SYNTHESIS

Journal of
Synthetic Organic
Chemistry

REPRINT

1988
No. 2
February

With Compliments of the Author.

GEORG THIEME VERLAG · STUTTGART · NEW YORK

Synthesis of Functionalized β -Amino α,β -Unsaturated Esters and Nitriles by Nucleophilic Vinylic Substitution

Begoña de Ancos,^a M. Carmen Maestro,^a M. Rosario Martín,^a Francisco Fariña^{a,b}

^a Departamento de Química C-I, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid, Spain

^b Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

The nucleophilic vinylic substitution of halogen by primary and secondary amines on methyl (*E*)- and (*Z*)-3-bromo-4,4-dimethoxy-2-butenates (**1**) and the corresponding nitriles (**2**) leads to methyl 3-amino-4,4-dimethoxy-2-butenates and the corresponding nitriles, respectively, in good yields. The stereochemistry of the reactions has also been studied.

We have previously reported that halogen substitution by amines and sodium thiolates can be carried out on 4-halo-5-methoxyfuran-2(5*H*)-ones to afford the corresponding enamines and vinyl thioethers.¹ Moreover, nucleophilic vinylic substitution studies on (*E*)- and (*Z*)-3-bromo-4,4-dimethoxy-2-butenic acid derivatives² suggested that this methodology may be useful for the preparation of highly functionalized enamines.

In this paper we describe a general synthesis of β -amino α,β -unsaturated esters and nitriles from the *E*- and *Z*-isomers of methyl 3-bromo-4,4-dimethoxy-2-butenates (**1**) and the corresponding nitriles (**2**) by substitution of the halogen with primary and secondary amines. Precedent for this methodology is the reported synthesis of β -cyano enamines by the reaction of β -chloroacrylonitrile with amines.⁴ The reactions proceed readily in carbon tetrachloride at room temperature and in good yields (Tables 1 and 2).

The stereochemical outcome from these reactions depends upon the amine type, activating group (ester or nitrile) and configuration of the starting bromo compound.

Thus, the *E*- and *Z*-esters **1** by treatment with pyrrolidine, morpholine and diethylamine afford the corresponding *E*-enamines **3a-c**, regardless of the initial stereochemistry. In contrast, the substitution of *E*- and *Z*-nitriles **2** proceeds with retention of configuration to yield the cyanoenamines (*E*)-**4a-c** and (*Z*)-**4a-c**, respectively. It is noteworthy that *Z*-cyanoenamines (*Z*)-**4a-c**, on standing at room temperature in carbon tetrachloride solution or under the reaction conditions used, slowly isomerize into the thermodynamically more stable *E*-enamines (*E*)-**4a-c**.

Table 1. Reaction of Methyl (*E*)- and (*Z*)-3-Bromo-4,4-dimethoxy-2-butenates (**1**) with Secondary and Primary Amines

Substrate	Amine		Reaction Time	Yield (%)	Product(s) (Ratio) ^a	
	R ¹	R ²			<i>E</i>	<i>Z</i>
(<i>E</i>)- 1	—(CH ₂) ₄ —		24 h	90	3a (100)	
(<i>Z</i>)- 1	—(CH ₂) ₄ —		15 h	92	3a (100)	
(<i>E</i>)- 1	—(CH ₂) ₂ O(CH ₂) ₂ —		20 d	100	3b (100)	
(<i>Z</i>)- 1	—(CH ₂) ₂ O(CH ₂) ₂ —		10 d	97	3b (100)	
(<i>E</i>)- 1	C ₂ H ₅	C ₂ H ₅	15 d	85	3c (100)	
(<i>Z</i>)- 1	C ₂ H ₅	C ₂ H ₅	8 d	95	3c (100)	
(<i>E</i>)- 1	—(CH ₂) ₂ —		24 h	77	3d (100)	
(<i>Z</i>)- 1	—(CH ₂) ₂ —		24 h	65		3d (100)
(<i>E</i>)- 1	C ₆ H ₅ CH ₂	H	4 d	90	3e (75)	
(<i>Z</i>)- 1	C ₆ H ₅ CH ₂	H	6 d	92	3e (10)	3e (90)
(<i>E</i>)- 1	<i>n</i> -C ₄ H ₉	H	3 d	92	3f (25)	3f (75)
(<i>Z</i>)- 1	<i>n</i> -C ₄ H ₉	H	3 d	67	3f (20)	3f (80)

^a Determined by ¹H-NMR.

