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# NOVEL RING TRANSFORMATION OF THIAZOLIDINE TO OXAZOLIDINE: ACYL HALIDE-PROMOTED INTRAMOLECULAR REARRANGEMENT OF 4(R)-HYDROXYMETHYL-3-METHYL-1,3-THIAZOLIDINE

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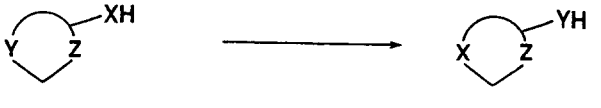
Abstract: An interesting transformation occurs during acylation of 4(R)-hydroxymethyl-3-methyl-1,3-thiazolidine when 4(R)-acylthiomethyl-3-methyl 1,3-oxazolidines are yielded: the reaction competing with O-acylation is controlled by the bulkiness of the acyl group.

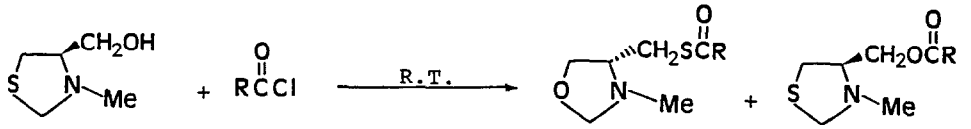
Nucleophilic substitution at a carbon directly attached to two hetero atoms is known to take place commonly, and there has been a wide diversity of intermolecular displacement that linear substances undergo upon nucleophilic attack.[1,2] However, no appropriate example for intramolecular nucleophilic substitution of cyclic substances(Eq. 1) has been found so far, despite that the substitution may provide an useful method for hetero atom conversion. In our recent study on the synthetic use of multifunctional amino acids and their derivatives,[3] we have found that a 1,3-thiazolidine derivative having 4(R)-hydroxymethyl group(1) is converted to 1,3-oxazolidine derivative(3) in the reaction with acyl halide(Eq. 2).

First attempt to bring about the intramolecular conversion of 1 to 4(R)-mercaptomethyl-3-methyl-1,3-oxazolidine(3') with a base such as triethylamine was unsuccessful, where 1 was quite stable. Then we in turn examined acyl halide as one of the promising catalysts for the conversion in the light of the substitution reaction of N-(phenylthio)methylpiperidine with acetyl chloride.[2a,4] Surprisingly, the hetero atom exchange indeed took place to give an oxazolidine derivative(Eq. 2).




( 1 )

X,Y,Z: Hetero atom



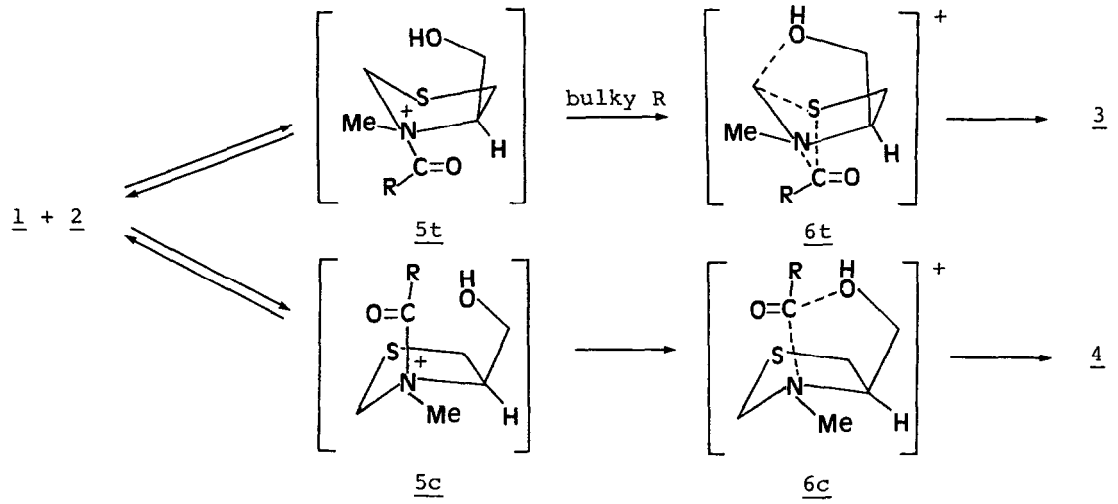

1 2 3 4 ( 2 )

In a typical reaction procedure, to a solution of isobutyryl chloride(3.0 mmol) in dry ether(5 mL) the thiazolidine(1,[5] 5.0 mmol)[6] dissolved in the solvent(5 mL) was added with stirring at room temperature. The mixture was stirred at ambient temperature for 4 hours, then neutralized by aqueous sodium bicarbonate, and extracted with the solvent. Besides the starting material 1,[7] two products obtained through silica gel column chromatography(solvent: ethyl acetate, TLC: $R_f$ 0.50 and 0.60), were identified to be thioester(30%) and ester (11%) by means of spectroscopies(MS, IR and NMR)(see Table note d). The thioester and ester were distinguishable in characteristic carbonyl absorptions in IR at 1678 $cm^{-1}$(thioester) and 1720 $cm^{-1}$(ester). In the similar manner a few other acyl halides were tested and similar products were obtained. In the case of 3a low field-shifted carbon resonance at 199 ppm corresponding to thioester carbonyl carbon also supported the structure estimated. Selected results are summarized in Table 1.

