1,4-ADDITIONS OF AMINES TO 5-METHOXYFURAN-2(5H)-ONE; AN EFFICIENT SYNTHESIS OF AMINO DIOLS

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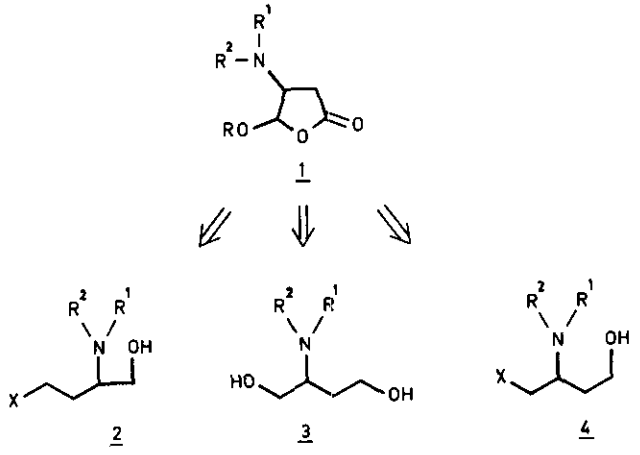
Abstract: The 1,4-addition of various primary and secondary amines to 5-methoxyfuran-2(5H)-one in N,N-dimethylformamide or methylene chloride at room temperature affords quantitatively 4-amino lactones 1a-g. The latter compounds are conveniently reduced to amino diols in high yields. Under similar conditions 1-(α)-methylbenzylamine gave optically active amino diols.

Amino alcohols have found widespread application as intermediates in organic synthesis. The 1,2- and 1,3-amino alcohol structural entity is common to several classes of biologically active compounds.[1] Furthermore, the synthesis of various ligands for transition metal catalysts is based upon amino alcohols.[2]

A number of routes to these compounds have been developed starting from, e.g. epoxides, cyanohydrines or amino acids.[3]

In recent years amino acids have also served as chiral building blocks for various optically active amino alcohols and derivatives which have found uses as chiral ligands or chiral auxiliaries in asymmetric syntheses.[4]

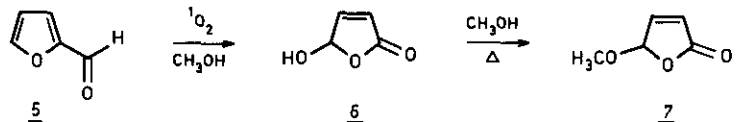


With the aim of developing new and flexible routes to amino alcohols and amino diols we have devised a synthetic strategy using 4-amino-substituted 5-alkoxybutyrolactones 1 as multifunctional synthons. Reduction reactions at the 2- and 5-positions of 1 would provide amino diols 3. The difference in oxidation state at the 2- or the 5-position in 1 allows selective modification, which would result in functionalized 1,2- (2) or 1,3-amino alcohols (4) respectively.

In this paper we describe an improved procedure to prepare amino lactones 1 and a novel synthesis of various amino diols 3.

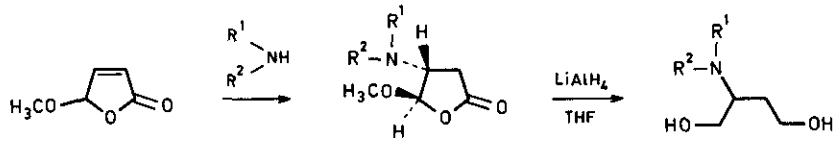
ADDITION OF AMINES TO 5-METHOXYFURAN-2(5H)-ONE; SYNTHESIS OF 4-AMINO LACTONES 1

The starting material 5-methoxyfuran-2(5H)-one (7) is readily prepared on a large (one mole) scale by Rose Bengal sensitized photooxidation of furfural (5) in methanol followed by esterification of the singlet oxygen reaction product 5-hydroxyfuran-2(5H)-one (6).[5] The reaction of lactone 7 with primary and secondary amines proceeds at room temperature in methylene chloride



5 6 7

or anhydrous dimethylformamide to provide 4-amino-substituted 5-methoxybutyrolactones 1. The results of the Michael type addition of several amines to 7 are summarized in Table 1. Exclusive 1,4-addition takes place without ring-opening of the lactone 7.[6]

