Tetrahedron Letters, Vol.31, No.28, pp 3999-4002, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PREPARATION OF β-AMINOESTERS FROM KETENE SILYL ACETALS AND N-(ALKYLAMINO)BENZOTRIAZOLES

Alan. R. Katritzky,* N. Shobana and Philip A. Harris
Department of Chemistry, University of Florida,
Gainesville, FL 32611-2046, USA.

Abstract: *A wide variety of β-aminoesters are prepared in good yields by the reaction of lithium ester enolates derived from ketene silyl acetals with N-(alkylamino)benzotriazoles. The secondary β-aminoesters readily cyclize to β-lactams (2-azetidinones) on deprotonation.*

β-Aminoacids and their derivatives are an important class of compounds; for example, they are precursors to the β-lactam moiety found in antibiotics.[1] Since the interest in β-lactams continues unabated,[2] refined methods for their preparation, and those of the β-aminoester precursors, are still of considerable value. Several methods are known for their preparation of simple β-aminoacids, such as β-alanine, usually involving hydrolysis of a suitable precursor. Examples include the Arndt-Eistert homologation reaction of N-protected α-aminoacids and the Michael addition of nitrogen nucleophiles to α,β-unsaturated acids, esters or nitriles.[3] A recent report from our group on the synthesis of β-amino esters involves the Reformatsky reaction of α-bromoesters on N-(dialkylamino)benzotriazoles giving various tertiary β-aminoesters in good yields.[4] Other known procedures involve the treatment of N-(1-methoxyalkyl)carbamates with lithium enolates yielding β-(methoxycarbonylamino)propanoates,[5] the hydrolysis of dihydroxyuracils in alkaline medium[6] to give β-amino acids, and the reduction of oximes, or N-acetyl oximes, of β-keto esters.[7]

Recently, Ojima *et. al.* found that ketene silyl acetals add to Schiff bases in the presence of titanium tetrachloride to yield either secondary β-aminoesters or the cyclized β-lactams depending on the nature of the substituents on the Schiff base employed.[8]

In continuation of our investigation[9] on the reaction of N-(alkylamino)benzotriazoles **1** with silyl enol ethers, we wish to report herein their reaction with the readily available ketene silyl acetals **2** to furnish β-aminoesters **3** in good yields. This method is applicable to either secondary or tertiary amino groups and a variety of substituents at the α and β positions can be introduced. The secondary β-aminoesters **3** readily cyclize to give the highly substituted β-lactams **4**.

The procedure is straightforward; methyl lithium is added to a cold solution of the silyl ketene acetal **2** (derived from the appropriate ethyl ester) in tetrahydrofuran to generate the lithium enolate *in situ*. The N-(alkylamino)benzotriazole **1** is then added to the solution at -30°C and stirring continued at room temperature overnight. Simple evaporation of the solvent and removal of the benzotriazole by-product by alkaline extraction gives the crude product (the benzotriazole can be recovered and reused). Purification of the β-aminoesters **3** can be achieved by an acid-base workup.

Since the preparation of ketene silyl acetals and N-(alkylamino)benzotriazole **1** are both well established, a number of variations in the substituents of the starting materials can be made. This method leads to a wide variety of α and β substituted, secondary and tertiary β-amino-esters in good yields as shown in Table 1.

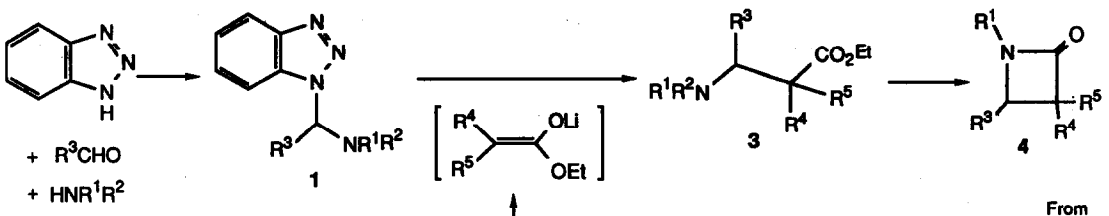
Table 1. Preparation and ^{1}H NMR Data of the β-Aminoesters 3 and β-Lactams 4.

