be almost none, *i.e.* 0.02 kcal/mol. However, the slight modification of recent MM2 (87) parameters for MVS can remedy Frierson's error.
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## Unusual Transacetylation in 3,4-Difunctionalized Pyrrolidine

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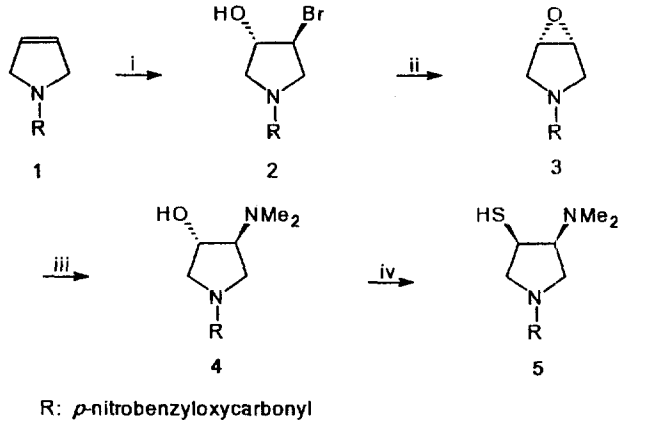
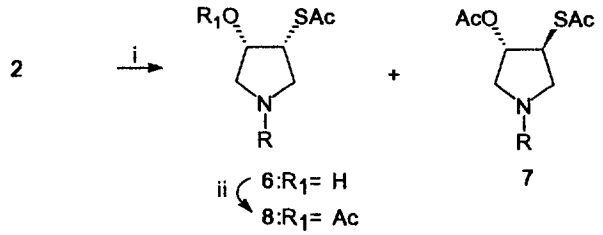
There are considerable interests in the chemistry of natural pyrrolidines and polyhydroxylated pyrrolidine derivatives. Anisomycin[1] and codonopsin[2] are well known biologically active natural pyrrolidines containing 3,4-dihydroxy group. Furthermore, a number of biological activities such as inhibition of glycosidase and inhibition of human immunodeficiency virus (HIV) replication[3] depend on the stereochemistry of polyhydroxylated pyrrolidines. And also they are utilized as useful intermediates for the synthesis of various alkaloids. Recently the pyrrolidine moieties in non-classical β-lactam antibiotics show very potent antimicrobial activities[4] and many investigations of the modified new pyrrolidine substituents are giving a great progress. In the process of preparing various 3,4-difunctionalized pyrrolidines, we isolated a transacetylated compound unexpectedly. Now we are presenting the preparation of the various pyrrolidine derivatives, and possible mechanistic pathway of the unexpected transacetylated compound in the reaction of halohydrin with potassium thioacetate.

The pyrrolidine epoxide **3** was prepared from the reaction of N-*p*-nitrobenzyloxycarbonyl(PNZ)-3-pyrroline **1** with NBS and perchloric acid[5], followed by the treatment of the resulting bromohydrin derivative **2** with 5% KOH. Different kinds of nucleophiles can be used to give new substituted pyrrolidines also. The aminohydroxy compound **4** was obtained from the reaction of pyrrolidine epoxide **3** and the dimethylamine. The amino-thio compound **5** can be obtained from the reaction of the amino-hydroxy compound **4** under Mitsunobu condition[6] as shown in Scheme 1. Our attempts to get hydroxy-thio compound *via* ring opening of **3** with thiolacetic acid in the presence or in the absence of Lewis acid, and potassium thioacetate were unsuccessful.

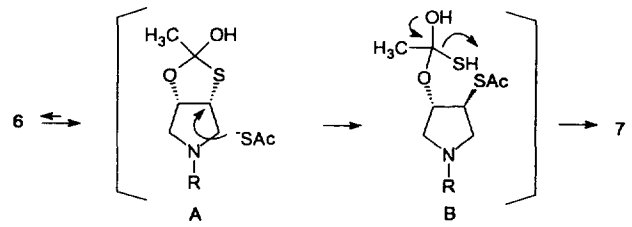



**Scheme 1.** Reagents and conditions: i, NBS, aq. $HClO_4$, THF, 80%; ii, 5% KOH, MeOH, 98%; iii, aq. $NHMe_2$, THF, reflux, 95%; iv, $PPh_3$, $(Pr^iOOCN=)_2$, AcSH, THF, then 4N NaOH, 72%.




**Scheme 2.** Reagents and conditions; i, KSAc, DMF-toluene, 80 ℃, 2-5 hr, 72%; ii, $Ac_2O$, Pyridine, DMAP, $CH_2Cl_2$, 92%.

