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A CONVENIENT METHOD FOR THE PREPARATION OF N-ACYL LACTAMS

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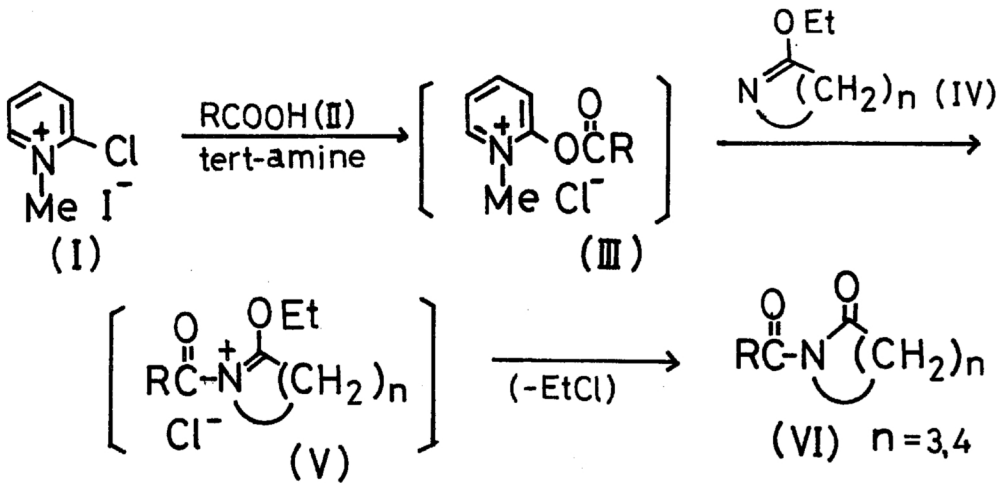
Various N-acyl lactams were prepared in good yields from free carboxylic acids and lactim ethers by employing 1-methyl-2-chloropyridinium iodide as a coupling reagent. Similarly, 1-acyl-3-methyl-4-imidazoline-2-thione or 3-acyl-2-thiazolidinethione was prepared in a fairly good yield from carboxylic acid, and 1-methyl-2-methylthioimidazole or 2-methylthio-2-thiazoline, respectively.

Over the years, a number of synthetic methods for the preparation of N-acyl lactams have been described in literatures.[1] Of these methods, the reaction of acyl halide with lactim ether[1-a] or N-trimethylsilyl lactam[1-b), 1-c] has been most widely used. However, little work has been reported on the preparation of N-acyl lactam directly from free carboxylic acid and lactim ether.

During our continuing studies on the exploration of new synthetic methods by use of 2-chloropyridinium salt (I), it was assumed that, in the case of the preparation of ester and amide, (I) reacted with carboxylic acid to produce a reactive key intermediate (III). The intermediate (III) in turn reacted with various nucleophiles to yield the condensation products.[2),3),4)]

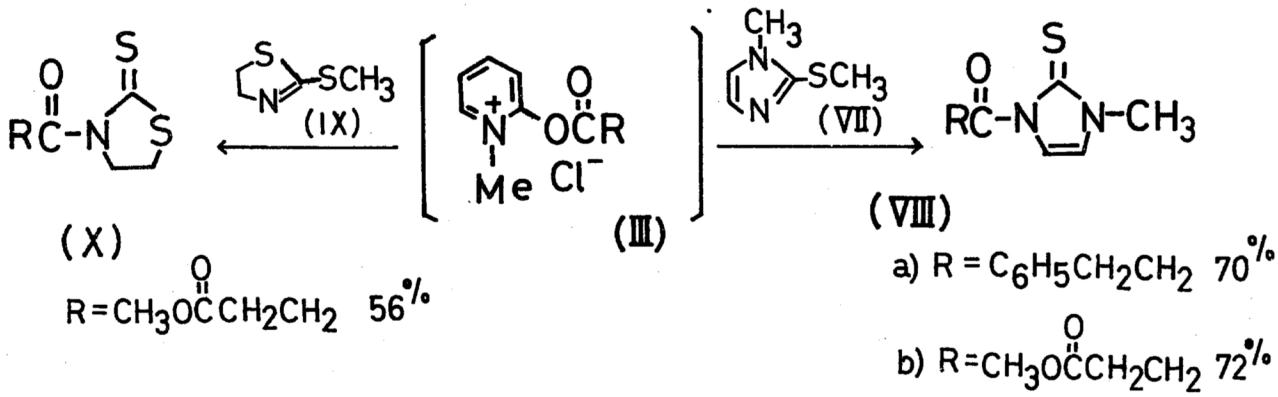
In the present study, a new method for the preparation of N-acyl lactams was investigated by emloying lactim ether (IV) as a nucleophile in the above reaction. Expectedly, N-acyl lactam was prepared in a good yield by treating equimolar amounts of free carboxylic acid and lactim ether (five or six membered ring system) with 1.3 molar amounts of pyridinium salt (I) and 1.1 molar amounts of triethylamine or tri-n-butylamine in dichloroethane or toluene.

