CHEMISTRY LETTERS, pp. 797-800, 1989.

Triethylgallium Mediated Lactamization of α,ω-Amino Carboxylic Acids

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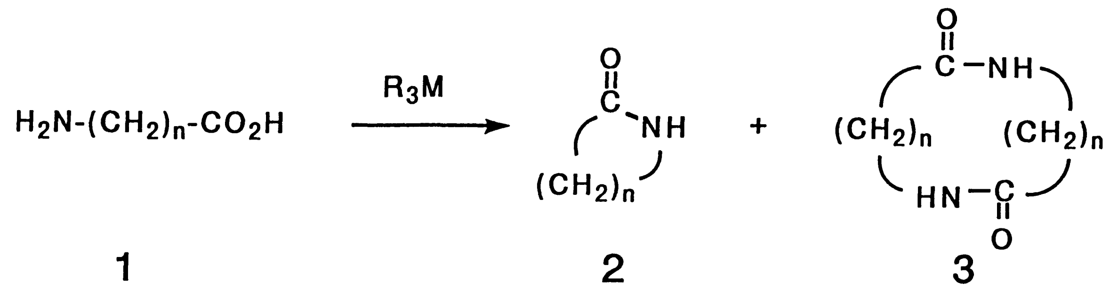
The 5-, 6-, 7-, and 8-membered lactams are obtained from the corresponding α,ω-amino carboxylic acids in good to high yields by treatment with triethylgallium in toluene or benzene.

Lactam macrocycles are an important and frequently encountered structure in biologically active natural products. Lactamization of simple α,ω-amino carboxylic acids has been accomplished by using catecholborane,$^{1)}$ dibutyltin oxide,$^{2)}$ titanium tetraisopropoxide,$^{3)}$ and Al_2O_3 (or SiO_2).$^{4)}$ The α,ω-amino acid derivatives activated as the thioesters have undergone lactamization with $SnCl_2$.$^{5)}$ Formation of macrocyclic lactams from α,ω-amino acid derivatives containing chelating polar groups has been accomplished with catecholborane$^{6)}$ and aminoborane.$^{7)}$ High dilution method has been frequently used for macrolactamization of a number of activated α,ω-amino acid derivatives.$^{8)}$ We report that Et_3Ga mediated lactamization of simple α,ω-amino acids proceeds without using high dilution method in higher yields than the previously reported metal mediated procedures (Eq. 1); the cyclization via R_3Al also proceeds well but better results are obtained with Et_3Ga.



(1)

$R_3M = Et_3Ga, R_3Al$

Table 1. Et_3Ga and R_3Al Mediated Lactamization

Entry	**1**	R_3M	Time/h	Condn.a)	Product yield / % b)	
	n	(equiv.)			**2**	**3**
1	3	Et_3Al (2)	5	A	82 (5)c)	-
2	3	Et_3Ga (1.5)	5	A	88 (5)c)	-
3	4	Me_3Al (2)	2	B	98 (6)c)	-
4	4	Et_3Ga (2)	3	B	86 (6)c)	-
5	5	Et_3Al (2)	5	A	69 (7)c)	-
6	5	Et_3Ga (1.5)	5	A	81 (7)c)	-
7	6	Et_3Al (2)	5	A	7 (8)c)	2 (16)c)
8	6	Et_3Ga (1.5)	5	A	18 (8)c)	4 (16)c)
9	6	Et_3Ga (1.5)	5	C	43 (8)c)	12 (16)c)
10	7	Me_3Al (2)	2	B	-	18 (18)c)
11	7	Et_3Ga (1.5)	5	A	-	6 (18)c)
12	7	Et_3Ga (1.5)	5	C	7 (9)c)	8 (18)c)
13	10	Et_3Al (2)	5	A	-	4 (24)c)
14	10	Et_3Ga (1.5)	5	A	-	10 (24)c)
15	11	Me_3Al (2)	2	B	-	9 (26)c)

a) A: substrate (1 mmol)/toluene (10 ml)/reflux. B: substrate (1 mmol)/benzene (10 ml)/reflux. C: substrate (1 mmol)/toluene (100 ml)/reflux.
b) Isolated yield through silica gel chromatography. c) Ring size.

The results are summarized in Table 1. Formation of 5- and 6-membered lactams proceeded with very high yields regardless of the aluminum and gallium reagents (entries 1-4). Other procedures1)-4) also produce these ring size lactams with high yields. The 7-membered lactam was obtained in higher yield with Et_3Ga than with Et_3Al (entries 5 and 6). The reaction progress in the condensation with Et_3Al (entry 5) was followed by time, and it was revealed that the reaction essentially completed after 1 hr and the starting material was recovered at this stage; **2** (69%) and **1** (30%)(n = 5). This observation suggested that Et_3Al would be decomposed gradually under toluene reflux. Therefore, it was anticipated that thermally more stable Et_3Ga may produce higher yield.