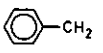
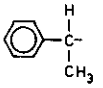


7 1 3

The results in methylene chloride as the solvent illustrate that the expected reaction rates are not entirely determined by the nucleophilicity of the amines. Presumably steric hindrance is an important factor which explains the finding that dibenzylamine did not provide the corresponding adduct 1 (R_1, R_2 = $CH_2C_6H_5$) under the reaction conditions described here. The effect of solvent polarity on the 1,4-addition reaction is substantial, especially with primary amines.[7] It was found that more polar solvents (e.g. DMF) increase the reaction rates drastically[7] (table 1). Although the 1,4-addition of amines to α,β-unsaturated carbonyl compounds is well documented, similar reactions with alkoxybutenolides have hardly been studied. Farina and coworkers[8] recently

observed exclusive 1,4-addition of a limited number of amines to the lactone (7). However long reaction times were required with only partial conversion of primary amines. The synthetic usefulness of the reported amine additions is rather limited due to the sensitive nature of the adducts which makes purification difficult. Small amounts of amines were found as a result of an elimination reaction (1 to 7) when amino lactones were distilled. Our results as summarized in Table 1 demonstrate the improvement on the amine addition; virtually quantitative conversions were reached in all cases whereas reaction times were reduced. For pyrrolidine and benzylamine quantitative yields were obtained in 5 and 30 min respectively (8 mmole scale). These reaction times compare favourably with those in previous studies[8] which resulted in reaction times of 5 and 15 days (70% conversion) respectively for 1a and 1f. In all cases only the trans diastereoisomers of 1 were found. The stereochemical assignment is based on the coupling constant between H_4 and H_5; $J_{4,5} \leq 2$ Hz for all compounds[9] (for spectral data, see Table 2). Nucleophilic attack occurs therefore exclusively from the side opposite the methoxysubstituent in accordance with observations by Farina et al.[8]

Table 1

		amino lactones (1)						amino diols (3)		
		solvent CH_2Cl_2		DMF						
no	R_1 | R_2	reaction time (hrs)	yield[a] (%)	reaction time (hrs)	yield[a] (%)	isolated yield (%)	bp (°C, torr)	no	isolated yield (%)	bp (°C, torr)
1a	$(CH_2)_4$	0.12	100			83	135 (0.005)	5a	73	145 (0.01)
b	$(CH_2)_5$	0.12	100			60	140 (0.005)	b	83	140 (0.01)
c	$(CH_2)_2O(CH_2)_2$	0.5 24	50 60	0.5	>95	25	170 (0.005)	c	86	140 (0.01)
d	C_2H_5 C_2H_5	1 24	50 65	0.5	>95	60	130 (0.005)	d	76	145 (0.01)
e	H n-C_4H_9	0.5 24	50 60	0.5	>95	62	130 (0.005)	e	75	130 (0.01)
f	H 	1 24	50 60	0.5	95	50	170 (0.001)	f	64	170 (0.005)
g	H (l-) 	1 24	40 45	1	95	50	180 (0.005)	g	72	170 (0.005)

[a] yield by NMR

The reaction of 7 with 1-α-methylbenzylamine affords two diastereoisomers 1g. This product contains three (consecutive) chiral centers with exclusively trans relationship ($J_{H4,5}$ = 2 Hz) between methoxy- and amino-substituents.

SYNTHESIS OF AMINO DIOLS 3

The conversion of the 4-amino-γ-butyrolactones 1 into 2-amino-1,4-diols 3 is readily accomplished at room temperature. Thus reduction of 1 with 2.5 equivalents of $LiAlH_4$ in tetrahydrofuran provides amino diols 3 in good to excellent yields. The results of the synthesis of amino diols are summarized in Table 1.

^1H Nmr spectra of the products are in accord with those expected for compounds 3 and showed the characteristic pattern for a 2-heterosubstituted 1,4-butanediol. Multiplets were observed for the CH_2 groups due to the presence of diastereotopic methylene protons. Spectral data for all new aminodiols are summarized in Table 3.

