A SIMPLE SYNTHESIS OF 4-OXAZOLIDINONES, 1,3-OXAZIN-4-ONES AND 1,3-OXAZEPIN-4-ONES FROM AMIDE ALCOHOLS

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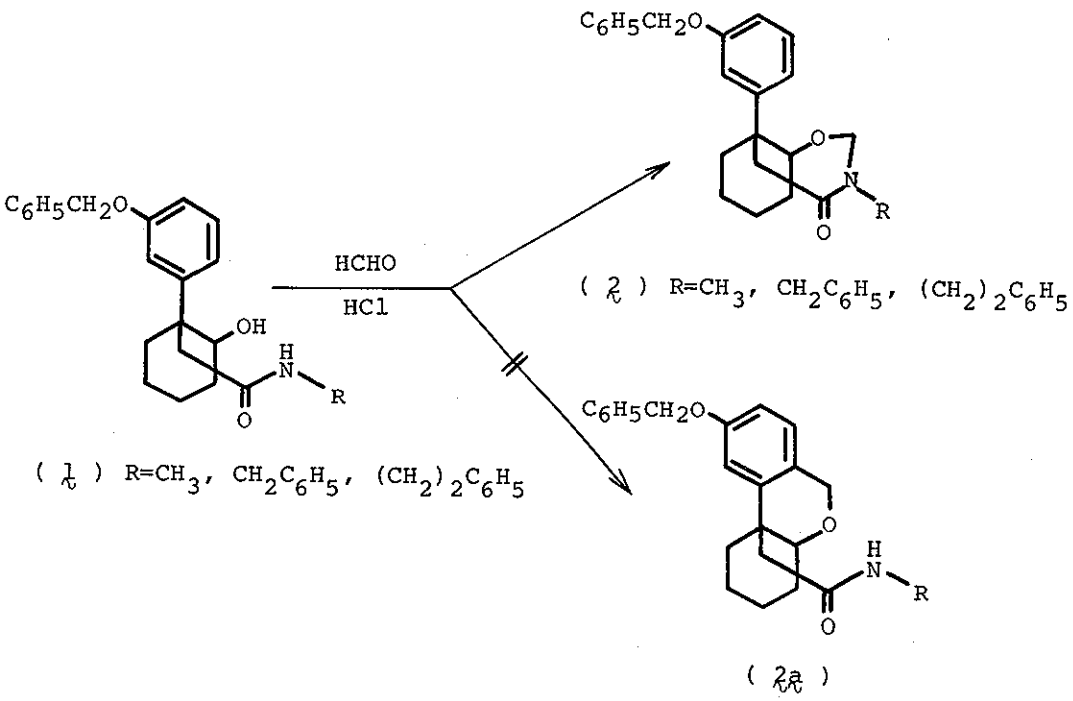
Acid-catalysed cyclisation of the secondary amides (3) having a hydroxyl group at α,β or γ-position with formaldehyde gave oxazolidine, 1,3-oxazine or 1,3-oxazepine derivatives, respectively.

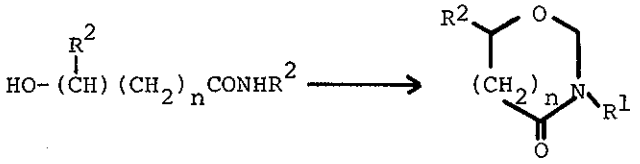
Previously, we have reported that a reaction of the secondary amides (1) having a hydroxyl group at γ-position with formalin in an acidic medium did not give the benzopyrans (2a) but the seven-membered compound, 1,3-oxazepin-4-ones (2), which formed a methylene bridge between hydroxyl and amide functions.[1] As an extension of our study, we investigated a general applicability of this reaction because there are only limited reports on a reaction of amides with carbonyl compounds.[2,3] Here, we wish to report an acid-catalysed cyclisation reaction of the secondary amides

possessing a hydroxyl group at α, β or γ-position with formaldehyde.



