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REACTIONS OF (2-OXO-1-AZETIDINYL)-THIOPHTHALIMIDES WITH NUCLEOPHILES

by

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Reaction of the title compounds with a variety of oxygen, nitrogen, carbon and sulfur nucleophiles proceeds by direct attack at the sulfur atom to provide novel substituted N-thio-2-azetidinones.

The significant biological activity of many recently described monocyclic ß-lactams has encouraged the design and synthesis of a number of novel ß-lactams. Since our development of the hydroxamate approach to the synthesis of ß-lactams,[1] we have been especially interested in the synthesis and study of various types of heteroatom activated ß-lactams.[2] Recently we reported that reaction of N-unsubstituted ß-lactams **1** with S-substituted thiophthalimides **2** provides an efficient route to the corresponding N-thio-2-azetidinone derivatives (Scheme 1).[3] Furthermore, depending on the conditions used, reaction of **1** with bisphthalimido sulfur **4** provided either the (2-oxo-1-azetidinyl)-thiophthalimide **5** or the bis-(2-oxo-1-azetidinyl)-sulfur **6**. The ability to form **6** suggested that reactions of **5** with other nucleophiles might proceed by attack at sulfur and not at the ß-lactam carbonyl. Herein we describe the preparation of a number of novel substituted N-thio-2-azetidinones **8** by the reaction of (2-oxo-1-azetidinyl)-thiophthalimides **5** with oxygen, nitrogen, carbon and sulfur nucleophiles **7**.

Scheme 1

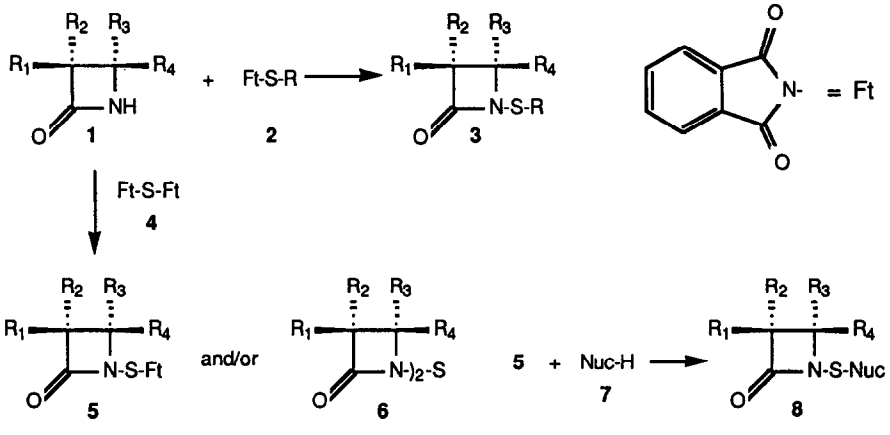
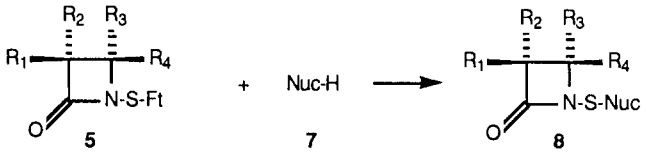
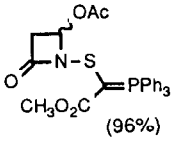
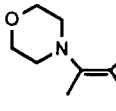
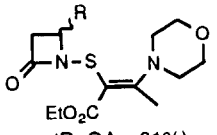
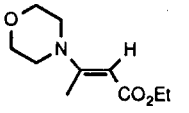


