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# PREPARATION OF N-THIOAMIDO-β-LACTAM AND 2-THIOHEXAHYDROPYRIMIDIN-4-ONE DERIVATIVES FROM N-MONOSUBSTITUTED THIOUREAS AND β-HALOACYL HALIDES

Tadashi OKAWARA, Kentaro NAKAYAMA, and Mitsuru FURUKAWA*

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-hon-machi, Kumamoto 862

The reactions of N-monosubstitued thioureas (1) with β-haloacyl halides (2) were carried out in 5% NaOH-$CH_2Cl_2$ in the presence of a phase transfer catalyst to afford N-thioamido-β-lactams (3 and 5), thioureido acids (4), and 5-hydroxy-2-thiohexahydropyrimidin-4-ones (6). The compounds, 3 and 4, were readily converted to 5,5-dimethyl-2-thiohexahydropyrimidin-4-ones (7) with 6N HCl.

The versatility of thioureas in the synthesis of heterocycles has been widely demonstrated in the past.[1] Although many reactions of thioureas with a variety of carboxylic acids, carboxylic esters, and aliphatic halides have been achieved, no study on the reaction with haloacyl halides is involved in these preparations.

Most of these reactions are studied on the formation of five- and six-membered ring compounds, and therefore little is known concerning the formation of four-membered ring compounds, except cyclizations to 1,3-thiazetin-4-one[2] by the reaction with phosgene or thiophosgene, to thiazetidine[3] by treating with methylene iodide, and to thietane[4] of 2-(3-hydroxylalkyl)- or 2-(3-chloroalkyl)-2-isothiourea.

In this paper, we wish to report novel cyclizations to four-membered ring compound, N-thioamido-β-lactam (3 and 5) and to six-membered ring compound, 5-hydroxy-2-thiohexahydropyrimidin-4-one (6) by the reaction of N-monosubstituted thioureas (1) with β-haloacyl chlorides (2) in 5% NaOH-$CH_2Cl_2$ in the presence of a phase transfer catalyst (PTC).

A typical procedure is as follows: to a stirred mixture of 1 (5 mmol), $CH_2Cl_2$ (20 ml), and aqueous 5% NaOH (5 ml) was gradually added 2 (5 mmol) under cooling with ice-water. Then additional 5% NaOH (10 ml) and benzyltriethylammonium chloride (20 mg) were added with stirring, and the stirring was continued for 12 hr at room temperature. The organic layer was separated, washed with water, dried over anhydrous $Na_2SO_4$, and evaporated. The residue was purified by recrystallization from ethanol-hexane or by silica-gel column chromatography ($CHCl_3$) to give N-thioamido-β-lactams 3 and 5. On acidfying the aqueous layer with 6N HCl, thioureido acids (4) and 5-hydroxy-2-thiohexahydropyrimidin-4-ones (6) were also isolated. The results are summarized in Table 1. In order to check whether the compounds 4 and 6 were formed through 3 and 5, respectively, or not, the conversions of 3 and 6 under similar conditions to 4 and 6 were also examined. However, such a conversion was not

