itoh, A.; Mizota, I.; Hachiya, I. *Chem. Lett.*, **2011**, *40*, 862-863. See also, ref. 2a.
- Under an argon atmosphere, a suspension of *N*-allylidene-triphenylmethaneamine **1** (59.0 mg, 0.20 mmol) in CH₃OH (1.4 mL) was stirred at room temperature for 10 minutes. Dried silica gel (500 mg) and CH₃OH (0.30 mL) were added to it. The reaction mixture was cooled to -78 °C. A solution of (1-ethoxy-2-methylprop-1-enyloxy)-trimethylsilane (56.0 mg, 0.30 mmol) in CH₃OH (1.2 mL) was added to the mixture. After the mixture was allowed to warm up to room temperature during 30 min with stirring, sodium cyanoborohydride (50.0 mg, 0.80 mmol) was added to the resulting mixture at -40 °C. The mixture was gradually warmed to room temperature during 16 h. Saturated aq. NaHCO₃ (10 mL) was added to quench the reaction. The mixture was filtered with suction through a Celite pad and washed with ethyl acetate. The mixture was extracted with ethyl acetate (3 x 5.0 mL). The combined extracts were dried over Na₂SO₄ and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-Hexane : EtOAc = 6 : 1 as an eluent) gave the aminopropylated compound **3a** (62.2 mg, 75%) as a pale yellow oil. Rf = 0.30 (*n*-Hex : EtOAc = 6 : 1); ¹H-NMR (500 MHz, CDCl₃) δ 1.14 (s, 6H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.38-1.45 (m, 2H), 1.49-1.53 (m, 2H), 2.09 (t, *J* = 6.7 Hz, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 7.16-7.19 (m, 3H), 7.24-7.28 (m, 6H), 7.45-7.47 (m, 6H); ¹³C-NMR (125 MHz, CDCl₃) δ 14.2, 25.1, 26.4, 38.3, 42.0, 44.0, 60.2, 70.9, 126.2, 127.7, 128.6, 146.3, 177.9; IR (neat) 3085, 3053, 3022, 2975, 2935, 2854, 1724, 1590, 1484, 1450, 1388, 1316, 1266, 1180, 1142, 1098, 1029, 902, 770, 745, 705 cm⁻¹; HRMS (EI): Calculated for C₂₈H₃₃NO₂ (M⁺) 415.2511, found 415.2520.
- Under an argon atmosphere, a suspension of *N*-(3-phenylpropylidene)triphenylmethaneamine **4a** (76.0 mg, 0.20 mmol) in CH₂Cl₂ (1.4 mL) was stirred at room temperature for 10 min. A solution of TiCl₄ (0.20 mL, 0.20 mmol) in CH₂Cl₂ (0.30 mL) was added to it. The reaction mixture was cooled to -78 °C, and a solution of (1-ethoxy-2-methylprop-1-enyloxy)trimethylsilane **2a** (37.0 mg, 0.22 mmol) in CH₂Cl₂ (1.20 mL) was added to the mixture. After the mixture was allowed to warm up to room temperature during 60 min with stirring, a solution of sodium cyanoborohydride (12.0 mg, 0.20 mmol) in CH₃OH (0.40 mL) was added to the resulting mixture at -40 °C. The mixture was gradually warmed to room temperature during 17 h. Saturated aq. NaHCO₃ (10 mL) was added to quench the reaction. The mixture was filtered with suction through a Celite pad and washed with ethyl acetate. The mixture was extracted with ethyl acetate (3 x 5.0 mL). The combined extracts were dried over Na₂SO₄ and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-Hexane : EtOAc = 6 : 1 as an eluent) gave the aminopropylated compound **5a** (75.7 mg, 77%) as a colorless oil. Rf = 0.50 (*n*-Hex : EtOAc = 6 : 1); ¹H-NMR (500 MHz, CDCl₃) δ 1.01 (s, 3H), 1.12 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.60-1.66 (m, 1H), 1.94-2.04 (m, 3H), 3.16-3.20 (m, 1H), 4.05-4.13 (m, 2H), 7.09-7.33 (m, 20H); ¹³C-NMR (100 MHz, CDCl₃) δ 14.2, 20.6, 24.6, 31.3, 41.7, 46.5, 50.4, 60.4, 70.7, 126.0, 126.5, 127.6, 127.7, 128.5, 129.8, 140.0, 146.1, 177.7; IR (neat) 3085, 3058, 3028, 2977, 2935, 2860, 1723, 1597, 1490, 1450, 1387, 1366, 1244, 1128, 1028, 903, 768, 744, 704 cm⁻¹; HRMS (EI): Calculated for C₃₄H₃₇NO₂ (M⁺) 491.2824, found 491.2832.
- Ketene silyl (thio)acetals are readily hydrolyzed under the influence of Brønsted acids in protic solvents. Related side reactions, see: ref 5.