Table 1

Reactions of (2-Oxo-1-azetidinyl)-thiophthalimides with Nucleophiles



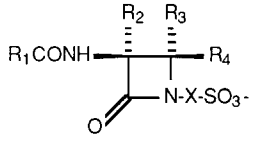
Entry	5 R_1	R_2	R_3	R_4	NucH (7)	Conditions	8[6](yield)
a[a]	H	H	H	OAc	$PhCH_2OH$ (500 mole%)	PhH, 24h, RT NEt_3 (cat)	(64%)
b[a]	H	H	H	OAc	 (200 mole%)	PhH, 15h, RT	(73%)
c[a]	H	H	H	OAc	$Ph_3P{=}CHCO_2CH_3$ (110 mole%)	PhH, 1.5h, RT	 (96%)
d[a]	H	H	H	OAc	 (200 mole%)	THF, reflux, 15h	 (R=OAc, 81%)
e[a]	H	H	H	$SCPh_3$	 (200 mole%)	THF, reflux, 24h	(R=$SCPh_3$,33%)
f[a]	H	H	H	OAc	$NaHSO_3$ (100 mole%)	THF/H_2O (1:1), 10 min, RT	(100%)[b]
g	$PhOCH_2CONH$,H		OAc	H	$NaHSO_3$ (100 mole%)	THF/H_2O (1:1), 10 min, RT	(82%)[b]

[a] Racemic

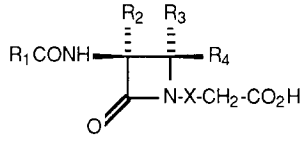
[b] Yield of crude salt. See the text for further discussion.

Most of the starting (2-oxo-1-azetidinyl)-thiophthalimides **5** were prepared from readily available ß-lactams as described earlier.[3] The 3-phenoxyacetamido-4-acetoxy-2-azetidinone (**1**, R_1 = $PhOCH_2CONH$, R^2 = H, R^3 = OAr , R^4 = H) precursor to **5g** (Table 1) was obtained by degradation of penicillin V.[4] Compound **5g** could not be cleanly separated from small amounts of the bis adduct **6**, but this did not interfere with subsequent reactions Results of the reactions of **5a-g** with nucleophiles are summarized in Table 1. In a representative reaction, the nucleophile (100 - 500 mole %, Table 1) was added to a solution of **5a-g** (100 mole %) under nitrogen or argon. The reaction was monitored for disappearance of starting material by TLC and either maintained at room temperature or heated as required to promote reaction (Table 1). Reaction of **5** with relatively weak nucleophiles (i.e. $PhCH_2OH$) required addition of catalytic (2 - 50 µl) triethylamine. In most cases, workup consisted of simply filtering the reaction mixture to remove precipitated phthalimide, concentrating the filtrate and chromatographing the residue on silica gel. The reactions with sodium bisulfite (Table 1, entries **5f,g**) were performed in mixed solvents (THF/H_2O) and produced salts (**8f,g**). Consequently, additional workup conditions were required. In these cases unreacted starting materials and phthalimide were removed by an ethyl acetate extraction. The residual aqueous layer was freeze dried to provide the crude salts **8f** (100%) and **8g** (82%), respectively. Compound **8g** was further purified by first converting it to its organic soluble tetra-n-butylammonium salt (in 80% yield) by treatment with $(nBu)_4NHSO_4$[5] followed by ion exchange chromatography (Dowex, K^+) and lyopholization to give the corresponding potassium salt in 72% yield. Although the structure of **8g** is consistent with the spectral data obtained,[6] and it is a close analogue of the biologically active monosulfactams **9**,[5] compound **8g** was found to be devoid of any biological activity.[7] This negative biological result was consistent with our earlier findings that the thiamazins **10**[8] are biologically inactive while the corresponding oxamazins **11**[2] have considerable activity against Gram negative organisms.

Extensions of the methodology described here are being developed for the synthesis of a variety of heteroatom containing molecules of biological interest.



8g X=S
9 X=O



10 X=S
11 X=O

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References and Notes

§On leave from the Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan (1983 - 1985).

≠Fellow of the Alfred P. Sloan Foundation (1981 -1985). Recipient of a NIH Research Career Development Award (1983 - 1988).