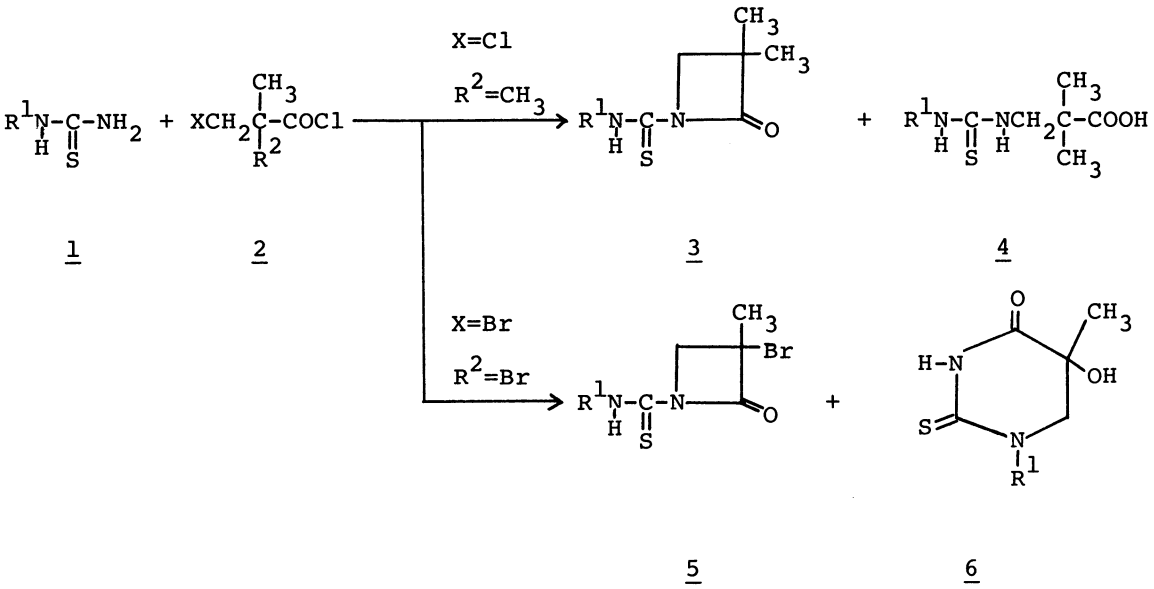


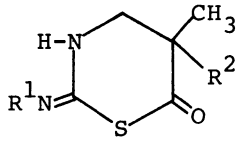
Table 1 N-Thioamido-4,4-dimethyl-β-lactam (3), Thioureido Acid (4), N-Thioamido-4-bromo-4-methyl-β-lactam (5), and 5-Hydroxy-5-methyl-2-thiohexahydropyrimidin-4-one (6)

| $R^1$ | Compound | Yield(%) | mp(°C) | IR $\nu_{max}^{KBr(film)}$ $cm^{-1}$ | $M^+$ |
|---|---|---|---|---|---|
| Naph | 3 | 63 | 168-169 | 3210,1760,1500 | 284 |
| Ph | 3 | 58 | 59-60 | 3240,1760,1528 | 234 |
| | 4 | 37 | 155 | 3370,3220,1700,1530 | 252 |
| $PhCH_2$ | 3 | 53 | 68-69 | 3300,1760 1530 | 248 |
| $c\text{-}C_6H_{11}$ | 3 | 51 | 105-106 | 3240,1760,1530 | 240 |
| | 4 | 20 | 188-189 | 3270,3220,1700,1510 | 258 |
| $CH_3$ | 3 | 41 | 70-71 | 3310,1760,1540 | 172 |
| | 4 | 27 | 152-153 | 3400,3220,1700,1520 | 190 |
| Ph | 5 | 35 | 65-67 | 3240,1760,1520 | 300,298 |
| | 6 | 31 | 196-197 | 3400,3240,1725,1500 | 236 |
| $PhCH_2$ | 5 | 36 | oil | 3310,1765,1520 | 314,312 |
| $c\text{-}C_6H_{11}$ | 5 | 27 | 97-98 | 3280,1760,1500 | 306,304 |
| Naph | 6 | 37 | 242-243 | 3360,1710,1510 | 286 |

All products gave satisfactory $^1$H-NMR spectral data and elemental analyses.

observed at any rate.

