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EFFICIENT N-SULFENYLATION OF 2-AZETIDINONES USING S-SUBSTITUTED THIOPHTHALIMIDES

by

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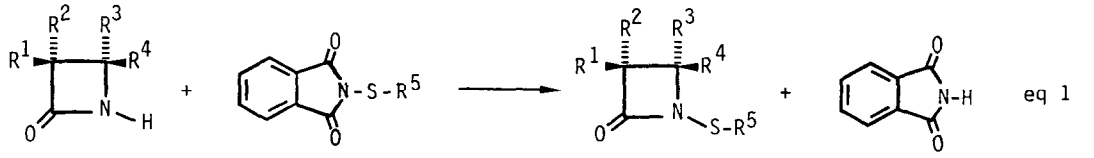
Reaction of N-unsubstituted β-lactams with various S-substituted thiophthalimides provides an efficient route to the corresponding N-thio-2-azetidinones.

As part of ongoing studies related to the synthesis of heteroatom activated β-lactam antibiotics[1], we required an efficient method for the preparation of substituted N-thio-2-azetidinones **3**. While a few simple N-thioaryl-2-azetidinones have been prepared by the reaction of 2-azetidinones with aryl sulfenyl halides[2], none of the related synthetic methods could be effectively utilized for our eventual goals. Because of the utility of substituted thiophthalimides **2**[3] as reagents for sulfenylations[4], we examined their reaction with 2-azetidinones **1** (eq. 1). We found that treatment of variously substituted β-lactams **1** with derivatives of **2** in the presence of a catalytic amount of triethylamine cleanly gave the desired substituted N-thio-2-azetidinones **3** in good to excellent yields[5]. Representative results are summarized in Table I.

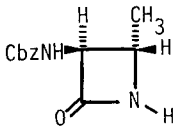
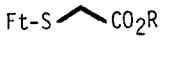
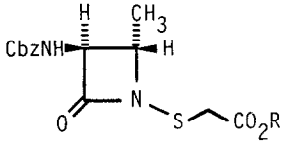
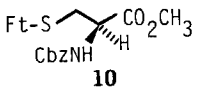
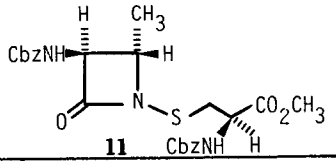
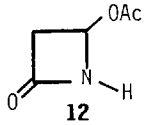
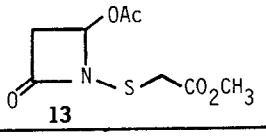
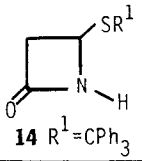
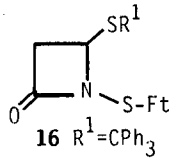
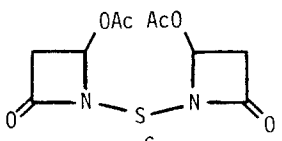
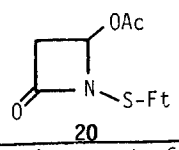
In a typical reaction, 1 mmol of the 2-azetidinone, 1 mmol of the substituted thiophthalimide and 2 μL of triethylamine were added to 20 mL of dry benzene and stirred under nitrogen at 25°C. The reaction was monitored by TLC. Upon completion, the solution was cooled in an ice bath and the precipitated phthalimide was removed by filtration. The filtrate was evaporated and the residue chromatographed on silica gel to provide the product in yields ranging from 46-96% (Table I).



1 + 2 → 3 + 4 eq 1

Table I

Products from the sulfenylation of 2-azetidinones with S-substituted thiophthalimides

entry	2-azetidinone	thiophthalimide	solvent[a] rxn time (h)	product	yield (%)
1	 **5**	 **6** R=CH_3	benzene (0.75)	 **7** R=CH_3[b]	90
2	**5**	**8** R=t-Bu	benzene (0.33)	**9** R=t-Bu	96
3	**5**	 **10**	benzene (2.0)	 **11**	66
4	 **12**	**6**	benzene (1.0)	 **13**	74
5	 **14** R^1=CPh_3	Ft-S-Ft **15**	DMF (15.0)	 **16** R^1=CPh_3	46
6	**17** R^1=CS_2Et	**15**	chloroform (2.75)	**18** R^1=CS_2Et	53
7	**12**	**15**	benzene (15.0)	 **19**[c]	64
8	**12**	**15**	chloroform (2.0)	 **20**	80

a All reactions were performed in the presence of a catalytic amount of triethylamine at room temperature.

b Obtained as a mixture of configurational isomers[5,14].

c See text for details.

