3-ACYL-2-(N-CYANOIMINO)THIAZOLIDINES AS AN ACYLATING AGENT. PREPARATION OF AMIDES, ESTERS, AND THIOESTERS

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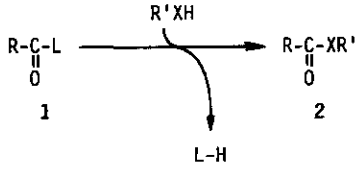
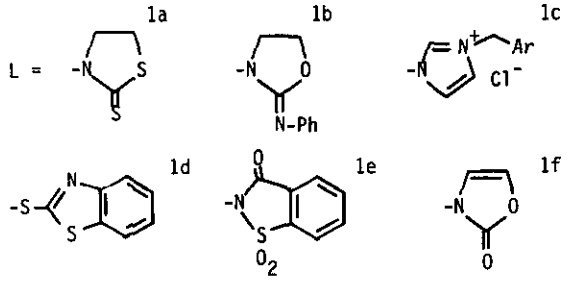
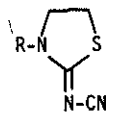
Abstract —— 3-Acyl-2-(N-cyanoimino)thiazolidines proved to be powerful acylating agents. They reacted easily with amines, alcohols, and thiols to give the corresponding amides, esters, and thioesters in good yields.

Some heterocycles are known to act as excellent leaving groups and this property is applicable to the preparation of various compounds. Carbonyl compounds such as 1, in which L is an appropriate heterocyclic leaving group, react with hetero nucleophiles (R'XH) providing various carbonylated products (2).[1] The known and representative heterocyclic leaving groups are shown below. Such heterocycles activate the carbonyl group, which is easily attacked by the nucleophiles (amines, alcohols, or thiols) under mild conditions and the corresponding amides, esters, and thioesters are readily available.[1]

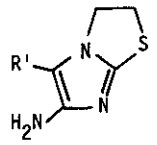




Although 2-(N-cyanoimino)thiazolidine (**3**), easily prepared by the reaction of cysteamine hydrochloride with dimethyl cyanodithioimidocarbonate,[2] seems to be useful for various organic transformations from a viewpoint of its diverse functionalities, there has been no reports concerning its chemical behaviors so far. In the preceding paper we have demonstrated the transformation of some 3-substituted 2-(N-cyanoimino)thiazolidines (**4**) into novel 6-amino-2,3-dihydroimidazo[2,1-b]thiazoles (**5**).[3] As one of the continuous studies on 2-(N-cyanoimino)thiazolidine heterocycles, in this paper we describe that 2-(N-cyanoimino)thiazolidine plays an important role for the leaving auxiliary, as illustrated by facile preparation of amides, esters, and thioesters.



3: R=H
4: R=CH_2-R'



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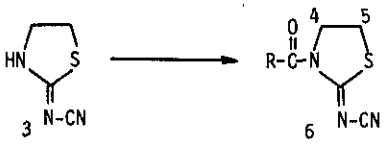
Acylation of **3** was readily achieved by the treatment with acyl chlorides or with carboxylic acids-DCC in excellent yields. The acylated 2-(N-cyanoimino)-thiazolidines (**6**) are isolable as stable crystalline products and physical data of **6** are summarized in Table I.



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Conditions A: RCOCl, Et_3N, CH_2Cl_2
B: $(RCO)_2O$
C: RCOOH, DCC, CH_2Cl_2

Table I. 3-Acyl-2-(N-cyanoimino)thiazolidines (6)

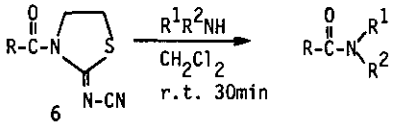
Compd	R	Method	Yield(%)	Mp (°C)	ν(KBr) C=O	δ($CDCl_3$) 4-H	5-H
6a	$CH_2C_6H_5$	A	80	154-155.5	1705	4.37t	3.32t
6b	C_6H_5	A	98	148-150	1675	4.37t	3.45t
6c	CH_2CH_3	A	91	64-65	1715	4.50t	3.47t
		C	55				
6d	$C(CH_3)_3$	A	87	105-106	1715	4.28t	3.45t
6e	CH_2COOEt	A	66	85-87	1700	4.46t	3.47t
6f	CH_3	A	73	144-145	1705	4.48t	3.48t
		C	87				

