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NEW SYNTHETIC METHODS FOR 4-AMINO-2(5H)-FURANONES

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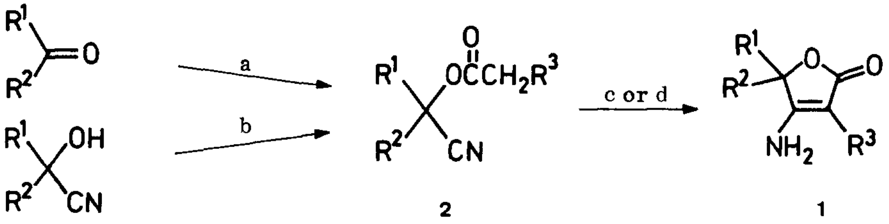
Two new efficient methods are disclosed for the synthesis of the title compounds: (1) base-promoted ring closure of 2-acyloxy alkanenitrile and (2) acid-mediated lactonization of t-butyl 4-alkoxy-3-amino-2-alkenoates.

The title compounds (**1**), when converted into urea derivatives by the reaction with isocyanates, show marked biological activities and may find their use as defoliant, plant growth retardants,[2] and anti-hypertensive agents.[3] The apparently low synthetic efficiency[4] of the novel compounds prompted us to investigate new approaches to this class of compounds. We report herein two short-step methods for the synthesis of **1**, namely, (1) base-promoted ring-closure of 2-acyloxy alkanenitrile (**2**) and (2) acid-mediated lactone formation of t-butyl 4-alkoxy-3-amino-2-alkenoates (**4**). This disclosure should be of great help for the synthesis of physiologically active tetronic acids and their derivatives.[5]

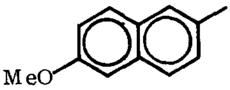
The first approach is illustrated in Scheme 1. The requisite intermediate **2** was prepared by silyl cyanation[6] of the starting ketone followed by acylation with iron(III) chloride catalyst (Method A),[7] or alternatively, acylation of the readily available cyanohydrin (Methods B - D) (Table 1). The resulting 2-acyloxyalkanenitrile (**2**) was treated with various bases[8] under different conditions. For example, the transformation of 2-acetoxy-2-methylpropanenitrile (**2a**) ($R^1 = R^2 = Me$, $R^3 = H$) to 3-amino-5,5-

Scheme 1



a: (i) Me_3SiCN, ZnI_2, (ii) $(R^3CH_2CO)_2O$, $FeCl_3$
b: $(R^3CH_2CO)_2O$ (or R^3CH_2COCl), Py (or Et_3N)
c: $LiN(SiMe_3)_2$, THF, -78 °C, d: NaH, THF, reflux

Table 1 Base-Promoted Synthesis of **1**

entry	R^1	R^2	R^3	Preparation of **2** Method and % Yield		Preparation of **1** Method and % Yield	
1	Me	Me	H	A	50	E	82
2	iPr	Me	H	B	65	E	62
3	$n\text{-}C_9H_{19}$	Me	H	B	82	E	63
4	Ph	Me	H	B	90	E	87
5	$PhCH_2$	Me	H	B	63	E	96
6		Me	H	B	92	E	95
7	$-(CH_2)_5-$		H	A	36	E	74
8	Et	Et	H	B	66	E	65
9	Me	Me	Me	A	46	E	88
10	Me	Me	Cl	A	81	E	16
11	Me	Me	COMe	C	90	F	28
12	Me	Me	Ph	D	32	F	55
13	Me	Me	SPh	D	43	F	22
14	Me	Me	SOPh	G	25	F	86

A: Cyanohydrin of the corresponding ketone was acetylated with acid anhydride and pyridine.

B: Ketone was treated with trimethylsilyl cyanide (ZnI_2 catalyst) and then with acetic anhydride ($FeCl_3$ catalyst).

C: Acetone cyanohydrin was treated with diketene and pyridine.

D: Acetone cyanohydrin was treated with the corresponding acid chloride and triethylamine.

E: The acyloxynitrile **2** was treated with 2.4 mol equivalents of $LiN(SiMe_3)_2$ at -78 °C in THF.

F: **2** was treated with an excess of sodium hydride in THF at reflux temperature.

