AN IMPROVED SYNTHESIS OF 1-ALKYL-4-IMIDAZOLIN-2-ONES

Ooi Wong*, Noriko Tsuzuki, Mark Richardson, Howard Rytting, Ryoji Konishi†, and Takeru Higuchi

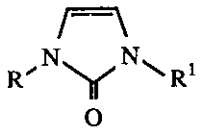
Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66045, USA

†Teikoku Seiyaku Co., OHkawa-Gun, Kagawa, Japan

Abstract - Two 1-alkyl-4-imidazolin-2-ones were prepared by acid-catalysed cyclization of N-(2,2-dialkoxyethyl)-N-alkylureas with improved yields of over 90%. The amount of HCl used in the reaction and the proper isolation procedure are the important factors in obtaining the high yields.

INTRODUCTION

There is increasing interest in 4-imidazolin-2-ones(A) in the recent



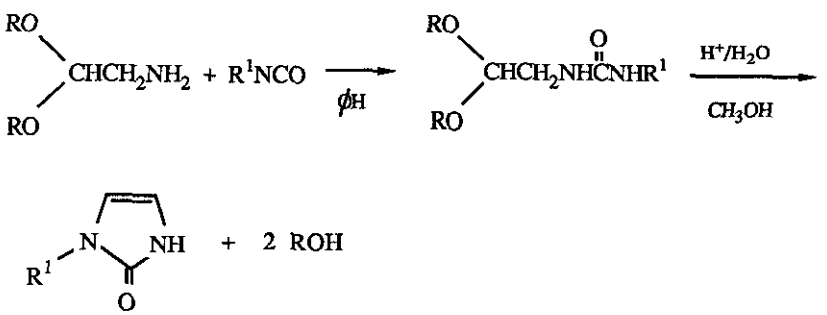
(A)

R, R^1 = H, alkyl or acetyl

literature[1-11]. They are important building blocks in the preparation of certain pharmaceutical chemicals[1,8]. However, some of these compounds are not commercially available. 4-Imidazolin-2-ones have been prepared by acid-catalysed cyclization of aminoacetaldehyde diethyl acetal[12] but serious side product formation makes this synthetic approach undesirable. Also, confirmation of the structure using this synthetic method was controversial[12]. Leonard and Wiemer[3] obtained an off white product (50%), A; R=CH_3, R^1=H by cyclization of N-(2,2-diethoxyethyl)-N-methylurea in the presence of 4 equivalents of HCl. We repeated this synthesis and obtained variable yields of the product ranging from a few

to 20%. The product was heavily contaminated with a yellowish side product. In this manuscript we report improved yields (over 90%) of 1-methyl-4-imidazolin-2-one by cyclization of two starting materials, N-(2,2-dimethoxyethyl)-N-methylurea and N-(2,2-diethoxyethyl)-N-methylurea. To test this improved method we also prepared 1-ethyl-4-imidazolin-2-one which was obtained in a very high yield(91%). The synthetic route for (A) is given in Scheme 1. Scheme 2 shows a possible mechanism of the cyclization step.