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6. Selected characterization data includes: **8a**: (oil) ^{1}HNMR ($CDCl_3$) δ 2.10 (s, 3H), 3.10 (dd, 1H), 3.45 (dd, 1H), 4.97 (s, 2H), 6.17 (dd, 1H), 7.38 (s, 5H). IR (neat) 1805, 1760 cm^{-1}. TLC (silica gel, ethyl acetate - hexanes, 1:1) R_f = 0.76. **8b**: (oil) ^{1}HNMR ($CDCl_3$) δ 2.13 (s, 3H), 3.05 (dd, 1H), 3.13 (t, 4H), 3.48 (dd, 1H), 3.68 (t, 4H), 6.11 (dd, 1H). IR (neat) 1790, 1755 cm^{-1}. TLC (silica gel, ethyl acetate - hexanes, 1:1) R_f = 0.47. **8c**: (oil) ^{1}HNMR ($CDCl_3$) δ 2.06 (s, 3H), 2.73 (dd, 1H), 3.21 (dd, 1H), 3.54 (s, 3H), 6.1 (br, 1H), 7.4 - 7.9 (m, 15H). IR (neat) 1770, 1760, 1630 cm^{-1}. TLC (silica gel, ethyl acetate - hexanes, 1:1) R_f = 0.25. **8d**: (Off white solid) ^{1}HNMR ($CDCl_3$) δ 1.28 (t, 3H), 2.12 (s, 3H), 2.65 (s, 3H), 2.86 (dd, 1H), 3.29 (dd, 1H), 3.41 (t, 4H), 3.77 (t, 4H), 4.20 (q, 2H), 6.13 (dd, 1H). IR (neat) 1780, 1755, 1673 cm^{-1}. TLC (silica gel, ethyl acetate - hexanes, 1:1) R_f = 0.15. **8e**: (oil) ^{1}HNMR ($CDCl_3$) δ 1.20 (t, 3H), 2.4 (m, 2H), 2.64 (s, 3H), 3.4 (m, 4H), 3.7 (m, 4H), 4.15 (q, 2H), 4.46 (m, 1H), 7.2 - 7.6 (m, 15H). IR ($CHCl_3$) 1770, 1665 cm^{-1}. TLC (silica gel, ethyl acetate - hexanes, 1:1) R_f =0.20. **8f** (Na salt and potassium salt): (glass) ^{1}HNMR (D_2O) δ 2.2 (s, 3H), 3.4 (dd, 1H), 3.8 (dd, 1H) 6.6 (m, 1H). **8f** (tetrabutyl ammonium salt): (oil) ^{1}HNMR ($CDCl_3$) δ 1.0 (t, 12H), 1.4 (m, 8H), 1.6 (m, 8H), 2.2 (s, 3H), 3.2 (dd, 1H), 3.4 (m, 8H), 3.6 (dd, 1H), 6.8 (m, 1H). ^{13}CNMR ($CDCl_3$) δ 13.7, 19.7, 20.9, 24.0, 46.6, 58.7, 78.9, 166.9, 170.0. IR ($CDCl_3$) 1780, 1750 cm^{-1}. **8g** (sodium salt and potassium salt) (white solid) ^{1}HNMR (D_2O) δ 2.2 (s, 3H), 4.7 (s, 2H), 5.2 (d, 1H), 6.5 (d, 1H), 7.1 - 7.6 (m, 5H). TLC (silica gel, ethyl acetate - acetic acid - water, 15:3:1) R_f = 0.41. **8g** (tetrabutylammonium salt): (Oil) ^{1}HNMR ($CDCl_3$) δ 1.0 (t, 12H), 1.5 (m, 16H), 2.1 (s, 3H), 3.2 (m, 8H), 4.5 (s, 2H), 5.3 (dd, 1H), 6.3 (d, 1H), 6.9 - 7.5 (m, 5H), 8.2 (d, 1H). ^{13}CNMR δ 13.3, 19.3, 20.4, 23.6, 58.0, 63.4, 66.7, 83.9, 114.5, 121.6, 129.3, 156.9, 166.0, 167.9, 169.2. IR ($CDCl_3$) 1795, 1760 cm^{-1}.

7. The corresponding aza compound similar to **8g** and **9**, but with X = $NRSO_3^-$, has recently been described in a German patent and, although not quantitatively described, it apparently has some biological activity: Breuer, H.; Denzel, T. German Patent DE 31 22 795 A1.

8. a) Woulfe, S. R.; Miller, M. J. submitted. b) Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. submitted.

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