Sulfenylation of the 3(S)-(benzyloxyformamido)-4(S)-methyl-2-azetidinone **5**[6], a useful intermediate in the synthesis of the monobactam antibiotics[7], with S-phthalimido-thioacetic acid esters **6** and **8**[8] provided the novel S-azetidinyl-thioacetates **7** and **9** respectively (Table I, Entries 1 and 2). The S-azetidinyl-cysteine derivative **11** was also prepared from 2-azetidinone **5** and the corresponding S-phthalimido-cysteine compound **10**[9] (Entry 3). Even the sterically hindered 4-tritylthio-2-azetidinone **14**[10] reacted with N-N'thiobisphthalimide **15**[11] to give **16** in moderate yield (Entry 5). Other 4-substituted 2-azetidinones (**12**[12] and **17**[13]) that are useful for the synthesis of bicyclic β-lactam antibiotics were also sulfenylated in the same manner (Entries 4 and 6). Interestingly, treatment of the 4-acetoxy-2-azetidinone **12** with **15** in refluxing benzene for 2 h gave a mixture of the S-azetidinyl-thiophthalimide **20** (45%) and the novel bis-azetidinyl sulfur compound **19** (39%). Longer reaction times in benzene gave predominatly the bis-sulfenylated product **19** (Entry 7). Compound **20** was isolated in 80% yield by performing the reaction in chloroform at room temperature (Entry 8).

Additional examples of a second nucleophilic displacement reaction on S-azetidinyl thiophthalimides are being explored. In addition, we are currently examining the scope of this sulfenylation reaction in attempts to make substituted N-thio-2-azetidinones suitable for biological testing.

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References and Notes

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+ On leave from Central Research Laboratories, Ajinomoto Co. Inc., Kawasaki, Japan.

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5. A partial list of characterization data includes: **7**, colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz, 30°C) δ = 1.45 (d, 3H), 3.5 (dd, 2H), 3.75 (s, 3H), 3.85 (m, 1H), 4.4 (dd, 1H), 5.1 (s, 2H); 5.6 (bd, 1H), 7.4 (s, 5H). At lower temperatures (-20°C) a 9:1 mixture of configurational isomers about the N-S linkage was discernable[14]. The coalescence temperature was near room temperature. IR (in $CDCl_3$) 1775 cm^{-1}. **9**, colorless oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 1.35 (d, 3H), 1.45 (s, 9H), 3.4 (dd, 2H), 3.9 (m, 1H), 4.3 (dd, 1H), 5.2 (s, 2H), 6.1 (bd, 1H), 7.4 (s, 5H); IR (in $CDCl_3$) 1775 cm^{-1}. **11**, colorless oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 1.3 (d, 3H), 3.15 (dq, 2H), 3.7 (m, 1H), 3.75 (s, 3H), 4.4 (dd, 1H), 4.7 (m, 1H), 5.15 (pair of s, 4H total), 6.0 (bd, 1H), 6.2 (bd, 1H), 7.3 (s, 10 H); IR (in $CDCl_3$) 1770 cm^{-1}. **13**, yellow oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 2.1 (s, 3H), 3.1 (dd, 1H), 3.4 (dd, 1H), 3.5 (dd, 2H), 3.8 (s, 3H), 6.2 (dd, 1H); IR (neat) 1785 cm^{-1}. **16** white solid; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 2.4 (t, 2H), 4.6 (dd, 1H), 7.2-7.6 (m, 15H), 7.8-8.1 (m, 4H); IR (in $CHCl_3$) 1805, 1780 cm^{-1}. **18**, yellow oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 1.4 (t, 3H), 3.25 (dd, 1H) 3.4 (q, 2H), 3.8 (dd, 1H), 6.0 (dd, 1H), 7.9 (m, 4H); IR (in $CHCl_3$) 1810, 1790 cm^{-1}. **19**, white powder, mp 126-128°C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 2.2 (s, 6H), 3.0 (dd, 2H), 3.5 (dd, 2H), 6.3 (dd, 2H); IR (KBr) 1790 cm^{-1}. **20**, white solid, mp 146-149°C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 2.1 (s, 3H), 3.0 (dd, 1H), 3.5 (dd, 1H), 6.3 (dd, 1H), 7.8-8.2 (m, 4H): IR (KBr) 1820, 1810 cm^{-1}.
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