Product	Yield (%)	m.p. (°C)	Molecular Formula[a]	^{1}H-NMR (CDCl3/TMS) δ, J (Hz)
3a	70	oil	$C_{17}H_{19}NO_2$	1.10 (t, 3H, J=7); 3.3 (dd, 1H, J=6,13); 3.8 (dd, 1H, J=9,13); 3.9 (dd, 1H, J=6,9); 4.05 (q, 2H, J=7); 6.52 (d, 2H, J=7); 6.63 (t, 1H, J=7); 7.09 (t, 2H, J=7); 7.3 (m, 5H)
3b	80	oil	$C_{18}H_{21}NO_2$	1.2 (t, 3H, J=7); 2.2 (s, 3H); 3.4 (dd, 1H, J=6,9.3); 3.85 (dd, 1H, J=8.8,9.3); 3.95 (dd, 1H, J=6,9.3); 4.15 (q, 2H, J=7); 6.5 (d, 2H, J=7); 7.0 (d, 2H, J=7); 7.2-7.5 (m, 5H)
3c	78	oil	$C_{15}H_{21}NO_3$	1.1 (t, 3H, J=7); 2.2-2.6 (m, 4H); 3.1 (m, 1H); 3.4 (m, 1H); 3.6 (t, 4H, J=4); 3.75 (dd, 1H, J=5,10.5); 4.1 (q, 2H, J=7); 7.2 (m, 5H)
3d[b]	75	87-90	$C_{21}H_{25}NO_3$	0.8 (t, 3/2H, J=7); 1.2 (t, 3/2H, J=7); 2.1-2.6 (m, 4H); 3.2-3.6 (m, 4H); 3.7 (m, 1H); 4.1 (m, 1H); 4.2 (m, 2H); 6.9-7.5 (m, 5H)
3e[c]	78	oil	$C_{19}H_{29}NO_2$	0.69 (d, 3H, J=7); 0.98 (d, 3H, J=7); 1.2 (m, 6H); 1.24 (t, 3H, J=7); 1.64 (m, 1H); 2.42 (m, 4H); 3.2 (m, 1H); 3.9 (m, 1H); 4.1 (m, 2H); 7.2-7.3 (m, 3H); 7.4-7.5 (m, 2H) 0.86 (d, 3H, J=7); 0.98 (d, 3H, J=7); 1.25 (t, 3H, J=7); 1.45 (m, 6H); 1.82 (m, 1H); 2.65 (m, 2H); 2.82 (m, 2H); 3.2 (m, 1H); 3.9 (m, 1H); 4.1 (m, 2H); 7.2-7.3 (m, 3H); 7.4-7.5 (m, 2H)
3f	70	oil	$C_{15}H_{21}NO_2$	1.15 (t, 3H, J=7); 1.7 (m, 4H); 2.5 (m, 5H); 3.5 (m, 1H), 3.85 (dd, 1H, J=5,10); 4.1 (m, 2H); 7.25 (m, 5H)
3g	72	70-72	$C_{20}H_{29}NO_3$	1.14 (t, 3H, J=7); 0.9-1.5 (m, 8H); 2.1 (m, 2H); 2.3 (m, 2H); 2.5 (m, 2H); 3.5 (s, 1H); 3.55 (m, 4H); 4.05 (q, 2H,J=7); 7.2 (m, 5H)
3h	78	oil	$C_{17}H_{25}NO_2$	1.15 (t, 3H, J=7); 1.1-1.6 (m, 8H); 2.1 (m, 2H); 2.15 (s, 3H); 3.1 (s, 2H); 4.05 (q, 2H, J=7); 6.45 (d, 2H, J=8); 6.9 (d, 2H, J=8)
3i	78	oil	$C_{15}H_{23}NO_2$	0.8 (t, 3H, J=6); 1.16 (t, 3H, J=7); 1.25 (m, 4H); 1.5 (m, 1H); 1.6 (m, 1H); 2.6 (m, 1H); 3.18 (dd, 1H, J=5,13); 3.3 (dd, 1H, J=8.6,13); 4.05 (q, 2H, J=7); 6.5 (m, 2H); 6.65 (m, 1H); 7.1 (m, 2H)
3j	75	oil	$C_{16}H_{25}NO_2$	0.8 (t, 3H, J=7); 1.17 (t, 3H, J=7); 1.25 (m, 4H); 1.5 (m, 1H); 1.6 (m, 1H); 2.15 (s, 3H); 2.6 (m, 1H); 3.15 (dd, 1H, J=5,13); 3.25 (dd, 1H, J=8.5,13); 4.05 (q, 2H, J=7); 6.45 (d, 2H, J=8); 6.9 (d, 2H, J=8)
4b	78	135-37	$C_{15}H_{15}NO$	2.25 (s, 3H); 3.57 (dd, 1H, J=3,6); 3.97 (m, 1H); 4.4 (dd, 1H, J=3,6); 7.08 (d, 2H, J=8); 7.25 (m, 7H)
4h	65	oil	$C_{15}H_{19}NO$	1.3-1.85 (m, 10H); 2.25 (s, 3H); 3.3 (s, 2H); 7.03 (d, 2H, J=8); 7.17 (d, 2H, J=8)
4i	75	oil	$C_{13}H_{17}NO$	0.85 (t, 3H, J=7); 1.2-1.9 (m, 6H); 3.25 (m, 2H); 3.65 (m, 1H); 6.9-7.3 (m, 5H)