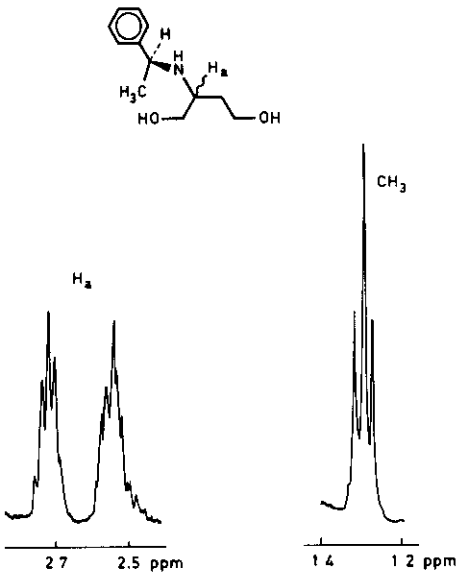


fig 1 ^1H NMR spectrum (CH_3, H_a absorptions) of amino diol 3g derived from S(-)-1-phenylethylamine adduct 1g

It should be mentioned that the reduction step proceeds without notable elimination of the amines. Two diastereoisomeric amino diols were obtained from the conversion of optically active amino lactones 1g (50:50 mixture). Two well separated multiplets were observed at 2.55 and 2.74 ppm assigned to the C_2 proton for each diastereoisomer of 3g (figure 1). In addition two partly separated doublets for the α-CH_3 substituent were found. No attempt was made sofar to separate these diastereoisomers into the enantiomerically pure amino diols. Separation followed by

reductive removal of the α-methylbenzyl group would provide a versatile route to both enantiomers of 2-amino-1,4-butanediol.

It can be concluded that the procedures described here give readily access to a variety of substituted amino diols. Selective protection of the hydroxyl group in the 1- or 4-position will provide 1,3- or 1,2-substituted amino alcohols respectively. These investigations are currently in progress.

EXPERIMENTAL

^{13}C- and ^{1}H-nmr spectra were recorded on Nicolet NT-200 and Varian VXR 300 spectrometers using Me_4Si as an internal standard and the chemical shifts are reported in δ units (ppm). Mass spectra were measured on a MS-9 mass spectrometer. Ir spectra were recorded on a Perkin-Elmer 257 Grating Spectrometer. All solvents and reagents were purified according to standard procedures. 5-Methoxyfuran-2(5H)-one was prepared according to the literature procedure.[5]

THE ADDITION OF AMINES TO 5-METHOXYFURAN-2(5H)-ONE (7)

General procedure: To a solution of 1.0 g (8.7 mmol) of 5-methoxyfuran-2(5H)-one in 10 ml of dry methylene chloride or N,N-dimethylformamide was added the amine (8.7 mmol). The mixture was stirred at room temperature for the appropriate time. The reaction was followed by ^{1}H-NMR until completion (Table 1 for amines used and reaction times). Subsequently the solvent was removed under reduced pressure to yield amino lactones 1 as oils. Products obtained in this way were pure according to ^{1}H-nmr spectra. The products were distilled in several cases (Table 1) to pure colourless oils, but this resulted in substantial loss of product. Furthermore a reverse Michael addition accompanied by distillation. For the reduction reaction described below amino lactones were used without further purification. Yields and bp's of the products are given in Table 1. The products were characterized by ir, ^{1}H- and ^{13}C-nmr, Ms and exact mass determination. Data are given in Table 2.

THE REDUCTION OF AMINO LACTONES; AMINO DIOLS 3

To a stirred solution of 0.30 g (8.0 mmol) of lithium aluminium hydride in 50 ml of tetrahydrofuran at 0°C under an inert atmosphere of nitrogen was added a solution of 4.0 mmol amino lactone dissolved in 15 ml of tetrahydrofuran. The resulting mixture was stirred for 30 min at 0°C and subsequently for 2 h at room temperature.

The excess lithium aluminium hydride was destroyed by adding carefully 1 ml of H_2O and 1 ml of an aqueous 10% KOH solution. The resulting salts were filtered off and extracted for 20 h with 50 ml of tetrahydrofuran at reflux temperature. The combined organic solutions were dried over Na_2SO_4,

the solvent was removed under reduced pressure and the resulting oil was distilled in vacuo to afford pure amino diols. Yields and bp's of the products are given in Table 1. The products were characterized by ir, ^{1}H- and ^{13}C-nmr, Ms and exact mass determination. Data are given in Table 3.

