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FACILE SYNTHESIS OF γ-, δ-, AND ε-LACTAMS BY CYCLODEHYDRATION OF ω-AMINO ACIDS ON ALUMINA OR SILICA GEL

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Summary: It has been found that γ-, δ-, and ε-amino acids cyclodehydrate easily to their corresponding lactams by the action of alumina or silica gel in boiling toluene.

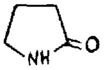
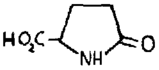
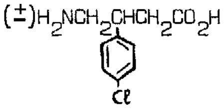
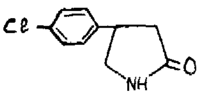
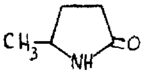
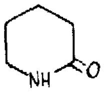
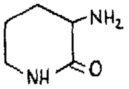
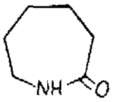
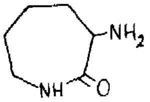
We have recently described a new method for the preparation of middle-size lactams based on the unexpected enhancing effect of γ-butyrolactone on the cyclodehydration of γ-, δ-, and ε-amino acids.[1] We wish now to report on another efficient, simple and inexpensive procedure for the same reaction, which depends on treatment of such ω-amino acids with alumina or silica gel in boiling toluene. We were prompted into trying these cyclodehydrations by the growing application of alumina and silica gel as catalysts or cocatalysts[2-6] as well as supports[6-9] for many different kinds of reactions in organic chemistry. We soon realized that both supports were equally effective in bringing about a very easy cyclodehydration of γ-, δ-, and ε-amino acids to the corresponding lactams.

Table I summarizes our main results. Since no attempts were made to optimize the indicated yields these can certainly be improved in many cases.

According to our experimental procedure lactams are simply obtained by stirring and refluxing a mixture of ω-amino acid (1 part in weight) and alumina or silica gel (3-4 parts in weight) in toluene (25-35 parts in volume), using a Dean-Stark trap to collect the water formed in the reaction. After the indicated reaction times the mixture is filtered and the solid is repeatedly washed with a mixture methylene chloride:methanol (9:1, v/v) to completely desorb the lactam. Evaporation of the filtrate and washings affords pure material in most cases. When small amounts of polymers are present the lactams are purified by treating with diethyl ether in which the polymers are insoluble.

Our method can also be used with amino acid hydrochlorides provided that an equivalent amount of concentrated aqueous sodium hydroxide be first added to free the amino acid and an extra quantity of solid support used to absorb the added water and to facilitate stirring and disgregation of the cake initially formed. That water is rapidly eliminated during the first

Table I. Preparation of Lactams from ω-Amino Acids using Alumina or Silica Gel[a)]

Amino Acid	Lactam	Reaction time	Support	Yield[b)]	m.p.[c)] (Lit. m.p.)
$H_2N(CH_2)_3CO_2H$		5 h	Al_2O_3	97(<1)	23-25°(24.6)[d]
$H_2N(CH_2)_3CO_2H$		5 h	SiO_2	97	"
$(+)HO_2C\underset{NH_2}{C}H(CH_2)_2CO_2H$		72 h	Al_2O_3	63[e)](0)	160°(157)[f)]
 $(\pm)H_2NCH_2CHCH_2CO_2H$		5 h	Al_2O_3	88(5)	119°(118)[g)]
$(\pm)H_2NCH_2\underset{OH}{C}HCH_2CO_2H$		24 h	Al_2O_3	38[e)];26[h)](0)	119°(120)[10]
$(\pm)CH_3\underset{NH_2}{C}H(CH_2)_2CO_2H$		5.5 h	Al_2O_3	93(6)	41-43°(43)[i)]
$H_2N(CH_2)_4CO_2H$		1.5 h	Al_2O_3	76(49)	37-39°(35-39)[10]
$H_2N(CH_2)_4CO_2H$		1.5 h	SiO_2	99	"
$(+)H_2N(CH_2)_3\underset{NH_2}{C}HCO_2H.HCl$		3 h	Al_2O_3	79(0)	38-41[j)](86)[10]
$H_2N(CH_2)_5CO_2H$		20 h	Al_2O_3	82(0)	69°(69-71)[10]
$H_2N(CH_2)_5CO_2H$		20 h	SiO_2	75	"
$(\pm)H_2N(CH_2)_4\underset{NH_2}{C}HCO_2H.HCl$		24 h	Al_2O_3	70(0)	76-77°(68-71)[k)]
$(+)H_2N(CH_2)_4\underset{NH_2}{C}HCO_2H.HCl$		20 h	Al_2O_3	71	60-63°[l)]
$(+)H_2N(CH_2)_4\underset{NH_2}{C}HCO_2H.HCl$		6 h	SiO_2	37	61-65°[m)]

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a) Chromatographic grade neutral Al_2O_3 (Merck) and SiO_2 (Carlo Erba) used.
b) Yields obtained in the absence of support, after a 24 h reflux period, shown in parentheses.
c) m.p. determined on a Kofler hotbench except low m.p. which were macrodetermined.
d) Dictionary of Organic Compounds, I. Heilbron Ed., Vol. 5, Eyre and Spottiswoode Publishers Ltd., London, 1965, page 2827.
e) A 3:1 toluene-pyridine mixture was used as solvent.
f) P. M. Hardy, Synthesis, 290 (1978). The reported $[\alpha]_D$ is-34.4° (c 1.1,1M $NaHCO_3$). Our product had $[\alpha]_D$ - 30° (c 1,1M $NaHCO_3$) and a commercial (Fluka) sample had $[\alpha]_D$ - 31°.
g) L. Borka, Acta Pharmaceutica Suecica, 16, 345 (1979).
h) Water (1 part) previously added to dissolve the amino acid; Al_2O_3 (6 parts) used.
i) Dictionary of Organic Compounds, I. Heilbron Ed., Vol. 4, Eyre and Spottiswoode Publishers Ltd., London, 1965, page2320.
j) 75% racemized product. The hydrochloride had m.p. 230° (Ref.[10], m.p. 218-220°) and the p-toluenesulfonamide showed m.p. 185° (Ref.[10], m.p. 185-186°) and $[\alpha]_D$ + 15° (c 2, DMF) (Ref.[10], $[\alpha]_D$ +60.9° (c 2, DMF)).
k) M. Brenner and H. R. Rickenbauer, Helv. Chim. Acta, 41, 181 (1958). Racemic product.
l) 41% racemized product. The hydrochloride had $[\alpha]_D$ - 16° (c 3, 1N HCl)(Ref.10 ,$[\alpha]_D$ -26.4°]
m) 45% racemized product. The hydrochloride showed $[\alpha]_D$ - 15° (c 2, 1N HCl).