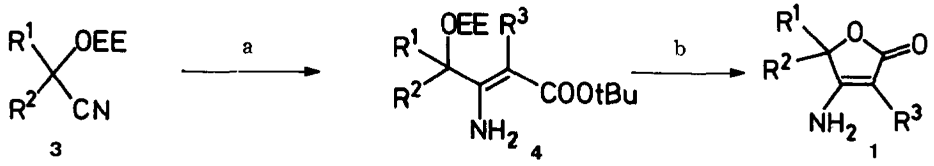
G: Oxidation of the corresponding sulfide with m-chloroperoxybenzoic acid. The overall yield from acetone cyanohydrin is given.

dimethyl-2(5H)-furanone (**1a**) ($R^1 = R^2 = Me$, $R^3 = H$) was studied first with KOtBu (THF, 0 °C), Mg[N(i-Pr)$_2$]$_2$ (THF, -78 to -74 °C), LiN(iPr)$_2$ (THF, -78 °C), and LiN(SiMe$_3$)$_2$ (THF, -78 °C), hereby giving the desired product in 4, 24, 60, and 82% yields, respectively. Thus, the last conditions were applied to other 2-acyloxyalkanenitriles (**2**) to give 5,5-disubstituted derivatives of **1** in good yields as shown in Table 1. It should be emphasized that whereas the intermolecular reaction of the lithium enolate of esters with nitriles fails to take place, the corresponding intramolecular transformation is readily attained.[9] When the starting material has a carbanion-stabilizing group R^3 at the α-carbon of the acetate moiety, sodium hydride was found to be a better base.

A typical procedure is as follows: A tetrahydrofuran (THF, 3 ml) solution of **2a** (0.127 g, 1.0 mmol) was added to LiN(SiMe$_3$)$_2$ (2.5 mmol in 3 ml of THF) drop by drop at -78 °C under an argon atmosphere. After 2 h, sat. ammonium chloride aqueous solution (5 ml) was added to the reaction mixture to quench the reaction. The resulting mixture was warmed to room temperature and concentrated under reduced pressure. The residue was extracted with methanol. The methanolic extract was concentrated and the residual oil was purified by preparative TLC (silica gel, dichloromethane-methanol 10 : 1) to give **1a** (0.104 g, 82% yield). Mp 205-207 °C. MS: m/z 127 (M^+); ^1H NMR (CDCl$_3$-DMSO-d$_6$ 1 : 1): δ 1.48 (s, 6 H), 4.48 (s, 1 H), 6.57 (br s, 2 H); IR (KBr): 3400, 3350 (sh), 3220, 3000, 1720, 1680, 1660, 1615, 1600 cm^{-1}. C, 56.55; H, 7.14; N, 10.90%. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02%.

When **2** (R^1 or $R^2 = H$) was subjected to the base-catalyzed cyclization, the desired product **1** (R^1 or $R^2 = H$) was produced in low yields. For example, **2b** ($R^1 = Me$, $R^2 = R^3 = H$) gave **1b** in only 6% yield. The low efficiency may be ascribed to a competitive hydrogen abstraction from C-H α to CN by the base. This drawback was overcome by the second approach shown in Scheme 2 which involves the reaction of O-protected cyanohydrins **3** with the magnesium enolate of t-butyl acetate[9] to give **4** followed by cyclization with hydrogen halide gas. The results summarized in Table 2 show that the desired 3-amino-2(5H)-furanones **1** (R^1 or $R^2 = H$) are produced in moderate to good yields. Hydrogen chloride and bromide are applicable which effect removal of both the O-protecting and the t-butyl ester groups, isomerization of the C=C bond, and lactonization, all in one operation. After these transformations, the final products **1** precipitate from the benzene or toluene solution. Purification of **1** was carried out by preparative TLC. It is worth pointing out that **1** is produced without hydrolysis of the enamine moiety.[10]

Scheme 2



a: $R^3CH{=}C(OtBu)OMgX$, Et_2O, 0 °C, b: HX, PhH (or PhMe), 0 to 5 °C

Table 2 Acid-Mediated Synthesis of **1**

entry	R^1	R^2	R^3	% Yield of **4**	HX	% Yield of **1**
1	Me	H	H	81	HCl	65
2	Me	H	H	--	HBr	72
3	Et	H	H	65	HBr	32
4	Me	H	Me	47	HBr	39
5	Me	Me	H	79	HCl	34
6	$-(CH_2)_5-$		H	46	HCl	47

A procedure for the preparation of 3-amino-5-methyl-2(5H)-furanone **1b** is typical. Dry hydrogen chloride gas was bubbled into a benzene (100 ml) solution of t-butyl 3-amino-4-(1-ethoxyethoxy)-2-pentenoate (**4b**) (100 mg) over a period of 2 h. Colorless material precipitated after 30 min's bubbling. The precipitates were collected and washed twice with benzene. Purification by preparative TLC (silica gel, dichloromethane-methanol 10 : 1, R_f 0.19–0.29) gave colorless solid **1b** (29 mg, 65% yield), mp 151-152 °C (lit^2 150-152 °C).

References and Notes

1 Trainee (1983-1985) from Nippon Soda Co., Ltd.

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4 The reported procedure starts with tetronic acids which are subjected to the reaction with phenylhydrazine and subsequent hydrogenolysis.[2]

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10 When **4b** was treated with dil hydrochloric acid (3% aq HCl-EtOH 1 : 3, r.t., 20 min), hydrolysis of the O-protecting group and the enamine moiety took place to give t-butyl 4-hydroxy-3-oxopentanoate in a quantitative yield.

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