Table 1. Reaction of 4(R)-Hydroxymethyl-3-methyl-1,3-thiazolidine(1)[a] With Acyl Halide(2) at Room temperature

| Run | 2(R=) | 1/2[b] | Reaction Time/h | Solvent | Ratio of Products 3($\nu_{C=O}$)[c]: 4($\nu_{C=O}$)[c] | Isolated[d] Yield[%] |
|---|---|---|---|---|---|---|
| 1 | 2a[e] | 4.5/4.5 | 1.5 | $CH_2Cl_2$ | 90(1690)[f]:10(1720) | 53 |
| 2 | 2b(t-Bu) | 6.0/3.0 | 4.0 | ether | 95(1670)[g]: 5(1720) | 59 |
| 3 | 2c(i-Pr) | 5.0/3.0 | 4.0 | ether | 70(1678) :30(1720) | 41 |
| 4 | 2d( Me ) | 3.0/2.0 | 4.0 | ether | 0 :100(1730) | 30[h] |

a) $[\alpha]_D^{24}$ -62.2°(c 2.18, $CHCl_3$).[5] b) mmol/mmol. c) IR absorption of carbonyl vibration($cm^{-1}$). d) As no other product besides 3 and 4 was detected, the conversion yield is considered to be ca. 100% in any case(see ref.7).
e) R=-CH(i-Pr)$C_6H_4$Cl-p. f) $^{13}$C-NMR($CDCl_3$, δ) 199 ppm(-S-C(=O)-). g) $[\alpha]_D^{24}$ +9.5° (c 1.26, $CHCl_3$). h) No thioester was obtained.




Scheme

Inspection of data of Table 1 reveals clear dependence of the thioester formation competing with the ester formation upon the bulkiness of the acyl halide. Ratio of 3 to 4 increases dramatically as R becomes bulky. This result seems to indicate importance of the steric requirement at the transition states or the intermediates of the reaction. It may be explained well by assuming two competing reaction courses dipicted in Scheme via two different acyl ammonium intermediates(5). The trans form(5t) is sterically more stabilized than the cis one(5c) while steric repulsion between C2 methylene and the bulky acyl group makes easier attack of alcohol oxygen at C2 carbon at the transition state(6t), eventually yielding 3.[8,10] On the other hand, intramolecular O-acylation of the cis form(5c) favorably proceeds with small R via a transition state(6c) to give 4. Thus medium bulkiness of R makes two processes competitive.

Following experimental results would support the intervention of the acyl ammonium ion 5: the addition of triethylamine(one equivalent) as a base into the reaction system gave rise to the great increase of 4 along with remarkable decrease of 3(3c:4c = ca. 10:90). In this case usual intermolecular O-acylation in the presence of triethylamine was strongly predominated. Furthermore diphenylketene[12] and methyl isocyanate used instead of the acyl halide formed only usual alcohol addition products(reaction time: 30 h).[13] This result is consistent with lack of possible formation of ammonium intermediates between 1 and them.

Thus, the preliminary results of the intramolecular rearrangement described in this article are of great interest in both synthetic and mechanistic aspects, and further studies are under active investigation.

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c) Böhme, H.; Hartke, K. ibid. 1960, 93, 1305.

5. The starting material 1 is a new compound to which satisfactory microanalysis data were given along with spectroscopic data consistent with its structure. Synthesis of 1 from L-cysteine methyl ester was accomplished by our original method which is submitted for publication.

6. Interestingly, product yield was hardly changed in the range from one to two equivalent of 1.

7. Starting material was always recovered but its amount was not determined since it is water soluble.

8. While a common acyclic system, like $RSCH_2NR'_2$ reacts with nucleophile to give $NuCH_2NR'_2$,[2] it is known that when either X or X' is ammonium group in $X\text{-}CR_2\text{-}X'$, nucleophilic reaction prefers to eliminate the amine group as a good leaving group.[9] However, in this case only C-S bond fission was observed without the C-N bond fission, in spite of the probable formation of the acyl ammonium ion 5. This presumably indicates the strong participation of sulfur atom in the intermediate 5t and the transition state 6t.[10]

9. Suzuki, K.; Sekiya, M. Chem. Lett. 1979, 1242.

10. Effect of bulkiness(Table 1) appears to be inconsistent with $S_N1$ type reaction involving initial formation of immonium intermediate($\geq C=\overset{+}{N}\leq$)[11] and therefore the concerted mechanism is acceptable.

11. Knoll, F.; Krumm, U. Chem. Ber. 1971, 104, 31.

12. Treatment of acyl halide such as 2c with base is reported to give ketene: R.S. Ward, In" The chemistry of ketenes, allene and related compounds. Part 1". S. Ratai, Ed.; John Wiley & Sons: New Yark, 1980, Chapter 7.

13. Isobutyric anhydride also reacted slowly(18 h), but afforded only O-acylation product(4c, 50%) by direct reactoin.

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