Table 2: Spectral data of amino lactones 1a-g

1a	^{1}H-NMR[a]	1.6-1.9 (m, 4H); 2.4-2.8 (m, 6H); 2.9-3.1 (m, 1H); 3.5 (s, 3H); 5.25 (d, 1H, J = 2 Hz)
	^{13}C-NMR[b]	174.09, 107.42, 64.83, 56.62, 51.13, 32.92, 22.82
	IR[c]	2950-2800 (C-H), 1790 (C=O), 1100-1040 (C-O)
	MS[d]	calc. 185.105; exp. 185.107
1b	^{1}H-NMR	1.5-1.6 (m, 6H); 2.4-2.6 (m, 6H); 3.0-3.3 (m, 1H); 3.5 (s, 3H); 5.3 (d, 1H, J = 2 Hz)
	^{13}C-NMR	176.39, 108.62, 68.14, 58.47, 52.58, 32.78, 27.43, 25.74
	IR	2950-2800 (C-H), 1795 (C=O), 1200-1000 (C-O)
	MS	calc. 199.121; exp. 199.122
1c	^{1}H-NMR	2.3-2.7 (m, 6H); 3.0-3.3 (m, 1H), 3.5 (s, 3H), 3.6-3.8 (m, 4H); 5.25 (d, 1H, J = 2 Hz)
	^{13}C-NMR	174.31, 106.95, 66.83, 66.38, 57.20, 50.62, 31.49
	IR	2950-2750 (C-H), 1790 (C=O), 1200-1000 (C-O)
	MS	calc. 201.101; exp. 201.103
1d	^{1}H-NMR	0.9-1.2 (s, 6H); 2.3-2.7 (q, 4H + m, 2H); 3.4 (m, 1H); 3.5 (s, 3H); 5.2 (d, 1H, J = 3 Hz)
	^{13}C-NMR	174.74, 107.66, 62.10, 56.59, 43.33, 31.14, 12.24
	IR	2950 (C-H), 1795 (C=O), 1150-1100 (C-O)
	MS	calc. 187.121; exp. 187.122
1e	^{1}H-NMR	0.8-1.0 (m, 3H); 1.1-1.5 (m, 5H); 2.0-3.0 (m, 4H); 3.3-3.4 (m, 1H); 3.5 (s, 3H); 5.1 (s, 1H)
	^{13}C-NMR	174.83, 108.21, 59.13, 55.96, 46.52, 34.12, 31.46, 19.63, 13.22
	IR	3360 (N-H); 2950-2800 (C-H), 1790 (C=O), 1150-1100 (C-O)
	MS	calc. 187.121; exp. 187.122

1f	^{1}H-NMR	1.6 (s, 1H); 2.3-2.4 (dd, 1H, J = 3 Hz); 2.8-2.9 (dd, 1H, J = 7 Hz); 3.4 (m, 1H); 3.5 (s, 3H); 3.8 (s, 2H); 5.1 (s, 1H); 7.3 (m, 5H)
	^{13}C-NMR	174.99, 138.86, 128.23, 127.79, 127.02, 108.81, 58.82, 56.43, 51.17, 34.44
	IR	3360 (N-H), 3050 (C-H, aryl), 2950-2800 (C-H), 1790 (C=O), 1200-1000 (C-O)
	MS	calc. 221,105; exp. 221.104
1g	^{1}H NMR	1.3-1.4 (dd, 3H, J = 3 Hz); 2.1 and 2.3 (dd, 1H, J = 8 Hz); 2.6 and 2.7 (dd, 1H, J = 4 Hz); 3.3 (s, 1H, J = 8 Hz); 3.3 and 3.5 (s, 3H); 3.7-3.9 (dq, 1H, J = 3 Hz); 4.9 and 5.2 (s, 1H), 7.0-7.4 (m, 5H).
	^{13}C-NMR	two diastereomers 174.92, 144.24, 128.39, 127.10, 126.34, 109.08, 108.77, 57.89, 57.18, 56.48, 56.41, 56.24, 55.97, 35.11, 34.57, 24.04, 23.98
	IR	3350 (N-H), 3050-2950 (C-H), 1795 (C=O), 1200-1100 (C-O)
	MS	calc. 235.121; exp. 235.120

[a] $CDCl_3$/TMS δ (ppm); [b] $CDCl_3$ δ (ppm); [c] neat (cm^{-1}); [d] exact mass.