Table 2. Reaction of (*E*)- and (*Z*)-3-Bromo-4,4-dimethoxy-2-butenitriles (**2**) with Secondary and Primary Amines

Substrate	Amine		Reaction Time	Yield (%)	Product(s) (Ratio) ^a	
	R ¹	R ²			<i>E</i>	<i>Z</i>
(<i>E</i>)- 2	—(CH ₂) ₄ —		1 h	90	4a (100)	
(<i>Z</i>)- 2	—(CH ₂) ₄ —		50 min.	85	4a (15)	4a (85)
(<i>E</i>)- 2	—(CH ₂) ₂ O(CH ₂) ₂ —		10 d	60	4b (100)	
(<i>Z</i>)- 2	—(CH ₂) ₂ O(CH ₂) ₂ —		6 d	90		4b (100)
(<i>E</i>)- 2	C ₂ H ₅	C ₂ H ₅	15 d	88	4c (100)	
(<i>Z</i>)- 2	C ₂ H ₅	C ₂ H ₅	4 d	90	4c (10)	4c (90)
(<i>E</i>)- 2	—(CH ₂) ₂ —		1 d	82	4d (100)	
(<i>Z</i>)- 2	—(CH ₂) ₂ —		1 d	60		4d (100)
(<i>E</i>)- 2	C ₆ H ₅ CH ₂	H	4 d	85	4e (85)	4e (15)
(<i>Z</i>)- 2	C ₆ H ₅ CH ₂	H	3 d	88	4e (85)	4e (15)
(<i>E</i>)- 2	<i>n</i> -C ₄ H ₉	H	2 d	87	4f (85)	4f (15)
(<i>Z</i>)- 2	<i>n</i> -C ₄ H ₉	H	1 d	80	4f (75)	4f (25)

^a Determined by ¹H-NMR.

Nevertheless, when the substitution is accomplished with aziridine on the four bromo derivatives (*E*)- and (*Z*)-**1** and (*E*)- and (*Z*)-**2**, the reaction proceeds in every case with retention of configuration. Similar results have previously been reported in the literature.⁵

On the other hand, esters **1** and nitriles **2**, all lead to a mixture of the two corresponding diastereoisomeric enamines with primary amines (*n*-butyl- and benzylamine). However, the *E/Z* ratio

depends essentially upon the activating groups and scarcely upon the stereochemistry of the substrate.⁶ Accordingly, *Z*-isomers predominate over *E*-isomers when the substitution is effected on haloesters and the *E*-enamines are the major components from the halonitriles.⁷

methyl (*Z*)-3-amino-4,4-dimethoxy-2-butenolate [(*Z*)-**3g**] is readily obtained via the enamine (*E*)-**3a** by treatment with aqueous ammonia.

The stereochemical results, summarized in Tables 1 and 2, can be explained on the assumption that the substitution reaction on **1** and **2** proceeds by a concerted process with retention of the configuration.¹⁰ The formation of inversion compounds presumably involves a rapid isomerization, which in some cases [(*E*)-**3a–c** from (*Z*)-**1**] is too fast to detect the primary products. However, an elimination-addition mechanism cannot be definitively excluded in *Z*-substrates, which possess bromo and hydrogen atoms in *trans* disposition.

Structural analysis of enamines (*E*)-**3a–f**, (*E*)-**4a–f** and (*Z*)-**3d–g**, (*Z*)-**4a–f** was made on the basis of their spectral data (Tables 3, 4 and 5).