The following experiment provides a typical procedure for the preparation of N-acyl lactams; to a mixture of 1-methyl-2-chloropyridinium iodide (332 mg, 1.3 mmol),



phenylacetic acid (136 mg, 1.0 mmol) and 2-ethoxy-1-pyrroline (114 mg, 1.0 mmol) in dichloroethane (2 ml) was added a dichloroethane solution (1 ml) of triethylamine (111 mg, 1.1 mmol) at 50°C under an argon atmosphere. The reaction mixture was stirred for 2 hr at the same temperature. After stirring for 15 hr at room temperature, ethyl acetate (15 ml) was added to the reaction mixture, and the resulting mixture was washed with water and dried. The organic layer was concentrated under reduced pressure. The residure was chromatographed on silica gel, and 1-phenylacetyl-2-pyrrolidinone was obtained in 90% yield (183 mg, mp 56-57°C, lit.[5] mp 57-58°C).

In a similar manner, various N-acyl lactams were prepared from carboxylic acids and lactim ethers in good yields as summarized in the Table.



Further, it was also found that 1-acyl-3-methyl-4-imidazoline-2-thiones (VIII)[6),7)] were formed in good yields by treating carboxylic acids and 1-methyl-2-methylthioimidazole (VII) with 2-chloropyridinium salt (I) and tri-n-butylamine.

Similarly, 3-(3-methoxycarbonylpropionyl)-2-thiazolidinethione[6),7)] was obtained in 56% yield when 2-methylthio-2-thiazoline and methyl hydrogen succinate were treated with 2-chloropyridinium salt (I) and tri-n-butylamine in refluxing toluene.

It is noted that the present method provides a practically useful method for the preparation of N-acyl lactam. Further studies on the application of the method to the synthesis of variotin[8)] which has hydroxyl group in N-acyl lactam skelton are now in progress.

Table. The Preparation of N-Acyl Lactam from Carboxylic Acid and Lactim Ether.

(II) R	(IV) n	Conditions	(VI) Yield (%)
$C_6H_5CH_2$	3	A[a)] 50°C 2 hr r.t. 15 hr	90
$C_6H_5CH_2$	4	B[b)] refl. 2 hr	72
$C_6H_5CH_2CH_2$	3	A 50°C 2 hr r.t. 15 hr	90
$C_6H_5CH_2CH_2$	4	B refl. 2 hr	84
$CH_3COCH_2CH_2$	3	A 50°C 2 hr r.t. 15 hr	67
$CH_3CH=CHCH=CH$	3	B 100°C 2 hr	63
$CH_3(CH_2)_6$	3	B refl. 2 hr	79
$CH_3(CH_2)_6$	4	B refl. 2 hr	79
$CH_3(CH_2)_7CH=CH(CH_2)_7$	3	B refl. 2 hr	76
$CH_3(CH_2)_7CH=CH(CH_2)_7$	4	B refl. 2 hr	85
$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2$	3	B 100°C 1.5 hr	94
$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2$	4	B 100°C 1.5 hr	70

a) triethylamine/dichloroethane.

b) tri-n-butylamine/toluene.

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6) Spectral data were consistent with those of the sample prepared according to the method described in literatures.[9]
VIIIb: mp 106-107°C; mass: m/e 228 (M^+), 114; ir: 1720 cm^{-1}; nmr $\delta(CCl_4)$: 7.40 (d, 1H), 6.70 (d, 1H), 3.80 (t, 2H), 3.70 (s, 3H), 3.55 (s, 3H), 2.70 (t, 2H).
X: mp 69-71°C; mass: m/e 233 (M^+), 114; ir: 1720, 1680 cm^{-1}; nmr $\delta(CCl_4)$: 4.63 (t, 2H), 3.72 (s, 3H), 3.20-3.70 (m, 4H), 2.70 (t, 2H).

7) VIIIb: Found: C, 47.51; H, 5.25; N, 12.07; S, 14.29%. Calcd. for $C_9H_{12}N_2O_3S$: C, 47.36; H, 5.30; N, 12.27; S, 14.05%. X: Found: C, 40.90; H, 4.80; N, 6.03; S, 27.73%. Calcd. for $C_8H_{11}NO_3S_2$: C, 41.19; H, 4.75; N, 6.00; S, 27.48%.

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