

MONITORED AMINOLYSIS OF 3-ACYLTHIAZOLIDINE-2-THIONE :
 A NEW CONVENIENT SYNTHESIS OF AMIDE

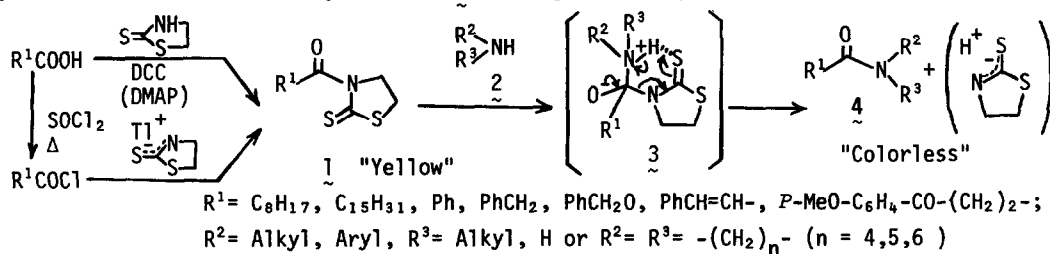
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Summary: 3-Acylthiazolidine-2-thiones (**1**) were easily prepared and they were treated with several amines in dichloromethane to give amides **4** in very high yields within a short time. Aminoalcohols and aminophenols were selectively converted into acylaminoalcohols and acylaminophenols, respectively, by this reaction. One can monitor the reaction by disappearance of the yellow color of the starting material **1**. Some amide alkaloids (**15-18**) have effectively been synthesized.

In recent years, many useful new reactions using thiazolidine-2-thione or 2,2'-dipyridyl disulfide have extensively been exploited.^{1,2)} We have also focused our interest on the exploitation of useful reactions utilizing the excellent leaving property of 2-thiocarbonyl-thiazolidino- or pyridine-2-thio-group. As a part of these studies, we previously reported the monitored reduction³⁾ of carboxylic acid into aldehyde or into alcohol *via* 3-acylthiazolidine-2-thione **1**. Recently we reported also a new general synthetic method⁴⁾ of ketene dithioacetal utilizing the bifunctionality of pyridine-2-thio group.

Now, 3-acylthiazolidine-2-thione **1** was found to be subject to the aminolysis under very mild conditions offering amide **4** in high yield. This reaction can be monitored by disappearance of yellow color of the starting material **1**. The general sequence is shown in Scheme 1.



Scheme 1

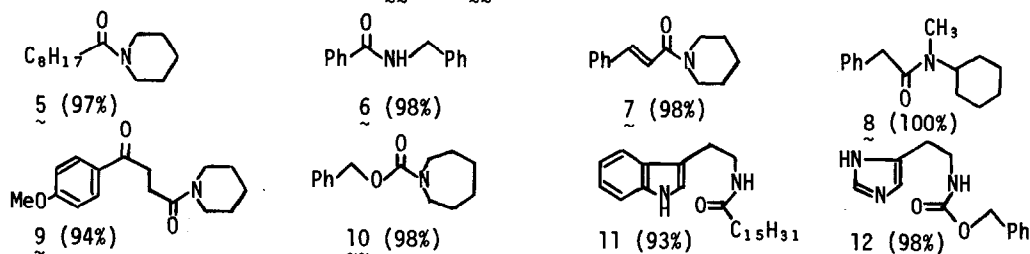
3-Acylthiazolidine-2-thione **1** is easily prepared by dehydration between carboxylic acid and thiazolidine-2-thione under the presence of dicyclohexylcarbodiimide³⁾ (DCC) [sometimes together with a catalytic amount of 4-dimethylaminopyridine⁵⁾ (DMAP)] or by treatment of carboxylic acid chloride with thallium (I) salt of thiazolidine-2-thione.³⁾

Aminolysis is done by the following procedure. A solution of amine **2** (1.1 mol equiv.) in CH_2Cl_2 was added to a yellow solution of 3-acylthiazolidine-2-thione **1** (1 mol equiv.) in CH_2Cl_2 at room temperature with stirring. Stirring was continued until the original yellow color of

the solution disappeared. The solvent was evaporated off *in vacuo* to leave a residue, which was dissolved in CHCl_3 and passed through a silica gel column impregnated with 10% AgNO_3 ⁶⁾ to afford only a desirable amide 4 in high yield. The result of the aminolysis of 3-hexadecanoylthiazolidine-2-thione with several amines is listed in Table 1.