[a] Satisfactory microanalyses were obtained for solids and correct accurate molecular masses were obtained for oils by MS.
[b] ^{1}H NMR shows overlapping signals of two diastereoisomers.
[c] ^{1}H NMR signals due to two diastereoisomers; signals can be interchanged.

The new products **3a-3i** were characterized by elemental analysis and by their ^{1}H (Table 1) and ^{13}C NMR spectra (Table 2). β-Aminoesters **3d** and **3e** containing two asymmetric carbon atoms were each obtained as a diastereoisomeric mixture. ^{1}H and ^{13}C NMR analysis clearly showed a diastereoisomeric ratio of about 1:1 for **3e**, whilst for **3d** an excess of one diastereoisomer was observed.

As representative procedures, the secondary β-aminoesters **3b, 3h,** and **3i** were cyclized to the respective β-lactams **4b, 4h** and **4i** in good yields by treatment with ethylmagnesium bromide in tetrahydrofuran.[10] The ^{1}H and ^{13}C NMR of the β-lactams are recorded in Tables 1 and 2.



1	R^1	R^2	R^3
a	Ph	H	H
b	p-Me-Ph	H	H
c	-$(CH_2)_2$-O-$(CH_2)_2$-		H
d	-$(CH_2)_2$-O-$(CH_2)_2$-		Ph
e	-$(CH_2)_5$-		*i*-Pr
f	-$(CH_2)_4$-		H

2	R^4	R^5
a	Ph	H
b	-$(CH_2)_5$-	
c	*n*-C_4H_9	H

4	R^1	R^3	R^4	R^5
b	p-Me-Ph	H	Ph	H
h	p-Me-Ph	H	-$(CH_2)_5$-	
I	Ph	H	*n*-C_4H_9	H

3	R^1	R^2	R^3	R^4	R^5	From 1	From 2
a	Ph	H	H	Ph	H	a	a
b	p-Me-Ph	H	H	Ph	H	b	a
c	-$(CH_2)_2$-O-$(CH_2)_2$-		H	Ph	H	c	a
d	-$(CH_2)_2$-O-$(CH_2)_2$-		Ph	Ph	H	d	a
e	-$(CH_2)_5$-		*i*-Pr	Ph	H	e	a
f	-$(CH_2)_4$-		H	Ph	H	f	a
g	-$(CH_2)_2$-O-$(CH_2)_2$-		Ph	-$(CH_2)_5$-		d	b
h	p-Me-Ph	H	H	-$(CH_2)_5$-		b	b
i	Ph	H	H	*n*-C_4H_9	H	a	c
j	p-Me-Ph	H	H	*n*-C_4H_9	H	b	c

