Tetrahedron Letters, Vol.31, No.12, pp 1713-1716, 1990
Printed in Great Britain

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

ELECTROCHEMICAL SYNTHESIS OF THE VINYLOGS OF N-ACYL N,O-ACETALS AND THEIR REACTIVITY

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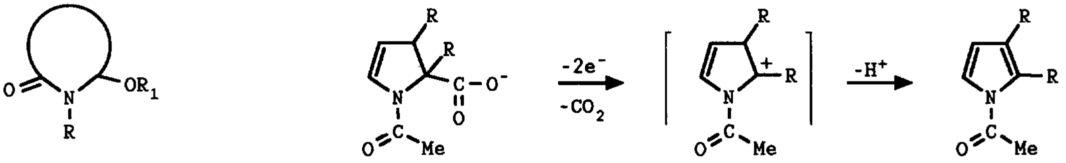
Abstract: Vinylogs of N-acyl N,O-acetals are formed in good yields by anodic oxidation, in methanol or water, of β-enaminoesters derived from pyroglutamic acid. These new acetals react easily with nucleophiles or silylated amines.

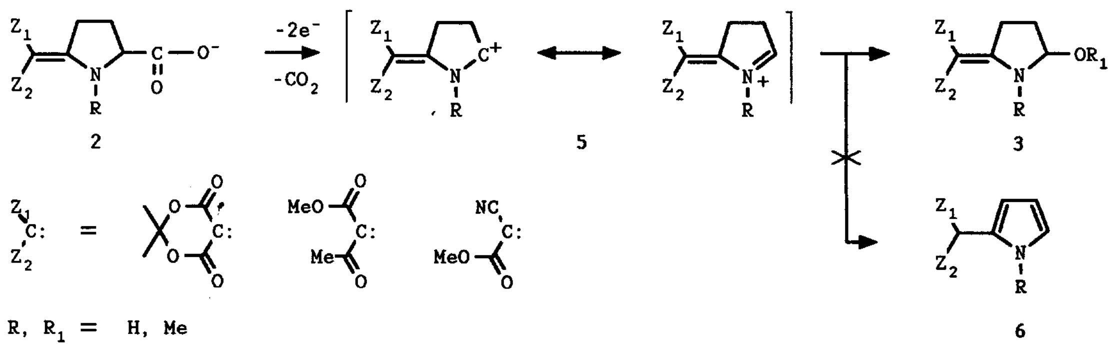
Anodic oxidation of N-acylamino acids was first reported in 1979.[1] The N-acyl N,O-acetals (1) obtained from that reaction, or from the anodic α-methoxylation of lactams (Shono's procedure)[2] or the reduction of imides (Speckamp's procedure),[3] have found many applications as versatile organic building blocks,[4] particularly in the synthesis of natural products.[5]



1 7 8

Scheme 1

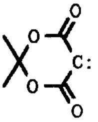
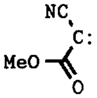
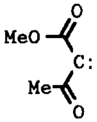
In this Letter, we report that vinylogs of N-acyl N,O-acetals 3[6] can be obtained in an excellent yield by anodic oxidation, in methanol or water, of β-enaminoesters 2, derived from pyroglutamic acid (vinylogous N-acylamino acids)(scheme 2).



Scheme 2

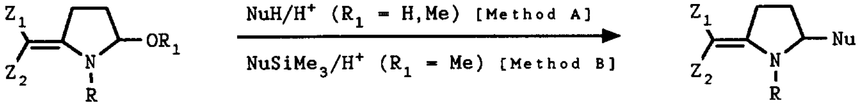
TABLE 1

Anodic oxidation of acids 2 : β-enaminoesters 3

Z_1 C: Z_2	R	R_1	Yield (%)*	mp. (°C)
	H	Me	62	126
	Me	Me	55	105
	Me	H	75	186
	H	Me	72	111
	H	H	77	162
	Me	Me	67	88
	Me	H	87	110
	H	Me	43	68

*Yield of pure, recristallized product.[12]

N-Acyl N,O-acetals 1 react easily with nucleophiles or silylated nucleophiles (acid catalysis).[7] In the same way, their vinylogous analogs 3 yielded derivatives 4 when they were opposed to water, methanol, amines or silylated amines, and a catalytic amount of an acid (scheme 3).



