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MONITORED AMINOLYSIS OF 3-ACYLTHIAZOLIDINE-2-THIONE : A NEW SYNTHESIS OF MACROCYCLIC AMIDES

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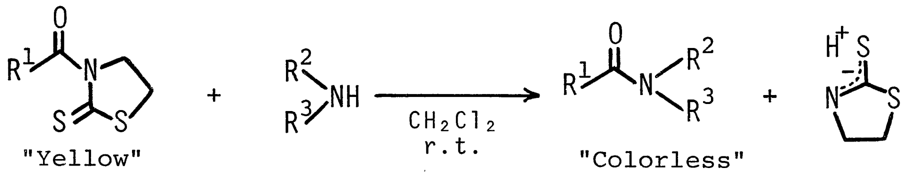
A new efficient procedure for synthesis of macrocyclic amides has been exploited by aminolysis of thiazolidine-2-thione amide (**1**) of dicarboxylic acid with diamines (**4**), or spermidine (**7**). A variety of macrocyclic diamides (**5** and **8**) and/or tetramides (**6**, **9**, **12**, and **13**) have been synthesized in high yields. One can monitor the reaction, since the original yellow color of the starting material (**1**) disappears at the end of the reaction.

In recent years, the biochemical studies on polyamines, (spermidine, homospermidine, and spermine) have been extensively developed.1) Many alkaloids containing such polyamines have also been isolated from plants,2) and most of these alkaloids have macrocyclic amide system.2) In the field of macrocyclic spermidine alkaloids, syntheses of tetrahydro-derivatives3) of lunaridine and codonocarpine, oncinotine,4) neo-oncinotine,4) and iso-oncinotine4) have been done. However, macrocyclic diamide ring formation is not always satisfactory in the yield. Hence, we have attempted exploitation of a new method for the macrocyclic diamide ring formation.5)

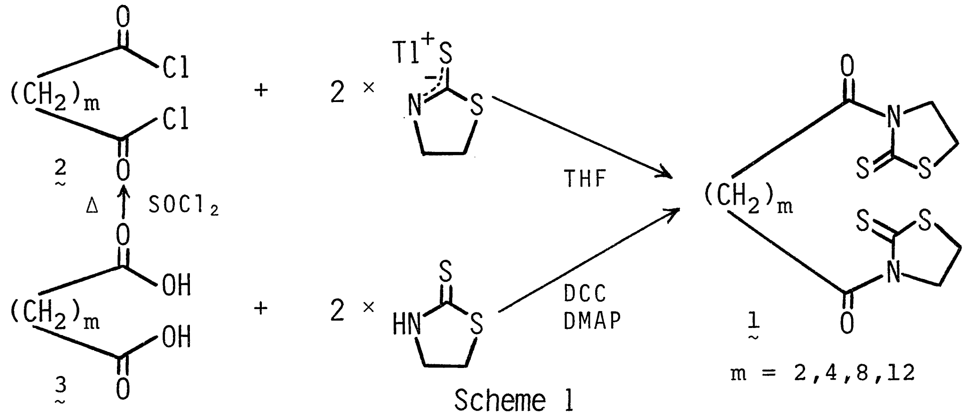
Now, we wish to report here an efficient method of the macrocyclic amide ring formation utilizing the monitored aminolysis of 3-acylthiazolidine-2-thione6) (see eq (1)).



(1)

Thus, some thiazolidine-2-thione derivatives **1** of dicarboxylic acids were prepared by the following methods6,7) (Scheme 1). Method A : Commercially available or freshly prepared dicarboxylic acid dichloride **2** (1 mol equiv.) is treated with thallium (I) salt of thiazolidine-2-thione (2.2 mol equiv.) at room temperature in THF. Method B : Dicarboxylic acid **3** (1 mol equiv.)

is condensed with thiazolidine-2-thione (4.4 mol equiv.) in the presence of dicyclohexylcarbodiimide (DCC) together with a catalytic amount of 4-dimethylaminopyridine[8] (DMAP). The result is shown in Table 1.