Table 3. Spectral Data of Methyl (*E*)-3-Alkylamino-4,4-dimethoxy-2-butenates **3a–f** and (*E*)-3-Alkylamino-4,4-dimethoxy-2-butenenitriles **4a–f**

Compound		¹ H-NMR (CDCl ₃ /TMS) ^a , δ				IR (film) ^b (cm ⁻¹)		MS ^c (75 eV)	
Y	R	HC(OCH ₃)	HC=	OCH ₃	(OCH ₃) ₂	ν _{C=O} /ν _{C≡N}	ν _{C=C}	m/z (%)	
a	CO ₂ CH ₃	1-pyrrolidinyl	6.55	4.31	3.49	3.38	1730–1685	1580	229 (M ⁺), 182 (100), 75
b	CO ₂ CH ₃	4-morpholinyl	6.56	4.74	3.58	3.44 ^d	1740–1695	1595	245 (M ⁺), 214, 75 (100)
c	CO ₂ CH ₃	(C ₂ H ₅) ₂ N–	6.69	4.46	3.52	3.42 ^d	1730–1680	1580	231 (M ⁺), 156, 75 (100)
d	CO ₂ CH ₃	1-aziridinyl	5.87	5.12	3.48	3.31	1720	1630	201 (M ⁺), 75 (100), 59
e	CN	1-pyrrolidinyl	5.28	3.74		3.45	2200	1590	196 (M ⁺), 75 (100)
f	CN	4-morpholinyl	5.32	4.05		3.47	2205	1595	212 (M ⁺), 75 (100), 47
g	CN	(C ₂ H ₅) ₂ N–	5.34	3.85		3.39 ^d	2200	1585	198 (M ⁺), 167, 75 (100)
h	CN	1-aziridinyl	5.04	4.67		3.41	2225	1615	168 (M ⁺), 75 (100), 47
i	CO ₂ CH ₃	C ₆ H ₅ CH ₂ NH–	6.12	4.54	3.51	3.41 ^d	1735–1665	1625	265 (M ⁺), 91 (100), 75
j	CO ₂ CH ₃	<i>n</i> -C ₄ H ₉ NH–	6.09	4.63	3.63	3.46	1700–1665	1625	231 (M ⁺), 75 (100)
k	CN	C ₆ H ₅ CH ₂ NH–	5.12	3.85		3.45 ^d	2205	1610	232 (M ⁺), 91 (100), 75
l	CN	<i>n</i> -C ₄ H ₉ NH–	5.20	3.88		3.44	2210	1615	198 (M ⁺), 75 (100)

Hitachi Perkin-Elmer R-24 or Varian EM-390 spectrometers. All signals are singlets.

Pye Unicam Sp 1100 or Perkin-Elmer 254 instruments.

^c Hewlett-Packard GC-MS System 5985 or 5995 models.

^d In CCl₄ solution.

Table 4. Spectral data of Methyl (*Z*)-3-Alkylamino-4,4-dimethoxy-2-butenates **3d–g** and (*Z*)-3-Alkylamino-4,4-dimethoxy-2-butenenitriles **4a–f**

Compound	Y	R	¹ H-NMR (CDCl ₃ /TMS) ^a , δ				IR (film) ^b (cm ⁻¹)		MS ^c (75 eV)
			HC(OCH ₃) ₂	HC=	OCH ₃	(OCH ₃) ₂	ν _{C=O} /ν _{C≡N}	ν _{C=C}	m/z (%)
	CO ₂ CH ₃	1-aziridinyl	4.65	5.43	3.62	3.26	1715	1625	201 (M ⁺), 75 (100), 59
	CN	1-pyrrolidinyl	4.57	4.02		3.26 ^d	2200	1590	196 (M ⁺), 75 (100)
	CN	4-morpholinyl	4.53	4.25		3.32	2210	1600	212 (M ⁺), 75 (100)
	CN	(C ₂ H ₅) ₂ N—	4.54	4.04		3.27 ^d	2160	1575	198 (M ⁺), 75, 47
	CO ₂ CH ₃	1-aziridinyl	4.98 ^e	4.73		3.46	2225	1615	168 (M ⁺), 75 (100), 47
	CO ₂ CH ₃	C ₆ H ₅ CH ₂ NH—	4.74 ^e	4.64	3.56	3.25 ^d	1735–1665	1625	265 (M ⁺), 91 (100), 75
	CN	<i>n</i> -C ₄ H ₉ NH—	4.79 ^e	4.78	3.64	3.35	1700–1665	1625	231 (M ⁺), 75 (100)
	CN	C ₆ H ₅ CH ₂ NH—	4.61	4.02		3.24 ^d	2205	1610	232 (M ⁺), 91, 75 (100)
	CN	<i>n</i> -C ₄ H ₉ NH—	4.68	4.02		3.32	2210	1615	198 (M ⁺), 75 (100)
	CO ₂ CH ₃	NH ₂ —	4.74 ^e	4.73	3.60	3.27	1690–1640	1580	175 (M ⁺), 75 (100)