Table 2. ^{13}C-NMR Chemical Shifts (δ) for β-Amino-Esters 3 and β-Lactams 4 ($CDCl_3$).

Product	NR^1R^2	R^3	R^4, R^5	C-α	C-β	C=O	OEt
3a	117.7, 127.9, 129.3, 141.2	—	113.0, 127.6, 128.8, 136.8	50.8	46.8	172.8	14.0, 60.9
3b	20.2, 126.5, 127.9, 129.7, 144.8	—	113.2, 127.5, 128.7, 136.2	50.7	47.1	172.5	13.9, 60.9
3c	53.5, 55.1, 66.9, 67.1	—	127.3, 127.8, 128.4, 137.2	49.6	61.9	173.0	14.1, 60.5
3d[a]	49.1, 66.9, 49.3, 67.3	127.0, 127.6, 128.3, 135.5 127.2, 127.8,128.7, 137.3	127.3, 127.9,128.8,132.9 127.5, 128.1, 129.1,135.2	53.4 53.2	70.9 71.8	171.8 172.9	13.6, 60.4 14.3, 60.5
3e[a]	26.8, 24.8, 51.9 27.2, 25.0, 52.1	19.2[#], 20.7[#], 28.8[#] 20.0[#], 21.2[#], 31.9[#]	126.8, 127.7, 129.1, 137.4 127.1, 128.2, 129.4, 138.6	54.2 54.2	71.4 71.9	173.7 173.7	13.9, 60.3 14.2, 60.4
3f	23.5, 54.1	—	127.3, 127.8, 128.6, 137.7	51.5	54.2	173.3	14.0, 59.6
3g	52.6, 67.4	127.3, 127.6, 130.8, 135.8	23.4, 23.6, 25.5, 31.4, 34.0	53.2	78.8	175.8	14.1, 60.1
3h	20.3, 112.9, 126.3, 129.6, 146.1	—	23.0, 26.0, 32.3	47.8	52.9	175.7	14.1, 60.1
3i	112.8, 117.4, 129.1, 147.8	—	13.8, 22.5, 29.3, 29.7	45.2	45.6	175.1	14.2, 60.4
3j	20.3, 113.0, 126.7, 129.1, 147.8	—	13.9, 22.6, 29.4, 29.7	45.2	45.6	175.1	14.2, 60.4
4b	20.9, 116.3, 128.9, 133.6, 135.8	—	127.4, 127.6, 129.6, 135.4	46.7	53.5	165.0	—
4h	20.8, 116, 129, 133, 136	—	23.2, 26.1, 31.1	51.6	55.1	170.8	—
4i	116.1, 123.6, 129, 138.5	—	13.9, 22.5, 28.6, 29.2	44.5	49.0	167.8	—

[a]Mixture of diastereoisomers, assignments were based on the relative intensities of the peaks.
[#]Assignments can be interchanged.

Experimental

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300MHz spectrometer. $CDCl_3$ was used as the solvent and TMS as the internal standard. (abbreviations used: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet and dd= doublet of doublets). Tetrahydrofuran and diethyl ether were predried and distilled from sodium.