The starting amide alcohols (3) have been prepared by a condensation of amines with lactones and hydroxy carboxylic acids or esters by the known methods.[4] A cyclisation was carried out by refluxing a solution of the amides (3) and paraformaldehyde in toluene or xylene in the presence of p-toluenesulphonic acid under the removal of water formed and then the product (4) was purified on silica gel column chromatography, whose results are shown in Table I. Moreover, we have examined this cyclisation reaction by using formalin and hydrochloric acid in boiling ethanol for 8 hr, and found that 1,3-oxazine formation proceeded smoothly but

Table I. The Cyclisation Reaction of the Secondary Amides, Possessing a Hydroxyl Group at α, β and γ-position

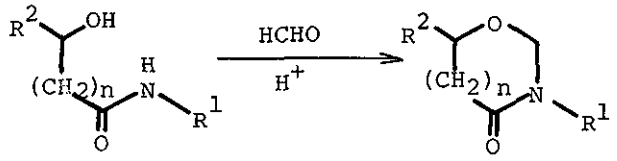


Compd. No.	n	R^1	R^2	Reaction Conditions Solv.[a]	Refluxing Time (hr)	Yield (%)[b]
1	0	CH_3	H	A	6	55.5
2	0	C_2H_5	H	A	5	54.5
3	0	$CH_2C_6H_5$	H	B	7	54.0
4	0	$(CH_2)_2C_6H_5$	H	A	6	80.9
5	0	$CH_2C_6H_5$	CH_3	B	3	57.7
6	0	$CH_2C_6H_5$	C_6H_5	B	5	44.1
7	0	$(CH_2)_2C_6H_5$	C_6H_5	A	6	54.6
8	1	CH_3	H	B	8	71.1
9	1	C_2H_5	H	B	8	66.0
10	1	C_6H_5	H	B	7	56.5
11	1	$CH_2C_6H_5$	H	B	8	92.1
12	1	$(CH_2)_2C_6H_5$	H	B	3.5	69.4
13	2	CH_3	H	A	6	50.4
14	2	C_2H_5	H	A	5.5	46.6
15	2	$CH_2C_6H_5$	H	B	9	45.5
16	2	$(CH_2)_2C_6H_5$	H	B	3	34.3

a) A=toluene B=xylene

b) With the exception of the isolated yield of the compounds, 1,2,3 and 4, gas chromatographic method was used for the determination.

five-membered ring did not form and seven-membered ones gave a poor result.



(3) (4)

n=0 R^1 and R^2: CH_3, H; C_2H_5, H; $CH_2C_6H_5$, H; $(CH_2)_2C_6H_5$, H; $CH_2C_6H_5$, CH_3; $CH_2C_6H_5$, C_6H_5; $(CH_2)_2C_6H_5$, C_6H_5

n=1 R^1 and R^2: CH_3, H; C_2H_5, H; C_6H_5, H; $CH_2C_6H_5$, H; $(CH_2)_2C_6H_5$, H

n=2 R^1 and R^2: CH_3, H; C_2H_5, H; $CH_2C_6H_5$, H; $(CH_2)_2C_6H_5$, H

The structure of our products was determined by microanalyses and spectral consideration as shown in Table II. 4-Oxazolidinones showed an amide carbonyl absorption at 1700 - 1705 cm^{-1} in ir spectrum and nmr spectrum revealed methylene protons at C-2 position having a long range coupling $J_{2,5}$ 1 Hz at δ 4.8 - 5.1 ppm. On the other hand, six- and seven-membered product showed C-2 methylene protons at δ 4.5 - 5.0 ppm as singlet.

Thus we could develop a simple synthesis of 4-oxazolidinones, 1,3-oxazin-4-ones and 1,3-oxazepin-4-ones from hydroxylated amides, and now are investigating an extension of this reaction to thiol derivatives and hydrazides.