3

4

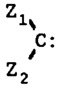
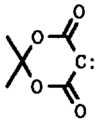
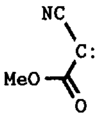
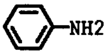
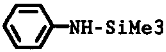
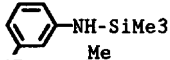
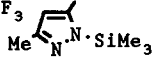
Scheme 3

In the anodic decarboxylation (2 → 3), the iminium salts 5 were intermediates, and it was interesting to note that in this reaction as well as for the substitutions (3 → 4), formation of pyrrole 6 was never observed (anodic decarboxylation of the enacylamino acid 7 mainly furnishes the pyrroles 8 (scheme 1)[8]).

Many cyclic β-enaminoesters are used in the synthesis of natural products ;[9] except the β-enaminoesters derived from succinimide[6,10] or pyroglutamic acid,[11] all these compounds are not substituted on the carbon α to the nitrogen atom ; the synthetic pathway described in this work provides a useful method for the preparation of these substituted cyclic β-enaminoesters 3, 4,[6] from a very available starting material, through easy transformation of functional group.

TABLE 2

β-enaminoesters 4

	R	R_1	NuH or $NuSiMe_3$	Yield (%)*	mp. (°C)
	H	Me	H_2O	72[a]	188
	H	Me	H_2O	85[a]	162
	Me	H	MeOH	90[a]	88
	Me	H		63[b]	150
	Me	Me		85[c]	150
	Me	Me		49[d]	85
	Me	Me		80[c]	154

*Yield of pure, recristallized product.[12]

[a]Method A : reflux 15 mn of a slightly acidified (HCl) solution of compound 3 in water or methanol. [b]Reflux 5h of a slightly acidified (HCl) solution of compound 3 and aniline in methylene dichloride. [c]Method B : see the "representative procedure". [d]Same as method B, with CH_2Cl_2 as a solvent, and a water bath at room temperature.

A general electrolysis procedure for a preparation of β-enaminoesters 3 is as follows : a mixture of acid 2 ($R = H$, $Z_1 = CO_2Me$, $Z_2 = CN$) (141.8g, 0.675 mole), sodium methoxide (2.5g), tetra-n-butylammonium hydrogen sulfate (2.5g) and methanol (2500 ml) was stirred into an undivided jacketed beaker equipped with a nitrogen inlet, 25 graphite-rods anodes and 25 graphite-rods cathodes and an exit tube for venting purposes. The carbon-rods (6.15 mm in diameter), immersed 20 cm into the suspension, were spaced 10 mm apart. During the electrolysis, the temperature was maintained at 15°. The current was adjusted at 500 mA ; the initial cell voltage was 3.9 V. After 80 h, the suspension was filtered, the solution was slightly acidified with hydrochloric acid and evaporated. The combined solids were recristallized from methanol. The yield of β-enaminoester 3 ($R_1 = Me$) was 72 % ; mp. 144°, IR (nujol) ν cm^{-1} : 3300 (N-H), 2200 (C≡N), 1720 (C=O), 1600 (C=C), 1210 (C-O) ; ^1H NMR ($CDCl_3$) δ ppm : 1.9-2.4 (m, 2H), 2.7-3.2 (m, 2H), 3.30 (s, 3H), 3.74 (s, 3H), 5.1 (m, 1H).

In a representative procedure for method B, triflic acid (0.2 ml) was slowly added via syringe through a septum cap, to a stirred mixture of β-enaminoester 3 (R, R_1 = Me) (2.1g, 10 mmole) and trimethylsilyl aniline (1.8g, 10 mmole). The reaction was exothermic and instantaneous. The solid was washed with methylene dichloride/ether, and the combined solvents were evaporated. The yield of crude β-enaminoester 4 (R = Me, Nu = C_6H_5-NH-) was 94 %. This product was recristallized from methylene dichloride/ether, mp. 150°, IR (nujol) ν cm^{-1} : 3330 (C=O), 2190 (C≡N), 1690 (C=O), 1600 (C=C), 1560 (C=C) ; ^1H NMR ($CDCl_3$) δ ppm : 1.6-2.9 (m, 2H), 3-3.6 (m, 2H), 3.35 (s, 3H), 3.71 (, 3H), 4.2 (s, 1H), 5.27 (t, J = 6.7 Hz, 1H), 6.3-7.5 (m, 5H).

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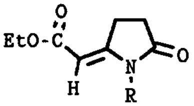

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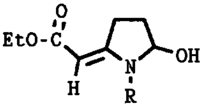

ii

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(12) All new compounds have been fully characterized by elemental analysis (C, H, N, O ± 0.4), IR, ^1H NMR. The assignment of the substituents of the exocyclic double bound as Z_1 = CO_2Me and Z_2 = CN, was made on the basis of NMR data.

(Received in France 22 November 1989)