Scheme 1



Scheme 2

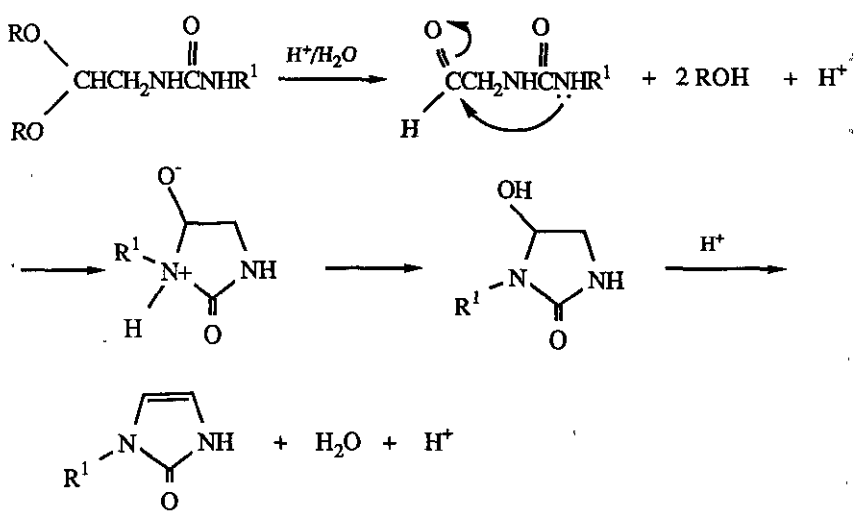


Table 1 shows the yields in percentage of 1-methyl-4-imidazolin-2-one obtained under different reaction conditions. The optimal yield from N-(2,2-diethoxyethyl)-N-methylurea is 29% when 1 equivalent of HCl was used. The low yields are attributed to incomplete extraction of 1-methyl-4-imidazolin-2-one[16]. The work-up procedures were carried out to remove as much solvent as possible from the neutralized reaction mixture followed by extracting the concentrated solution with chloroform, resulting in incomplete extraction. However, if the reaction mixture was extracted exhaustively with chloroform the yields are increased significantly, run 2 (both a and b, 38% and 56% respectively). In this regard, it would be advantageous to remove all the solvent from the reaction mixture to dryness and extract the target compound from the solid residue. By doing this, the yields increased remarkably to over 90%.

The amount of HCl used in the reaction mixture seems to be important in this type of cyclization. If insufficient HCl(run 1) was used, the yield was lowered due to incomplete reaction. However, increasing amounts of HCl caused more yellowish side product, with the reaction mixture turning deep yellow even before the isolation of the product was carried out, especially when N-(2,2-diethoxyethyl)-N-methylurea was used as the starting material. The formation of the yellowish side product is less serious in the case of N-(2,2-dimethoxyethyl)-N-methylurea and can be kept to a minimum by maintaining the pH of the reaction mixture near neutral during the course of isolation of the product.

EXPERIMENTAL

APPARATUS

Melting points were measured on a Thomas Hoover capillary melting point apparatus with an uncorrected thermometer. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer using $CDCl_3$, CCl_4 and d_6-DMSO as the solvents, infrared spectra on a Beckman AccuLab 4 spectrophotometer, and mass spectra were done by the mass spectroscopy laboratory of the department of chemistry, University of Kansas. HPL chromatograms were obtained at 220 nm by using a Spectroflow 783 programmable absorbance detector in conjunction with an Altex pump model 110A and a reverse-phase column RP-18 Spheri 5 4.6 x 100 mm and a guard column, SI-GU (both purchased from Brownlee Labs). Eluent for the HPL

chromatograms was acetonitril(1):water(2) with flowrate of 0.5 ml/min. Thin layer chromatograms were obtained by using high performance silica gel TLC plates (HPTLC - GHLF) purchased from Analtech and ethyl acetate as the developing solvent system. The spots were visualized by iodine vapour since these imidazolin-2-ones do not show uv absorption.

PROCEDURE

1-Methyl-4-imidazolin-2-one from N-(2,2-Dimethoxyethyl)-N-methylurea

N-(2,2-Dimethoxyethyl)-N-methylurea[13] (27.5 g, 0.17 mole) was dissolved in a mixture of methanol (670 ml) and water (340 ml). A solution of 0.48 M HCl (400 ml) was added dropwise from a dropping funnel. After stirring the reaction mixture for 3 days, it was neutralized with dilute NaOH solution. The pH of the solution was maintained neutral during the removal of the solvent by a rotovap under reduced pressure until a dry white solid remained in the flask. The solid was extracted four times with chloroform and the combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent gave 1-methyl-4-imidazolin-2-one(15.5 g, 93%), mp 140-142°C (sublimed). ^{1}H nmr ($CDCl_3$): δ 3.27(3H, s, CH_3-N), 6.50(1H, t, J=2Hz, HC=CH), 6.63(1H, t, J=2Hz, HC=CH). (d_6-DMSO): 3.11(3H, s, CH_3N); 6.30(1H, t, J=2Hz, HC=CH); 6.38(1H, t, J=2Hz, HC=CH); 11.67(1H, s, broad, NH, D_2O exchanged). ν_{max}(KBr): 1680(C=O); 1610, 1580 cm^{-1}(C=C). m/z 98, $C_4H_6N_2O$ requires 98. HPLC R_t 3.10 min. TLC R_f value = 0.08.