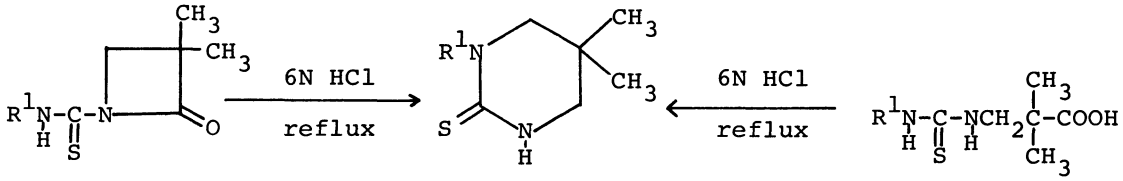
The assignment of the structures of 3 and 5 was based on IR and mass spectral data. The IR spectra showed the carbonyl and thioureido absorptions at 1760-1765 and 1500-1530 $cm^{-1}$, respectively, and the mass spectra had the typical fragments of ketenes, azomethines, alkenes, and isocyanates derived from β-lactams. The compounds 4 exhibited the carboxylic acid and thioureido absorptions at 1700 and 1510-1530 $cm^{-1}$, respectively, apparently indicating the structure of the thioureido acid. The structure was also supported by $^1$H-NMR and mass spectral data. In the compound 6, another isomeric structure, in which the $R^1$ group attaches to the $N^3$ atom, is possible. The coupling of the hydrogen at $N^1$ with that at $C^6$ on $^1$H-NMR spectrum of thymine glycol was reported.[5] In the isomeric compound of 6 having the hydrogen at $N^1$, the coupling with the neighboring hydrogen at $C^6$ must be observed. However, even in the case that the signals of the hydrogens at $N^1$ and $C^6$ were amplified the sweep width six times, such a coupling was not shown. Therefore, the assigned structure of 6 in which phenyl group is attached to $N^1$ atom is suitable. The structure of 6 was also supported by comparison of the similar compounds, 5,5-dimethyl-2-thiohexahydropyrimidin-4-one(8), having a hydrogen on $N^1$ atom. The signal of the hydrogen at $N^3$ of the compound 6 appeared at 8.6-8.9 ppm. On the other hand, the compound 8 showed the hydrogen at 7.9-8.2 ppm.



7

In this reaction, the formation of 2-imino-tetrahydro-1,3-thiazin-4-one (7) is also possible, but such a compound could not be isolated. Although the compound 6 possesses a tertiary hydroxy group at $C^5$, the conversion to 1-phenyl-2-thiothymine by dehydration resulted in failure.

A novel conversion of N-thioamido-β-lactam (3) to 5,5-dimethyl-2-thiohexahydropyrimidin-4-one (8) was also found. Heating 3 with 6N HCl for 1 hr caused ring cleavage, followed by recrystallization to 8 in good yields, though reflux in 1N HCl for 12 hr gave no product. The results are shown in Table 2.




3 8 4

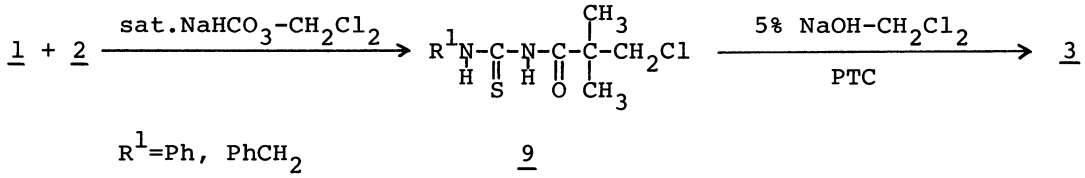
The compound 8 showed the carbonyl and thioureido absorptions at 1700-1720 and 1532-1560 $cm^{-1}$, respectively. This structure was also supported by $^1$H-NMR and mass spectral data, and established by the alternative preparations[6] from thioureido acids 4 in 80-95% yields.

Table 2 5,5-Dimethyl-1-substituted-2-thiohexahydropyrimidin-4-one (8)

| $R^1$ | mp(°C) | Yield(%) | IR$\nu_{max}^{KBr}$ $cm^{-1}$ | $M^+$ |
|---|---|---|---|---|
| Naph | 237-238 | 91 | 3340,1720,1540 | 284 |
| Ph | 200-201 | 92 | 3350,1710,1532 | 234 |
| $PhCH_2$ | 138-139 | 85 | 3200,1718,1560 | 248 |
| $CH_3$ | 165-166 | 71 | 3360,1700,1560 | 172 |

All products gave satisfactory $^1$H-NMR spectral data and elemental analyses.

When the reaction of 1 with 2 was carried out in a saturated $NaHCO_3$-$CH_2Cl_2$ solution, chloropivaloyl thioureas 9 were produced in 70-72% yields. The compound 9 was readily converted to 3 by stirring it in 5% NaOH-$CH_2Cl_2$ at room temperature in the presence of PTC in 80-85% yields. From this result, it is apparent that the formation of the β-lactam 3 proceeded via the intermediate 9.




These reactions proceeded even without PTC, but the yields were considerably lower.

Further applications of these reactions to the preparation of other heterocyclic compounds are being currently investigated.

References

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