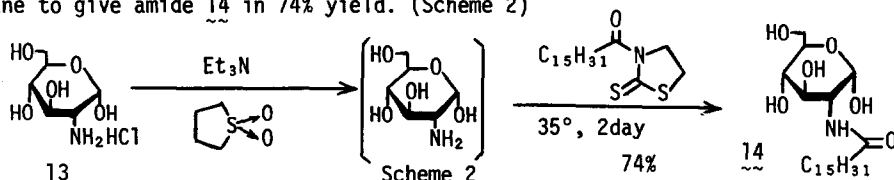
Rate of this aminolysis is shown to be affected by the electron density of N atom and sterical environment of amine. Comparison of the reaction rate among amines led to the following order : aliphatic amine > aromatic amine; $\text{RCH}_2\text{NH}_2 > \text{R}'\text{CH-NH}_2 > \text{R}'\text{C-NH}_2$; $\text{R-NH}_2 \geq \text{R}'\text{NH}$; $(\text{CH}_2)_n \text{NH}$ ($n=4\sim 6$) > $\text{R}'\text{NH}$.

The similar aminolyses of other 3-acylthiazolidine-2-thiones gave also excellent yields of amides 5~10 within a short time. Diamines, histamine and tryptamine, were available for this reaction and the corresponding amide 11 and 12 were afforded in high yield.



Subsequently, the reaction of 3-hexadecanoylthiazolidine-2-thione (1 mol equiv.) with several aminoalcohols or aminophenols (1.1 mol equiv.) was tried at room temperature to give selectively only desirable amide having free hydroxyl group(s) in satisfactory yield. (see Table 2). Thus, this aminolysis can be performed without protection of hydroxyl group(s) even in ethanol.

N-Hexadecanoylation of glucosamine hydrochloride 13 was performed in the presence of Et_3N in sulforane to give amide 14 in 74% yield. (Scheme 2)



Finally this aminolysis was conveniently applied to the syntheses of some amide alkaloids. Fagaramide⁷⁾ 15 obtained from *Fagara macrophylla*, dolichotheleine⁸⁾ 16 from *Dolichothele sphaerica*, and maytenine⁹⁾ 17 from *Maytenus chuchuhuasha*, were synthesized in good yield, respectively. (Scheme 3)

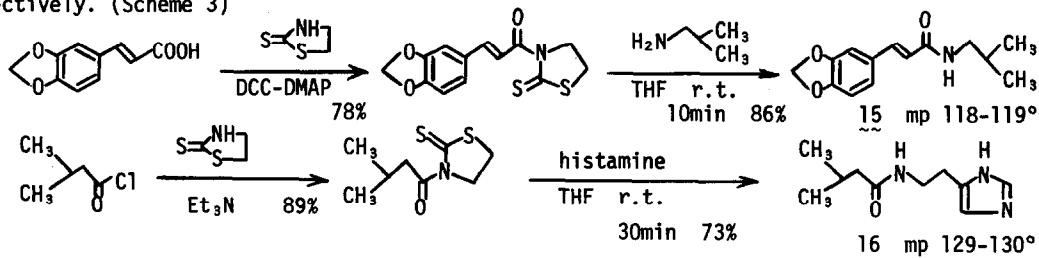

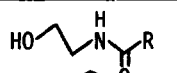
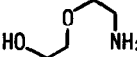
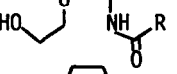
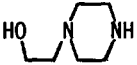
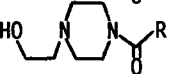

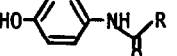
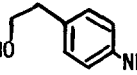
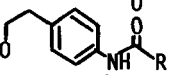
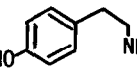
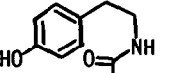
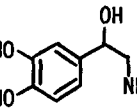
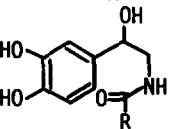