The reaction with amines was first examined. Two acylthiazolidines (**6a** and **6b**) were chosen as the aliphatic and aromatic representative substrates, respectively. The substrates were subjected to the reaction with various amines in a dichloro-

methane solution. In almost all of runs, the reaction took place immediately at room temperature to afford the corresponding amide. It is especially noteworthy that isolation of the product was achieved by only simple extraction operations, as the produced 2-(N-cyanoimino)thiazolidine is very soluble in aqueous alkaline solution due to its relatively strong acidic character. Various amides were prepared by this method and the results are summarized in Table II, which shows that all the runs gave satisfactory results. The reaction with ethanolamine resulted in an exclusive formation of the corresponding amide and any amount of the ester was not detected (run 10).

A typical procedure is presented here. To a stirred solution of the phenylacetyl thiazolidine (**6a**) in dichloromethane was added 1.1 molar equivalents of benzylamine at room temperature. Immediately the formed 2-(N-cyanoimino)-thiazolidine (**3**) precipitated and the reaction was completed within 5 min. After stirring for 30 min, almost all of **3** was filtered off and the organic layer was washed with 5% NaOH aq. solution, water, 5% HCl aq. solution, and then water. After drying, evaporation of the solvent leaved N-benzylphenylacetamide in pure state in 99% yield.

Table II. Preparation of the Amides

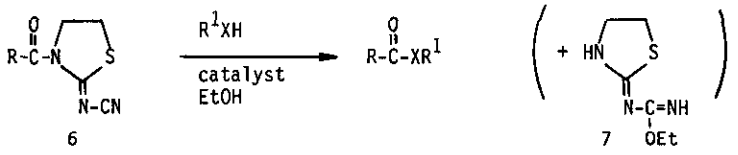


R^1	R^2	R=$CH_2C_6H_5$		R=C_6H_5	
		Yield(%)	Mp (°C)	Yield(%)	Mp (°C)
$CH_2C_6H_5$	H	99	121-122	97	106-107
n-C_4H_9	H	100	53-55	100	39-40
i-C_4H_9	H	100	77-78	100	54.5-56
sec-C_4H_9	H	100	66-67.5	100	84.5-85.5
t-C_4H_9	H	88[a]	116-117	89[b]	136-137
cyclohexyl	H	100	139-140	100	151-152
C_6H_5	H	98[c]	118-119	98[d]	164.5-165.5
$-(CH_2)_5-$		100	oil	94	oil
$-(CH_2)_2O(CH_2)_2-$		97	66.5-67.5	100	72-73
CH_2CH_2OH	H	91	59-60	80	oil
CH_2COOEt	H	100	80.5-82	100	58-59

a After 6h. *b* After 18h. *c* After 65h under reflux. *d* After 72h under reflux in $CHCl_3$

Next, the reaction with ethanol or thiols was tried. Although the reaction of **6a** with ethanol was found to proceed very slowly, a catalytic amount of sodium ethoxide or sodium hydroxide accelerated the reaction to give the ethyl ester (**9a**) in good yield. Isolation of the product was also achieved simply. Although sulfuric acid also catalyzed the reaction, contamination of the by-product (**7**; 12%) made difficult to isolate the desirable product. The reaction with thiols was also found to take place smoothly by the addition of a small amount of sodium ethoxide to give the correspounding thioesters. These results are summarized in Table III.

Table III. Preparation of the Ester and Thioesters



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R^1	X	Catalyst	Conditions	Yield(%) R=$CH_2C_6H_5$		R=C_6H_5
C_2H_5	O	NaOEt	EtOH 60°C 30min	80		—
C_2H_5	O	NaOH	EtOH 60°C 30min	92		—
C_2H_5	O	c.H_2SO_4	EtOH 60°C 4.5h	83	(7:12%)	—
C_6H_5	S	NaOEt	EtOH 60°C 30min	100		91
n-C_7H_{15}	S	NaOEt	EtOH 60°C 30min	100		94
CH_2CH_2OH	S	NaOEt	EtOH 60°C 30min	100		93

In summary, 3-acyl-2-(N-cyanoimino)thiazolidines were found to serve as excellent agents for acylation of amines, alcohols, and thiols from viewpoints of easy handling of the reagents, strong reactivity, great chemoselectivity, and simple separation of products. Further studies on 3-acyl-2-(N-cyanoimino)thiazolidines are now in progress.

REFERENCES AND NOTES

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