Actually, this proved to be the case (entry 6). Normally, it is difficult to make 8-12 membered rings via the cyclization methods;9) especially formation of 8- and 9-membered rings is extremely hard to achieve. As expected, the 8-membered ring was obtained by using Et_3Al in only 7% along with 2% of **3** (16-membered ring)(entry 7). The yield was improved with Et_3Ga under the same reaction condition (A) (entry 8), and finally under the condition (C) Et_3Ga gave 43% yield of the 8-membered lactam (entry 9). To the best of our knowledge, such an efficient synthesis of **2** (n = 6) from **1** has not been accomplished. Even by using this procedure, the 9-membered ring was obtained only in 7% yield (entry 12, cf. entries 10 and 11). Attempts to obtain 12- and 13-membered rings were unsuccessful (entries 13 - 15), and instead the dimers were obtained along with polymers.

Formation of ε-caprolactam (**2**, n = 5) is representative. A hexane solution of Et_3Ga (0.73 M, 2.1 ml) was added to a suspension of 6-aminocaproic acid (135.4 mg, 1.032 mmol) in toluene (10 ml) under nitrogen atmosphere. The mixture was refluxed for 5 hr with stirring, and then cooled to room temperature. Water (0.1 ml) was added and the mixture was stirred for 1 hr. The resulting white precipitate was filtered and the mother liquor was concentrated. Purification through silica gel (5 g) column chromatography with chloroform-methanol (50 : 1) gave ε-caprolactam (95.0 mg, 81.3% yield).

The intermolecular amide bond formation between carboxylic acids (or esters) and amines is accomplished with dimethylaluminum amides10) or with boron reagents.11) The intramolecular β-lactam formation from β-aminoacid ester is achieved by using $i\text{-}Bu_3Al$.12) The present results clearly demonstrate that R_3Al mediated method can be applied to the lactam formation of the 5 - 8 membered rings from α,ω-amino acids, and more importantly that Et_3Ga is a useful reagent, more efficient than R_3Al, for macrolactamization to the 7 - 9 rings. Comparison between the Al and Ga procedures is made in Fig. 1. Macrolactamization with Et_3In was also attempted. Unfortunately, this reagent was less effective than Et_3Al and Et_3Ga. The thermal stability of these three reagents is in an order of $Et_3In > Et_3Ga > Et_3Al$. Presumably, Et_3In is too stable to cause the cyclization.

We thank Sumitomo Chemical Co. Ltd. for giving us Et_3Ga-hexane and Et_3In-hexane solution. We are now pursuing research of organic synthesis via Ga-N bond.

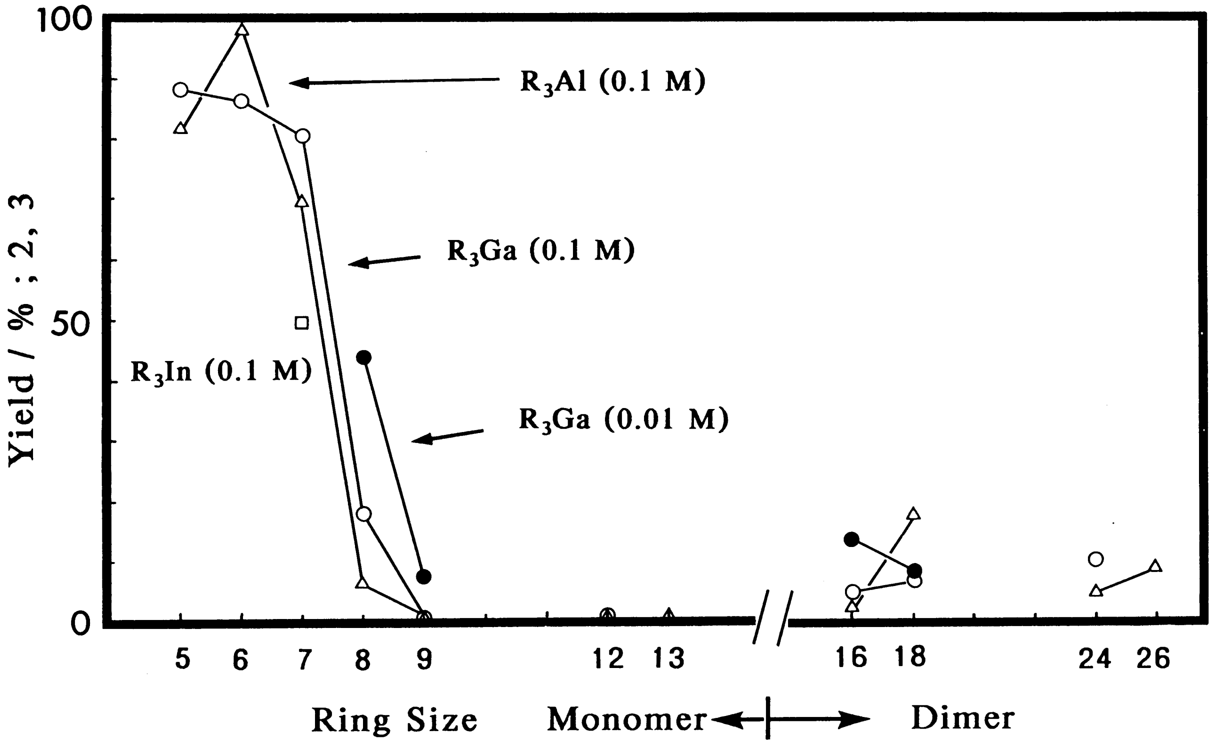


Fig. 1. Comparison between the Al and Ga Methods.

△; Et_3Al or Me_3Al, ○; Et_3Ga, □; Et_3In

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(Received February 27, 1989)