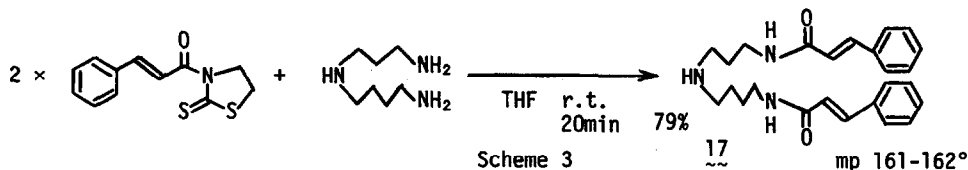
Table 1 Aminolysis of 3-Hexadecanoylthiazolidine-2-thione with Several Amines 2

amine 2		reaction	yield(%)	mp
R ²	R ³	time	of amide 4	(°C)
<i>n</i> -Bu	H	1min	96	70-71
<i>sec</i> -Bu	H	30min	97	71-72.5
<i>tert</i> -Bu	H	70hr	98	63-64
cyclohexyl	H	5min	92	92-93
C ₆ H ₅ CH ₂	H	2min	96	93-94
Ph	H	95hr	91	88-89
<i>P</i> -CH ₃ -C ₆ H ₄ -	H	150hr	93	93-94
<i>n</i> -Bu	CH ₃	5min	98	oil
<i>n</i> -Bu	<i>n</i> -Bu	15min	99	oil
cyclohexyl	CH ₃	10min	99	oil
C ₆ H ₅ CH ₂	CH ₃	8min	95	47-48
-(CH ₂) ₄ -		1min	98	oil
-(CH ₂) ₅ -		1min	99	oil
-(CH ₂) ₆ -		1min	99	oil

Table 2 Aminolysis of 3-Hexadecanoylthiazolidine-2-thione with Aminoalcohols and Aminophenols

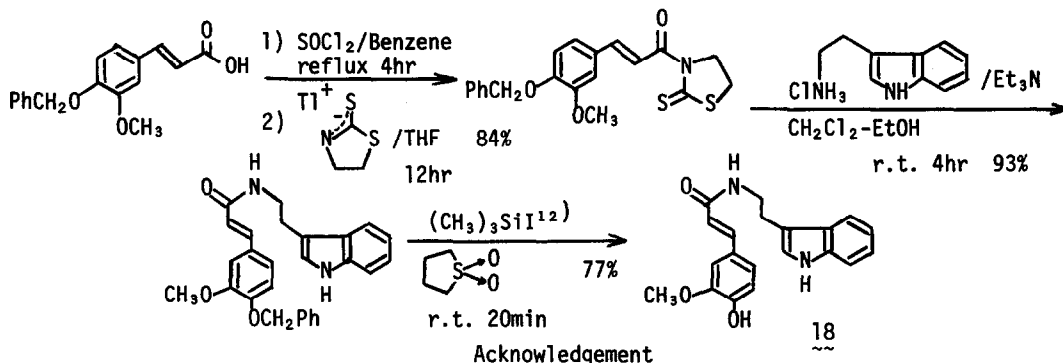
aminoalcohol aminophenol	solvent	reaction time	product ^{a)}	yield (%)	mp (°C)
	CH ₂ Cl ₂	20min		91	96-97
	CH ₂ Cl ₂	30min		75	83-83.5
	CH ₂ Cl ₂	3min		95	60-61
	THF	7day		63	134-135
	THF	7day		61	131-132
	EtOH-THF	3min		95	104-105
	EtOH-THF	5hr		51	104-105.5

a) R = (CH₂)₁₄CH₃



Although maytenine 17 had been synthesized¹⁰⁾, our method was shown to be superior to that in yield and mildness of the reaction conditions.

N-Ferulyltryptamine (18)¹¹⁾, a very minor component (40 $\mu\text{g}/\text{kg}$) isolated from aqueous acetone extracts of ground kernels of *Zea mays*, was also synthesized as follows.



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References and Notes

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