The benzotriazole derivatives **1a**, and **1c-1f** were prepared as reported previously.[11,12] Novel benzotriazole derivative **1b** was prepared in 85% yield by refluxing equimolar amounts of hydroxymethylbenzotriazole and *p*-toluidine in benzene in a Dean-Stark apparatus for 4hrs : m.p. 130-134°C (C_6H_6:EtOH). ^{1}H NMR (DMSO-d_6): 2.12 (s, 3H, CH_3); 6.15 (d, 2H, -CH_2- , J=7Hz); 6.74-6.94 (d, 4H, Ar, J = 8.5 Hz); 7.1 - 7.2(t, 1H, NH, J= 7Hz); 7.36 - 7.4 (t, Ar, 1H, J = 8 Hz); 7.5 - 7.6 (t, 1H, Ar, J = 7.5 Hz); 8.0 - 8.15 (m, 2H, Ar). The ketene silyl acetals of ethyl phenylacetate, ethyl caproate and ethyl cyclohexanecarboxylate were prepared by the known procedures.[13,14]

β-Aminoesters 3 : A General Procedure:

The silyl ketene acetal **2** (450mg, 1.9 mmol) was dissolved in tetrahydrofuran (20ml) and methyl lithium (1.35 ml, 1.9 mmol) was slowly added with stirring at -30°C. After stirring for 90 min at room temperature, the solution was recooled to -30°C and the N-(alkylamino)benzotriazole **1** (1.5 mmol) dissolved in tetrahydrofuran (15ml) was added. After the addition the solution was allowed to warm to room temperature and left stirring overnight. The solvent was removed and the residue dissolved in ether and washed with dilute sodium hydroxide solution to remove the by-product benzotriazole. The ether was evaporated and the crude product taken in the minimum amount of ether and extracted with dilute hydrochloric acid. After neutralization with dilute sodium hydroxide solution, the precipitate formed was extracted with ether and evaporation (except in the case of **3d** in which case the precipitate was filtered off) gave the pure β-amino ester. The yields and properties are given in Table 1.

The secondary β-amino esters **3b**, **3h** and **3i** were cyclized to the β-lactams **4b**, **4h** and **4i** by treatment with ethylmagnesium bromide in THF at 0°C, as described by Shono.[10] The yields and properties are given in Table 1.

References

1 A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 1973, 327.

2 *Tetrahedron Symposium in Print*, No 10; J. E. Baldwin, ed.; *Tetrahedron*, 1983, **39**, 2445-2608.

3 J. H. Jones in "Comprehensive Organic Chemistry", I. O. Sutherland, ed., Pergamon Press, Oxford, 1979, II, Part 6, p 834.

4 A. R. Katritzky and K. Yannakopoulou, *Synthesis*, 1989, 747.

5 T. Shono, N. Kise, F. Sanda, S. Ohi and K. Tsubata, *Tetrahedron Lett.*, 1988, **29**, 231.

6 V. Rachina and I. Blagoeva, *Synthesis*, 1982, 967.

7 E. Fischer and R. Groh, *Liebig Ann., 1911*, **383**, 363; A. Skita and C. Wulff, *Liebig Ann.*, 1927, **453**, 190.

8 I. Ojima, S. Inaba and K. Yoshida, *Tetrahedron Lett.*, 1977, 3643.

9 A. R. Katritzky and P. A. Harris, *Tetrahedron*, 1990, 987.

10 T. Shono, K. Tsubata and N. Okinaga, *J. Org. Chem.*, 1984, **49**, 1056.

11 A. R. Katritzky, B. Pilarski and L. Urogdi, *Org. Prep. Proc. Int.*, 1989, **21**, 135.

12 A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala and L. Urogdi, *J. Chem. Soc. Perkin Trans I*, 1988, 225.

13 H. Emde, D. Domsch, H. Fegez, U. Frick, A. Gotz, H. H. Hergott, K. Hofmann, W. Kober, K. Krageloh, T. Oesterle, W. Steppan, W. West and G. Simchen, *Synthesis*, 1982, 1.

14 M. W. Rathke and D. F. Sullivan, *Synthetic Comm.*, 1973, **3**(1), 67.

(Received in USA 25 April 1990)