Scheme 1

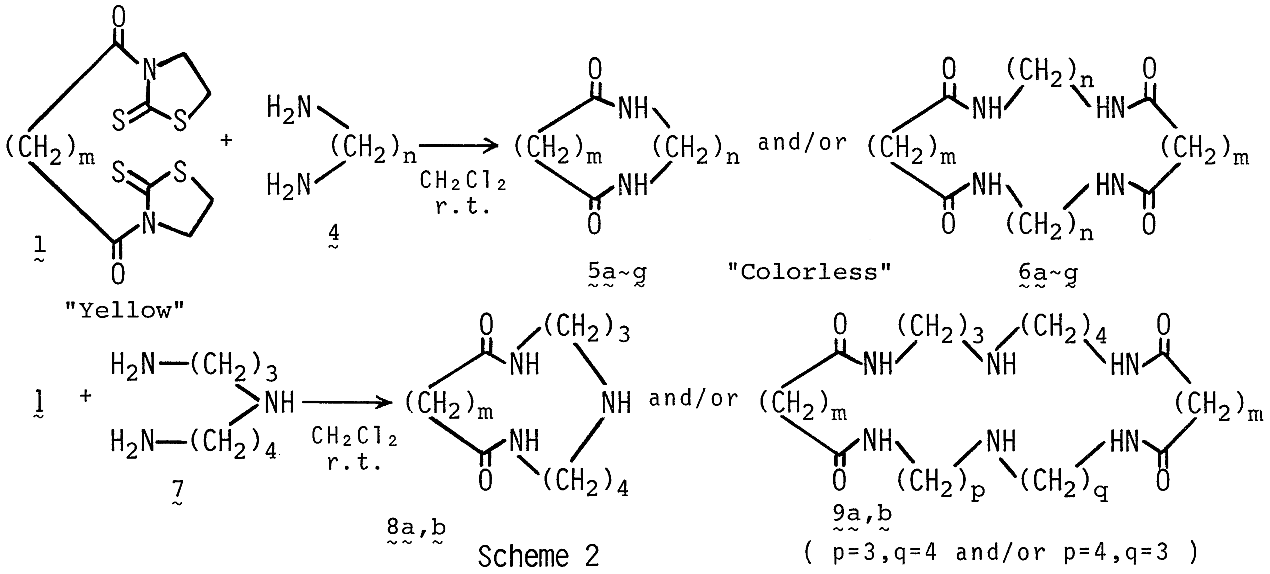
Table 1 Preparation of 3-Acylthiazolidine-2-thione **1**

dicarboxylic acid chloride **2** or diacid **3**	method	yield(%) of **1**	mp (°C)
2 m = 2	A	83	170-173
2 m = 4	A	82	126-128
2 m = 8	A	83	110-112
3 m = 12	A	85	109-112
3 m = 12	B	41	

The structure of compound **1** was assigned on the basis of the elemental analysis and the spectroscopic data. For example, compound **1** (m=4) : yellow prisms (from $CHCl_3$). *Anal.* Calcd for $C_{12}H_{16}O_2N_2S_4$: C, 41.38 ; H, 4.63 ; N, 8.04. Found : C, 41.28 ; H, 4.62 ; N, 7.87, M^+ *m/e*=348, ν_{max}^{KBr} 1695 cm^{-1}, δ $CDCl_3$ 1.76 (4H, m), 3.27 (4H, t, *J*=8 Hz), and 4.56 (4H, t, *J*=8 Hz). ^{13}C NMR δ $CDCl_3$ 28.4 ($-\underline{C}H_2-S-$), 56.1 ($\underline{C}H_2-N=$), 174.3 ($-\overset{O}{\underline{C}}-N=$), and 201.5 ($-\overset{S}{\underline{C}}-$). The X-ray analysis of compound **1** (m=4) supported the amide structure,[9] as we assigned.

The macrocyclic amide ring formation was performed by the following dilution procedure. Over 2 hr, a yellowish solution of 3-acylthiazolidine-2-thione **1** (0.80 mmol) in 20 ml of CH_2Cl_2 and a solution of diamine **4** (0.96 mmol) in 20 ml of CH_2Cl_2 were dropwise added using the double mechanically driven syringes to a large amount of CH_2Cl_2 (130 ml) with stirring at room temperature in N_2. After evaporation of the colorless solution *in vacuo*, the remaining residue was chromatographed on a column prepared from sephadex LH-20 and MeOH by MeOH to afford macrocyclic diamide **5** and/or tetramide **6** in good yield (see Table 2). The similar treatment of compound **1** (m=8, m=12) with spermidine **7** was tried as a model experiment for the ring formation of lunaridine[2] or codonocarpine[2] to give desirable macrocyclic diamide **8a** or **8b** in high yield. Compound **1** (m=8) was also subjected to this aminolysis with cyclic diamine **10** or **11** to give macrocyclic tetramide 12 (93%) or 13 (70%).

