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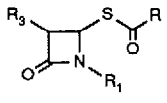
AN EFFICIENT METHOD FOR THE SYNTHESIS OF 4-BENZOYLTHIOAZETIDINONES

Mark P. Wentland,* Philip E. Hansen, Steven R. Schow,[1] and Sol J. Daum

Medicinal Chemistry Department
Sterling Research Group
Rensselaer, NY 12144

Summary: The kinetically-controlled S-benzoylation of secondary thioformamides in the presence of triethylamine at low temperature provided S-benzoylthioimidates **6**. Without isolation, these unstable intermediates were utilized in the ketene-imine cycloaddition reaction with phthalimidoacetyl chloride/triethylamine to give 4-benzoylthioazetidinones **7** in yields up to 95%.

Monocyclic β-lactams and, in particular, their 4-acylthio variants **1** have been extremely valuable intermediates in the preparation of new antibacterial agents. The most notable example is the methodology developed by Woodward and coworkers, where the synthesis of penems **2** has been realized *via* an intramolecular Wittig olefination [e.g., **1** (R_1 = C(=PPh_3)CO_2R') → **2**].[2] 4-Acylthioazetidinones have also been used for preparing cephems[3] and analogues of the monocyclic β-lactam natural product nocardicin A.[4]



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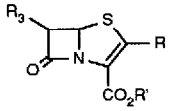

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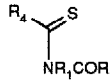
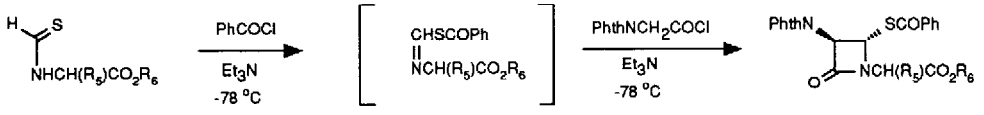


4

Among the procedures reported for the syntheses of 4-acylthioazetidinones **1**, several excellent methods utilize natural penicillin derivatives as starting materials.[5] Most other 4-acylthioazetidinones have been made by replacement of the acetoxy group in 4-acetoxyazetidin-2-one by salts of thioacids.[2,6] The remarkably efficient and general method, the ketene-imine cycloaddition, was used to make 4-acetoxyazetidin-2-one and numerous related β-lactams.[6,7] To our knowledge, however, the ketene-imine cycloaddition reaction has not been used directly to make 4-acylthioazetidinones. This is probably a consequence of the instability and elusive nature of **3**, the requisite S-acylthioimidate intermediate.

We envisioned a process whereby acylation of a thioformamide under **kinetically-controlled** conditions (i.e., low temperature) would discourage the S → N acyl migration (i.e., **3** → **4**) S-acylthioimidates generally undergo. Subsequent cycloaddition with, for example, the ketene derived from phthalimidoacetyl chloride/ triethylamine would generate the β-lactam. We now wish to report our results showing that 4-benzoylthioazetidinones **7** can be efficiently prepared using this modification of the ketene-imine cycloaddition reaction.

S-Benzoylation of racemic diphenylmethyl α-[(thioxomethyl)amino]benzeneacetate **5a**[8] was accomplished using benzoyl chloride and triethylamine in CH_2Cl_2 at -78 °C (see Experimental[9]). Subsequent addition of phthalimidoacetyl chloride gave, after work-up and chromatography, a 95% yield of azetidinone **7a**.[9-12]



5 **6** **7**

a; R_5 = Ph, R_6 = $CHPh_2$

b; R_5 = H, R_6 = CH_3

Using a similar procedure, methyl *trans*-4-(benzoylthio)-3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-oxo-1-azetidineacetate[10] (**7b**, mp 119-120 °C, 62%) was made from **5b**.[13]

S-Acylthioimidates **3** are well-documented intermediates in the acylation of thioamides.[14,15] The products generally observed from these reactions are the thermodynamically more stable N-acylthioamides **4** resulting from an intramolecular S → N acyl migration.[14] A low temperature two-phase liquid-solid system has been used to generate examples of **3** which after isolation were thermally rearranged to the more stable species **4**.[14] For the examples of **3** that have been isolated and characterized, the R, R_1, and R_4 appendages were either aryl or alkyl groups.[14-16] An interesting facet of Walter's study was the relationship found between the size of the R, R_1, and R_4 groups and the stability (i.e., rate of S → N migration), stereochemistry, and conformation of **3**.[14]

We are aware of only one example of **3** derived from a thioformamide (i.e., R_4 = H).[17] Here, thioformamide was acylated with benzoyl chloride in the **absence** of base. The S-benzoyl adduct **3** ($R_1 = R_4$ = H, R = Ph) was isolated and characterized as its HCl salt. The fact that this salt is isolable and that no free base forms of **3** (R_4 = H) have been reported is in concert with the proposed mechanism[14] for the intramolecular migration that requires a) the presence of a nitrogen lone pair and b) the ability of **3** to adopt an E-configuration relatively free of steric encumbrances.

To ascertain if the kinetically-controlled conditions used were a necessary component for the success of our reactions, a duplicate of the **5a** → **7a** transformation was performed with the **only** difference being that all manipulations were done at ambient temperature. Compound, **4** [R = Ph, R_1 = $CH(Ph)CO_2CHPh_2$, R_4 = H] was cleanly secured.[10] This result strongly suggests that at -78 °C the rate of S → N acyl migration in **6a** is slow relative to the rate of cycloaddition, but at ambient temperature the rate is such that the migration is essentially complete by the time the other reagents are added.

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9. Experimental **Diphenylmethyl *trans*-4-(benzoylthio)-3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-oxo-α-phenyl-1-azetidineacetate (7a).** Benzoyl chloride (1.55 g, 11 mmol) in 20 mL of CH_2Cl_2 was added over 10 min to a stirred solution (maintained at -78 °C, N_2 atmosphere) of **5a**[8] (3.61 g, 10 mmol), triethylamine (2.23 g, 22 mmol), and 50 mL of CH_2Cl_2. After stirring 15 min at -78 °C phthalimidoacetyl chloride (2.46 g, 0.011 mol) in 30 mL of CH_2Cl_2 was added over 15 min. The solution was stirred at -78 °C for an additional 3 h and allowed to warm to ambient temperature and left standing for 24 h. Following an aqueous $NaHCO_3$ wash, drying ($MgSO_4$) and concentration under reduced pressure, the crude product was chromatographed on a Waters Prep 500 HPLC (Prep PAK-500/silica) using 2:1/hexane:ethyl acetate as eluent to provide 6.20 g (95%) of **7a**[10-12] (foam). Anal. Calcd for $C_{39}H_{28}N_2O_6S$: C, 71.77; H, 4.32; N, 4.29. Found: C, 72.16; H, 4.32; N, 4.00. Scale-up of this reaction also gave excellent results. For example, on a 50 mmol (of **5a**) scale, a yield of 89% was realized.
10. ^{1}H-NMR, IR, and mass spectra were consistent with the assigned structures of all new compounds. Carbon, hydrogen, and nitrogen elemental analyses were also obtained and were within ±0.4% of the theoretical values. We acknowledge the assistance of our Analytical Chemistry Department in obtaining these spectral data..
11. This represents a mixture (3:2 by ^{1}H-NMR integration) of diastereomers epimeric about the α-carbon of the acetate side chain.
12. The *trans* stereochemistry was assigned on the basis of a) a coupling constant of J = 2.5 Hz between H-3, H-4 and b) similar results observed in the cycloaddition with alkylthioimidates: Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323.
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