Table 3: Spectral data of aminodiols 3a-3g

3a	^{1}H-NMR[a]	1.5-2.0 (m, 6H); 2.5-2.9 (m, 5H); 3.3-3.7 (m, 4H); 4.65 (s, 2H, OH)
	^{13}C-NMR[b]	62.25, 61.67, 60.21, 49.67, 30.83, 22.94
	IR[c]	3500-3200 (O-H), 2950-2800 (C-H), 1070-1020 (C-O)
	MS[d]	calc. 159.125; exp. 159.127
3b	^{1}H-NMR	1.4-2.0 (m, 8H); 2.5-3.0 (m, 5H); 3.3-3.8 (m, 4H); 4.4 (s, 2H, OH)
	^{13}C-NMR	65.97, 62.21, 60.46, 49.54, 28.02, 26.33, 24.30
	IR	3500-3200 (O-H), 2950-2750 (C-H), 1200-1050 (C-O)
	MS	calc. 173.142; exp. 173.142
3c	^{1}H-NMR	1.4-2.0 (m, 2H); 2.5-2.9 (m, 5H); 3.4-3.9 (m, 8H); 4.2 (s, 2H, OH)
	^{13}C NMR	67.13, 64.68, 61.42, 60.51, 48.69, 28.16
	IR	3600-3200 (O-H), 2900-2800 (C-H), (1200-1050) (C-O)
	MS	calc. 175.121; exp. 175.121

3d ^{1}H-NMR 1.0-1.2 (t, 6H); 1.5-1.8 (q, 2H); 2.4-2.7 (q, 4H); 2.8-3.1 (q, 1H); (3.6) (s, 2H, OH); 3.5-3.8 (m, 4H)

^{13}C-NMR 61.85, 60.58, 60.41, 43.00, 28.73, 13.95

IR 3600-3200 (OH, broad), 2950-2850 (C-H), 1200-1000 (C-O, broad)

MS calc. 161.142; exp. 161.141

3e ^{1}H-NMR 0.8-1.1 (m, 3H); 1.2-1.9 (m, 6H); 2.5-2.8 (m, 3H); 3.4-3.9 (m, 4H); 4.1 (s, 2H, OH)

^{13}C-NMR 62.30, 60.71, 58.63, 46.11, 32.34, 31.95, 20.00, 13.53

IR 3500-3100 (OH), 3000-2800 (C-H), 1100-1050 (C-O)

MS[e] calc. 130.123; exp. 130.121 ($M^{+}-CH_2{=}\overset{+}{O}H$)

3f ^{1}H-NMR 1.5-1.8 (q, 2H, J = 5 Hz); 2.6-3.0 (q, 1H, J = 5 Hz); 3.4-3.7 (m, 4H); 3.8 (s, 2H); 3.9 (s, 2H, broad); 7.3 (m, 5H)

^{13}C-NMR 139.31, 128.20, 127.88, 126.88, 62.36, 60.81, 57.94, 50.57, 32.50

IR 3500-3200 (OH), 3050-3000 (C-H aryl), 2950-2850 (C-H), 1100-1000 (C-O)

MS calc. 195.126; exp. 195.124

3g ^{1}H-NMR 1.3 (dd, overlap, 3H, J = 5 Hz), 1.6-1.7 (m, 2H), 2.5 and 2.7 (q, 1H, J = 5 Hz), 3.3-3.4 (m, 4H), 3.4 (s, broad OH), 3.9 (q, 1H, J = 5 Hz), 7.2 (m, 5H)

^{13}C-NMR two diastereomers

145.30, 145.07, 128.44, 127.02, 126.30, 63.68, 62.11, 61.45, 60.82, 55.81, 55.71, 55.15, 54.86, 34.05, 32.57, 24.72, 23.82

IR 3500-3400 (OH), 3050-2900 (C-H), 1100-1000 (C-O)

MS[e] calc. 178.123; exp. 178.121 ($M^{+}-CH_2{=}\overset{+}{O}H$)

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[a] $CDCl_3$, TMS δ (ppm); [b] $CDCl_3$ δ (ppm); [c] neat (cm^{-1}); [d] exact mass; [e] the exact mass of the parent peak could not be determined due to rapid loss of a $CH_2{=}\overset{+}{O}H$ fragment (M^{+} = 31).

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