1-Methyl-4-imidazolin-2-one from N-(2,2-Diethoxyethyl)-N-methylurea

The procedure for this preparation was the same as that for the dimethoxy analog. N-(2,2-Diethoxyethyl)-N-methylurea[14] (21.3 g, 0.11 mole) in a mixture of methanol (520 ml) and water (260 ml) and a solution of 0.48 M HCl (310 ml) was stirred at room temperature for 2 days (TLC showed that the reaction was complete at 30 h). The usual work-up gave 1-methyl-4-imidazolin-2-one (10.5 g, 95%).

1-Ethyl-4-imidazolin-2-one

N-(2,2-Dimethoxyethyl)-N-ethylurea[15] (10 g, 0.057 mole) in a mixture of methanol (240 ml) and water (115 ml) and a solution of 0.48 M HCl (133 ml) was stirred at room temperature. The reaction was followed by TLC and found to be

complete after 20 h. After stirring the reaction mixture for an additional 4 h, the usual work-up gave 1-ethyl-4-imidazolin-2-one (5.8 g, 91%), mp 124-126°C. ^{1}H nmr (CCl_4): δ 1.97(3H, t, J=7Hz, CH_3CH_2-N), 3.60(2H, q, J=7Hz, CH_3CH_2-N), 6.07(1H, t, J=2Hz, HC=CH), 6.23(1H, t, J=2Hz, HC=CH), Signal for the NH was not observed in the spectrum. (d_6-DMSO): δ 1.67(3H, t, J=7Hz, CH_3CH_2N); 3.53(2H, q, J=7Hz, CH_3CH_2N); 6.30(1H, t, J=2Hz, HC=CH); 6.42(1H, t, J=2Hz, HC=CH); 11.67(1H, s, broad, NH, D_2O exchanged). ν_{max}(KBr): 1670(C=O); 1580 cm^{-1}(C=C). m/z 112, $C_5H_8N_2O$ requires 112. TLC R_f value = 0.16.

Table 1 Yields of 1-methyl-4-imidazolin-2-one from different reaction conditions

		yields(%)	
Run	Eq of HCl	a	b
1	0.5	19[c]	13[c]
2	1.0	29[c], 38[d]	41[c], 56[d], 85[e]
3	2.0	25[c], 96[e], 95[e]	93[e], 93[e]
4	3.0	12[c]	91[e]
5	4.0	18[c]	2[c]
6	5.0		2[c]

a The starting material was N-(2,2-diethoxyethyl)-N-methylurea.

b The starting material was N-(2,2-dimethoxyethyl)-N-methylurea.

c The product was isolated by concentrating the neutralized reaction mixtureand extracting the condensed residue 4 times with chloroform.

d The product was isolated by exhaustive extraction of the condensed residue as in c with chloroform.

e The product was isolated by removal of all the solvent from the neutralized reaction mixture to dryness and extraction of the solid 4 times with chloroform.

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13. This compound was prepared in almost quantitative yield by reaction of aminoacetaldehyde dimethoxy acetal with methyl isocyanate in benzene. ^{1}H nmr ($CDCl_3$): δ 2.85(3H, d, J=5Hz, CH_3N); 3.43(2H, t, J=5Hz, $-CH_2-$); 3.51(6H, s, CH_3O); 4.50(1H, t, J=5Hz, -CH-); 5.90(2H, m, NH). ν_{max} (film): 3380(NH); 1640, 1580(C=O); 1130 cm^{-1}(acetal).
14. Prepared in almost quantitative yield in the same way as that for its dimethoxy analog as in ref 13. ^{1}H nmr (CCl_4): δ 1.21(6H, t, J=7Hz, CH_3CH_2O); 2.16(3H, d, J=5Hz, CH_3NH); 3.37(3H, J=6Hz, $-CH_2-$); 1.95(4H, m, CH_3CH_2O-); 4.45(1H, t, J=6Hz, -CH-); 5.36(2H, m, NH). ν_{max} (KBr): 3340(NH); 1630, 1580(C=O); 1130 cm^{-1}(acetal)
15. Prepared in almost quantitative yield in the same way as that for its methyl analog as in ref 13. ^{1}H nmr (CCl_4): δ 1.15(3H, t, J=7Hz, CH_3CH_2N-); 3.33(6H, s, CH_3O); 4.33(1H, t, J=6Hz, $CHCH_2-$); 3.23(2H, multiplets, $-CH_2-$); 6.17(2H, m, NH). ν_{max} (film): 3360(NH); 1640, 1570(C=O); 1130 cm^{-1} (acetal).
16. Its solubility in water and methanol is practically high but has not been determined.

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