When bromohydrin **2** was treated with potassiun thioacetate, a separable mixture of thioacetyl compound **6** and unexpected transacetylated compound **7** in *ca.* 1 : 2 molar ratio was obtained. The expected thioacetyl compound **6** can be easily confirmed, but unexpected new compound **7** was identified from $^1$H-NMR, mass, and NOE experiment. $^1$H-NMR spectrum of **7** clearly showed two methyl peaks centered at δ 2.36 and 2.12. In general, it is difficult to determine the stereochemistry in substituted pyrrolidine systems by using the chemical shifts and coupling constants when their conformations are flexible[7]. For clarity, thioacetyl compound **6** was further acetylated to the diacetyl compound **8** under the standard condition (Scheme 2). The compound **7** and **8** was identified by NMR and the stereochemistry was confirmed by NOE experiment. From NOE experiment, 2.6% enhancements of C-3 and C-4 signals were observed from the *cis* compound **8** by irradiation on the 4-H and 3-H, respectively, but there was no enhancement from the *trans* compound **7**. Interestingly two hydrogens which are positioned



**Scheme 3.**

in same site on 2- or 5-positions, are strongly enhanced also by irradiation on the 3-H or 4-H.

The possible mechanistic pathway of the unusual transacetylated compound was proposed in Scheme 3. It was reported that benzylidene acetals can be opened by NBS to give benzoylated derivatives[8] *via* similar pathway. And the recent exploitation of ring opening products from vicinal diol cyclic sulfates[9] and sulphamidates[10] by various nucleophilic attack suggested that a related similar cyclic intermediate might be applicable. The possible bicyclic intermediate *A* can be opened by the thioacetate anion from the opposite site to give *trans* intermediate *B* which can be transformed to give the transacetylated product **7**, MS (70 eV): $m/z=383$ (M+1). For reasonable configuration of **6**, the thioacetate group should be *cis* to the hydroxy group. And the bicyclic intermediate attacked by thioacetate ion should acetylate the hydroxy group. Also a base catalyzed N→O transacetylation in pyrrolidine system was reported[11]. Those reported investigations support the bicyclic intermediate pathway was as shown above.

## Experimental Section

**General.** $^1$H-NMR spectra were measured on a Varian Gemini-200 or a Bruker AM-300 spectrometer with tetramethylsilane ($Me_4Si$) as an internal standard. Chemical shifts were reported as δ values in parts per million relative to $Me_4Si$. Mass spectra were recorded on a Shimadzu GCMS-GP1000 spectrometer with EI ionization. The $^1$H-$^1$H NOE experiments in the different mode were performed at 25℃ for 30-60 mg of sample in 0.5 m*l* of $CDCl_3$.

***N*-PNZ-3β-bromo-4α-hydroxy-pyrrolidine (2) and *N*-PNZ-3,4α-oxido-pyrrolidine (3)** were prepared according to the published procedures[5].

**2**: NMR ($DMSO-d_6$) δ 3.80 (m, 2H), 4.07 (m, 1H), 4.31 (m, 2H), 5.28 (s, 2H), 5.84 (br s, 1H), 7.63 (d, $J=9$ Hz, 2H), 8.25 (d, $J=9$Hz, 2H); MS *m/z* (relative intensity) 346 (2), 344 (2), 265 (8), 264 (8), 247 (30), 209 (40), 194 (5), 192 (5), 165 (25), 136 (100).

**3**: NMR ($CDCl_3$) δ 3.43 (dd, $J=5$, 5 Hz, 1H), 3.78 (s, 2H), 3.88 (dd, $J=2$, 2 Hz, 1H), 5.24 (s, 2H), 7.51 (d, $J=9$ Hz, 2H), 8.22 (d, $J=9$ Hz, 2H).

***N*-PNZ-4β-dimethylamino-3α-hydroxy-pyrrolidine (4).** To a solution of 150 mg (0.56 mmol) of **3** dissolved in 5 m*l* of THF was added 0.7 m*l* of dimethylamine (40 wt% solution in water). Water (5 m*l*) was added and the solution was heated to reflux for 2.5 hr and then concentrated to give oily residue, which was then dissolved in EtOAc (20 m*l*). The organic solution was washed successively with water and brine and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated to yield 165 mg (95%) of **4** as an oil: NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.81 (m, 1H), 3.33 (m, 2H), 3.66 (m, 2H), 4.28 (m, 1H), 4.62 (s, 1H), 5.16 (s, 2H), 7.48 (d, $J=9$ Hz, 2H), 8.15 (d, $J=9$ Hz, 2H).