30 minutes of refluxing. With these amino acid hydrochlorides running the reaction on basic alumina, even in the presence of pyridine, gave no results.

It was assumed that cyclodehydrations on the solid supports must be preceded by slow solution of the amino acid in the organic medium and adsorption on the surface of the support and, therefore, low yields were expected for very insoluble ω-amino acids such as *glutamic acid and* 4-amino-3-hydroxybutyric acid. In fact, with these compounds, no cyclodehydration was observed in normal reaction conditions. However, when a cosolvent such as pyridine was used to increase the solubility of the amino acid, or water was initially added to complete dissolve it, thus allowing the amino acid to be absorbed by the support, the cyclodehydrations proceeded normally although in moderate yields (see Table I).

In some cases different kinds of alumina were used and their efficiency compared to that of silica gel. As shown in Table II neutral alumina and silica gel gave the best results although sometimes the differences between the various aluminas were not significant. Use of silica gel gave rise to small amounts of polymeric material whose quantity seemed to increase with increasing reaction time, thus lowering the yield of lactam.

Table II. Yields of Lactams Obtained by Cyclodehydration of ω-Amino Acids Using Different Supports. Reaction Times Shown in Parentheses.

Amino Acid	Basic Al_2O_3	Acid Al_2O_3	Neutral Al_2O_3	SiO_2
4-aminobutyric acid	95% (5h)	—	97% (5h)	97% (5h)
5-aminovaleric acid	—	—	76% (1.5h)	99% (1.5h)
6-aminocaproic acid	32% (6h)	50% (6h)	53% (6h)	82% (6h)
6-aminocaproic acid	—	—	82% (24h)	75% (20h)
L-lysine	25% (6h)	—	27% (6h)	37% (6h)

Grinding together or separately the amino acid and the support before running the reaction, as indicated for some processes carried out on alumina[3], had no influence on the yields. The supports can be reused immediately without any special treatment or reactivation.

Regarding those cyclodehydrations carried out with optically active products it was found that no significant racemization seemed to occur with L-glutamic acid but with L-ornithine and L-lysine, as shown in Table III, a considerable loss of optical activity of the corresponding lactams was observed.

Table III. Racemization in Cyclodehydration of Optically Active ω-Amino Acids with Al_2O_3.

Amino Acid	Reaction time	Yield of lactam	$[\alpha]_D$	Racemization
L-glutamic acid	72 h	63%	-30°(c 1,1M $NaHCO_3$)[a)]	~ 4%
L-ornithine	3 h	79%	+15°(c 2, DMF)[b)]	75%
L-lysine	6 h	27%	-20°(c 2, 1N HCl)[c)]	26%
L-lysine	20 h	71%	-16°(c 3, 1N HCl)[c)]	41%
L-lysine	44 h	90%	-7°(c 3, 1N HCl)[c)]	74%

a) A commercial (Fluka) sample of L-pyroglutamic acid had [α] -31° (c 1, 1M $NaHCO_3$).
b) [α] of p-toluensulfonamide (Ref.[10] gives a value of +60.9° in DMF).
c) [α] of hydrochloride (ref.[10] gives a value of -26.4° in 1N HCl).

The data obtained with L-lysine clearly show a reaction-time depending loss of the optical activity.

Concerning some structural features which may intervene in the cyclodehydration of ω-amino acids the fact that no lactamization of N-acetyl-4-aminobutyric acid to N-acetyl-γ-butyrolactam was observed using the described reaction conditions indicates that a free amino group is necessary. Other factors such as ring size and steric strain of the lactams are certainly important since 3-aminopropionic acid, 11-aminoundecanoic acid and isonipecotic (4-piperidincarboxylic) acid did not cyclodehydrate on either alumina or silica gel.

As compared to other recent methods[10,11] for the preparation of lactams by cyclodehydration of the corresponding ω-amino acids the principal advantages of our procedure are its simlicity as well as the low cost and ready availability of the adsorbent materials used as reagents[12]. The fact that it is possible to use aqueous solutions of the amino acids is another clear advantage of our method. On the other hand the racemization that might occur with certain optically active ω-amino acids constitutes a troublesome factor when dealing with such products. Finally, the yields obtained in our procedure are comparable to those of more sophisticated methods[13].

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12. Undoubtedly the cyclodehydration of ω-amino acids on alumina or silica gel might occur on other chromatographic supports. Thus, a reaction run with 4-aminobutyric acid and Florisil gave, after a 4 h reflux period in toluene, a 70% yield of γ-butyrolactam.
13. In our hands the method of G. Pifferi *et al.* (Ref.[10]) based on the use of hexamethyldisilazane gave yields of 57% and 51% for the cyclodehydrations of L-lysine and L-ornithine respectively, as compared to the indicated yields of 82% and 91%.

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