Table II. Physical Constants and Spectral Data of the Cyclisation Products

Compd. No.	b.p.[mmHg]or m.p./Recryst. Solvent[a)]	IR max cm^{-1} ($CHCl_3$)	NMR ($CDCl_3$) δ
1	74-76 (1.2)	1705	2.93(3H,s,N-CH_3), 4.28(2H,br s,C_5), 5.06 (2H,m,C_2)
2	71-72 (0.6)	1700	1.19(3H,t,J=7Hz,$CH_2\underline{CH_3}$), 3.42(2H,q,J=7Hz,$\underline{CH_2}CH_3$), 4.26(2H,m,C_5), 5.08(2H,m,C_2)
3	110 (0.6)	1705	4.31(2H,t,J=1Hz,C_5), 4.51(2H,s,N-$\underline{CH_2}C_6H_5$), 4.96(2H,t, J=1Hz,C_2), 7.33(5H,s,C_6H_5)
4	131-132 (0.7)	1705	2.89(2H,t,J=7Hz,$\underline{CH_2}C_6H_5$), 3.60(2H,t,J=7Hz,N-$\underline{CH_2}CH_2$), 4.19(2H,t,J=1Hz,C_5), 4.83(2H,t,J=1Hz,C_2), 7.26(5H,s,C_6H_5)
5	112-113 (0.8)	1700	1.42(3H,d,J=7Hz,-CH_3), 4.2-4.7(3H,m,N-$\underline{CH_2}$-C_6H_5 and C_5), 4.86(2H,d,J=1Hz,C_2), 7.30(5H,s,C_6H_5)
6	63-65/E	1705	4.53(2H,s,N-$\underline{CH_2}C_6H_5$), 5.07(2H,m,C_2), 5.29(1H,t,J=1Hz,C_5), 7.32, 7.43(10H, each s, C_6H_5×2)
7	183-185 (0.6)	1705	2.84(2H,t,J=7Hz,$CH_2\underline{CH_2}C_6H_5$), 3.57(2H,t,J=7Hz,N-$\underline{CH_2}CH_2$) 4.89(2H,d,J=1Hz,$C_2$), 5.19(1H,t,J=1Hz,$C_5$), 7.32, 7.36 (10H,each s, C_6H_5×2)
8	73-74 (3)	1640	2.49(2H,t,J=6Hz,C_5), 2.86(3H,s,N-$\underline{CH_3}$), 4.02(2H,t,J=6Hz, C_6), 4.73(2H,s,C_2)
9	76-78 (3)	1640	1.14(3H,t,J=7.5Hz,$CH_2\underline{CH_3}$), 2.80(2H,t,J=6Hz,C_5), 3.37 (2H,q,J=7.5Hz,N-$\underline{CH_2}CH_3$), 3.99(2H,t,J=6Hz,C_6), 4.76(2H, s,C_2)
10	62-63/E	1655	2.65(2H,t,J=6Hz,C_5), 4.08(2H,t,J=6Hz,C_6), 5.03(2H,s,C_2), 7.30(5H,br s, C_6H_5)

11	130-131 (0.7)	1640	2.43(2H,t,J=6Hz,C_5), 3.88(2H,t,J=6Hz,C_6), 4.33(2H,s, N-$C\underline{H}_2C_6H_5$), 4.56(2H,s,C_2), 7.19(5H,s,$C_6\underline{H}_5$)
12	70-71/E	1640	2.53(2H,t,J=6Hz,C_5), 2.90(2H,t,J=7Hz,$CH_2C\underline{H}_2C_6H_5$), 3.56 (2H,t,J=7Hz,N-$C\underline{H}_2CH_2$), 3.93(2H,t,J=6Hz,$C_6$), 4.49(2H,s,$C_2$), 7.26(5H,s,$C_6\underline{H}_5$)
13	62-63 (0.5)	1645	1.5-2.0(2H,m,C_6), 2.73(2H,m,C_5), 3.02(3H,s,N-CH_3), 3.93(2H,t,J=6Hz,C_7), 4.82(2H,s,C_2)
14	80 (1.2)	1645	1.14(3H,t,J=7Hz,$CH_2C\underline{H}_3$), 1.6-2.1(2H,m,C_6), 2.70(2H,m,C_5), 3.47(2H,q,J=7Hz,N-$C\underline{H}_2CH_3$), 3.91(2H,t,J=5Hz,C_7), 4.82(2H,s, C_2)
15	81-82/E	1650	1.6-2.1(2H,m,C_6), 2.80(2H,m,C_5), 3.92(2H,t,J=5Hz,C_7), 4.67(2H,s,N-$C\underline{H}_2C_6H_5$), 4.79(2H,s,C_2), 7.27(5H,s,$C_6\underline{H}_5$)
16	55-57/E,P	1645	1.5-2.0(2H,m,C_6), 2.57-2.96(4H,m,$CH_2C\underline{H}_2C_6H_5$ and C_5), 3.53-3.92(4H,m,N-$C\underline{H}_2CH_2$ and C_7), 4.61(2H,s,C_2), 7.21(5H,s,$C_6\underline{H}_5$)

a) E=ether P=petr.ether

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