***N*-PNZ-4β-dimethylamino-3β-mercapto-pyrrolidine (5).** To a solution of 260 mg (0.84 mmol) of **4** and 330 mg (1.25 mmol) of triphenylphosphine in 20 m*l* of anhydrous THF was added dropwise a solution of 255 mg (1.26 mmol) of diisopropyl azodicarboxylate in 5 m*l* of THF at 0℃ under nitrogen atmosphere and stirred for 30 min at the same temperature. Thiolacetic acid (96 mg, 1.26 mmol) was added dropwise to the mixture. After stirring for 2hr at 0℃ and then at room temperature for 4 hr, the reaction mixture was concentrated *in vacuo* to give an oily residue which was purified by silica gel column chromatogrphy with $CH_2Cl_2$-acetone (9 : 1) to afford 250 mg of the thioacetate. This was dissolved in 5 m*l* of MeOH and 0.25 m*l* of 4N NaOH was added at 0℃ and stirred for 15 min at that temperature. After addition of 1N HCl (1 m*l*), the reaction mixture was diluted with EtOAc (30 m*l*) and the organic phase was washed with water. Drying ($Na_2SO_4$) and concentration afford 197 mg (72%) of **5** as an oil: NMR ($CDCl_3$) δ 2.33 (s, 6H), 3.12 (m, 1H), 3.35 (m, 1H), 3.55 (m, 2H), 4.04 (m, 2H), 4.85 (br s, 1H), 5.20 (s, 2H), 7.53 (d, $J=9$ Hz, 2H), 8.24 (d, $J=9$ Hz, 2H).

***N*-PNZ-3α-acetylthio-4α-hydroxy-pyrrolidine (6) and *N*-PNZ-4α-acetyloxy-3β-acetylthio-pyrrolidine (7).** A solution of 1.2 g (3.47 mmol) of **2** and 1.2 g (10.5 mmol) of potassium thioacetate in 20 m*l* of DMF-toluene (1 : 1) was heated at 80℃ for 3-5 hr under nitrogen atmosphere. The solution was poured into water (100 m*l*) and extracted with EtOAc (50 m*l*×3). The organic layer was washed successively with water and brine and dried over anhydous $MgSO_4$. The solution was filtered, concentrated, and chromatographed on a column of silica gel with $CH_2Cl_2$-acetone (19 : 1) to give **6** (280 mg, 23%) and **7** (650 mg, 49%).

**6**: NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.42 (m, 2H), 3.61 (m, 1H), 3.87 (m, 1H), 4.01 (m, 2H), 4.24 (br s, 1H), 5.18 (s, 2H), 7.48 (d, $J=9$ Hz, 2H), 8.16 (d, $J=9$ Hz, 2H).

**7**: NMR ($CDCl_3$) δ 2.21 (s, 3H), 2.36 (s, 3H), 3.41 (t, $J=10.5$ Hz, 1H), 3.65 (m, 1H), 3.76 (m, 1H), 3.99 (m, 1H), 4.15 (m, 1H), 5.25 (s, 2H), 5.43 (q, $J=3.6$ Hz, 1H), 7.54 (d, $J=8.6$ Hz, 2H), 8.24 (d, $J=8.6$ Hz, 2H); MS *m/z* (relative intensity) 383 (5.5), 247 (24.9), 203 (18.1), 136 (43.9), 106 (12.5), 89 (21.0), 43 (100.0).

***N*-PNZ-4α-acetyloxy-3α-acetylthio-pyrrolidine (8).** To a solution of 120 mg (0.35 mmol) of **6** in $CH_2Cl_2$ (12 m*l*) was added dry pyridine (55 mg, 0.69 mmol), $Ac_2O$ (107 mg, 1.04 mmol), and 4-(dimethylamino)pyridine (4.8 mg, 0.04 mmol). This mixture was stirred at room temperature for 2 hr and then poured into a mixture of 1N HCl (10 m*l*) and ice-water (10 m*l*). The organic phase was washed with 5% aqueous $NaHCO_3$ and water, dried ($Na_2SO_4$), and filtered. Evaporation under reduced pressure to remove the solvent afforded an oil. The crude product was chromatographed on a silica gel column eluting with $CH_2Cl_2$-acetone (19 : 1). The solvent was evaporated under reduced pressure to give **8** (123 mg, 92%) as an oil: NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.37 (s, 3H), 3.54 (m, 2H), 3.78 (m, 1H), 3.98 (m, 2H), 5.14 (dd, $J=1.7$, 1.7 Hz, 1H), 5.24 (s, 2H), 7.53 (d, $J=8.6$ Hz, 2H), 8.22 (d, $J=8.6$ Hz, 2H); MS *m/z* (relative intensity) 383 (1.0), 323 (0.9), 316 (1.5), 281 (3.9), 247 (11.5), 203 (9.3), 136 (29.7),

43 (100.0).

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