Hitachi Perkin-Elmer R-24 A or Varian EM-390 spectrometers.

Pye Unicam Sp 1100 or Perkin-Elmer 254 instruments.

Hewlett-Packard GC-MS System 5985 or 5995 models.

^d In CCl₄ solutions.

^e The assignments may be interchanged.

Table 5. ^{13}C -NMR Data

Compound	^{13}C -NMR (CDCl_3) ^a , δ				Compound	^{13}C -NMR (CDCl_3) ^a , δ			
	$\text{C}=\text{O}/\text{C}\equiv\text{N}$	$=\text{C}-\text{N}$	$=\text{C}-\text{H}$	$\text{C}(\text{OCH}_3)_2$		$\text{C}=\text{O}/\text{C}\equiv\text{N}$	$=\text{C}-\text{N}$	$=\text{C}-\text{H}$	$\text{C}(\text{OCH}_3)_2$
(<i>E</i>)-3a	168.5	156.0	99.7	84.8					
(<i>E</i>)-3b	168.4	158.4	100.3	89.0					
(<i>E</i>)-3c	168.5	156.9	100.0	84.7					
(<i>E</i>)-3d	166.8	164.3	102.8	100.2	(<i>Z</i>)-3d	165.7	160.4	102.2	100.1
(<i>E</i>)-4a	121.0	155.9	102.9	61.9					
(<i>E</i>)-4b	120.0	158.8	103.7	66.5					
(<i>E</i>)-4c	121.0	157.3	104.2	62.6	(<i>Z</i>)-4c	118.8	154.3	102.8	59.7
(<i>E</i>)-4d	116.2	166.8	101.6	81.2	(<i>Z</i>)-4d	112.9	165.6	100.9	79.8
(<i>E</i>)-3e	168.0	156.6	98.6	83.6	(<i>Z</i>)-3e	170.6	157.3	101.2	82.7
(<i>E</i>)-3f	168.5	157.0	98.6	82.3	(<i>Z</i>)-3f	170.7	157.7	101.2	81.4
(<i>E</i>)-4e	119.3	157.9	99.4	60.7	(<i>Z</i>)-4e	— ^b	161.5	99.5	64.4
(<i>E</i>)-4f	119.9	158.3	99.8	59.6	(<i>Z</i>)-4f	120.3	155.6	100.6	57.6
					(<i>Z</i>)-3g	170.6	157.5	124.6	100.6

^a Bruker WM 200 SY spectrometer.^b Signal not found in ^{13}C -NMR spectrum of the mixture of diastereoisomers.**Methyl 3-Alkylamino-4,4-dimethoxy-2-butenates and 3-Alkylamino-4,4-dimethoxy-2-butenitriles: General Procedure:**

To a solution of the methyl (*E*)- or (*Z*)-3-bromo-4,4-dimethoxy-2-butenate (**1**) or (*E*)- or (*Z*)-3-bromo-4,4-dimethoxy-2-butenitrile (**2**) (4 mmol) in CCl_4 (10 mL) is added the amine (8 mmol). The mixture is kept at room temperature until the starting acetal disappears (monitored by ^1H -NMR). After removal of salts, the solvent is evaporated *in vacuo*. The purity of the crude compounds (monitored by ^1H -NMR) is, in every case, suitable for preparative purposes. Attempts to obtain analytical samples by chromatographic methods (column and TLC) or distillation *in vacuo* failed due to partial decomposition. Reaction times, yields and *E/Z* ratios of enamines are shown in Tables 1 and 2.