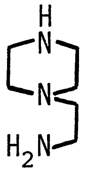
The structures of these macrocyclic amides were determined by the high-resolution mass spectroscopy and the other spectroscopic tools.



Scheme 2

Table 2 Macrocyclic Amide Formation

compound 1	diamine 4 or spermidine 7	macrocyclic diamide 5 or 8		M^+	yield	macrocyclic tetramide 6 or 9		M^+	yield
			[ring size]	m/e	(%)		[ring size]	m/e	(%)
m = 2	n = 2	5a	[8]			6a	[16]	284.148	84
m = 2	n = 3	5b	[9]			6b	[18]	312.179	82
m = 4	n = 3	5c	[11]			6c	[22]	368.241	89
m = 4	n = 4	5d	[12]			6d	[24]	396.273	80
m = 4	n = 6	5e	[14]	226.169	34	6e	[28]	452.336	37
m = 8	n = 6	5f	[18]	282.223	66	6f	[36]	564.465	12
m = 12	n = 6	5g	[22]	338.292	83	6g	[44]	676.583	8
m = 8	7	8a	[20]	311.254	89	9a	[40]		
m = 12	7	8b	[24]	367.317	85	9b	[48]	734.638	5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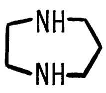
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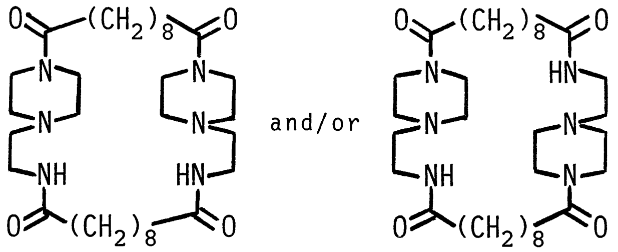

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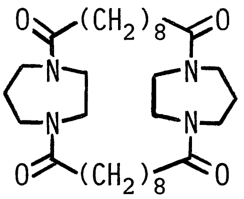
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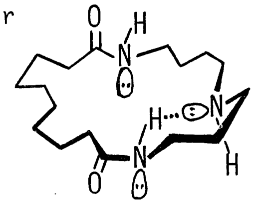
Subsequently, we attempted the ring formation of macrocyclic diamide **8a** by the single addition method different from the foregoing procedure.

Thus a solution of spermidine **7** (0.96 mmol) in 20 ml of CH_2Cl_2 was dropwise added to a stirred yellowish solution of compound **1** (m=8) (0.80 mmol) in 150 ml of CH_2Cl_2 by the single mechanically driven syringe over 2hr. When all of the solution of spermidine **7** was added, the original yellow color of **1** (m=8) disappeared and the amide **8a**$^{10)}$ was obtained in high yield (83%) which is comparable with that (89%) in the case by the double addition method. Surprisingly the secondary amino group of the product **8a** formed at the early stage of the aminolysis did not react with the excess remaining reactant **1** (m=8). This fact may be explainable by a potential hydrogen bonding forming a stable six-membered ring system (see Fig) between lone pair of the secondary amino group and a hydrogen of an amide in the molecule, which decreases the nucleophilicity of the secondary amino group. This is very informative for the synthesis of spermidine alkaloids, which is now in progress.



Fig

We believe that this macrocyclic amide ring formation is very useful as the synthetic method not only for the spermidine alkaloids but also for a variety of macrocyclic amides which appeal to organic and bioorganic chemists.$^{11)}$

References and Notes

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5) Cf. For formation of lactams from ω-amino acids using catecholborane, see D. B. Collum, S-C. Chen, and B. Ganem, *J. Org. Chem.*, **43**, 4393 (1978).

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10) Tetramide **9a** (M^+ *m/e*=622.513) was also obtained in 11% of yield.

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