Methyl (*Z*)-3-amino-4,4-dimethoxy-2-butenate [(*Z*)-3g]:

To a 1 M aq. NH_3 solution (10 mL) is added methyl (*E*)-4,4-dimethoxy-3-(1-pyrrolidinyl)-2-butenate (**3a**; 0.23 g, 1 mmol). The mixture is stirred two hours at 40°C . The crude material is extracted with EtOAc (3×5 mL), the organic layer dried (MgSO_4), and the solvent evaporated *in vacuo* to give (*Z*)-3g; yield: 0.12 g (70%).

Financial support from Comisión Asesora de Investigación Científica y Técnica is gratefully acknowledged.

Received: 26 August 1987

A One-Pot Synthesis of β -Acylenamines

Souheir El Cherif, Loïc René*

INSERM, Pharmacologie, 17 rue du Fer à Moulin, F-75005 Paris, France

β -Acylenamines (β -amino α,β -unsaturated ketones) **4** are prepared in good yields in a Mannich reaction by heating a mixture of ketone **1**, triethyl orthoester **2** and secondary amine **3** in a pressure vessel.

β -Acylenamines (β -amino α,β -unsaturated ketones) are versatile synthetic tools,¹ which are mostly prepared from a β -diketone and an amine,² from a ketone and *N,N*-dimethylformamide acetal,³ and from an oxymethylene ketone⁴ or a β -dialkoxy ketone⁵ and an amine. Other methods such as the acylation of an enamine,⁶ from a β -cyanovinyl ketone and a secondary amine,⁷ from ketene and an enamine,⁸ from a cyano derivative and a ketone,⁹ from an oxime sulfonate and a silyl enol ether,¹⁰ from an acetylenic ketone and an amine,¹¹ from a β -chlorovinyl ketone and an amine,¹² from a 2-alkylthio-1-alkenyl or a 2-alkylsulfinyl-1-alkenyl ketone and an amine,¹³ by the palladium assisted amination of an olefin,¹⁴ and by the palladium induced dehydrogenation of a β -amino ketone¹⁵ are described in the literature.

- (1) Fariña, F., Maestro, M. C., Martín, M. R., Martín, M. V., Sánchez, F. *Synthesis* **1983**, 397.
- (2) Fariña, F., Martín, M. R., Martín, M. V., Sánchez, F. *J. Chem. Res.* **1982**, (S) 142, (M) 1508.
- (3) For the syntheses of compounds (*E*)- and (*Z*)-**1** and (*E*)-**2**, see: Fariña, F., Martín, M. R., Martín, M. V., Sánchez, F. *Synthesis* **1977**, 642.
For the synthesis of compound (*Z*)-**2** see, Ref. 2.
- (4) Scotti, F., Frazza, E. J. *J. Org. Chem.* **1964**, 29, 1800.
See also: Pohland, A. E., Benson, W. R. *Chem. Rev.* **1966**, 66, 161.
- (5) Truce, W. E., Gobarty, M. L. *J. Org. Chem.* **1970**, 35, 2113.
- (6) Chalchat, J. C., Théron, F., Vessière, R. *Bull. Soc. Chim. Fr.* **1970**, 4486.
- (7) Chalchat, J. C., Théron, F. *Bull. Soc. Chim. Fr.* **1973**, 3391.
- (8) Fariña, F., Martín, M. R., Martín, M. V., Sánchez, F. *Rev. R. Acad. Cienc. Exactas, Fis. y Nat., Madrid* **1979**, 73, 599.
- (9) Fariña, F., Martín, M. R., Martín, M. V., Sánchez, F. *J. Chem. Res.* **1981**, (S) 206, (M) 2547.
- (10) Rappoport, Z. *Acc. Chem. Res.* **1981**, 14, 7.

We now report that β -acylenamines of type **4** can be easily obtained in a Mannich reaction by heating a mixture of triethyl orthoformate, ketone and secondary amine in a pressure vessel according to the method explored by Wolfbeis¹⁶ that we have already applied for nitroenamines¹⁷ and cyanoenamines.¹⁸