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PAPER

Comparison of the reactivity of β-thiolactones and β-lactones toward ring-opening by thiols and amines†

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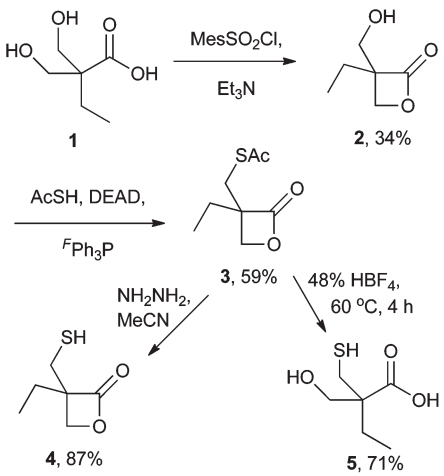
An investigation into the comparative reactivity of simple β-lactones and β-thiolactones toward a thiol and a primary amine is reported. A simple 3-mercaptomethyl-2-oxetanone is found to undergo rearrangement in the presence of aqueous base to give the corresponding thietane-3-carboxylic acid rather than the 3-hydroxymethyl-2-thietanone. Implications for the use of β-thiolactones in bioorganic and medicinal chemistry are discussed.

Introduction

We are interested in the chemistry of the β-thiolactones (2-thietanones) as surrogates for the β-lactones and β-lactams in bioorganic and medicinal chemistry,[1,2] and as precursors[3] to substituted monothioacids for use in coupling reactions.[4] An integral part of this investigation is the study of the reactivity and stability of these under-explored[5–30] sulfur-based heterocycles, whose longer carbon–sulfur bonds cause them to adopt puckered conformations[1,13,31–33] closer to the cyclobutanones than to their oxygen and nitrogen counterparts. One way to approach this problem and to put the chemistry of the β-thiolactones in context is to carry out direct comparisons with that of the more familiar β-lactones. Accordingly, we describe an investigation into the relative stabilities and reactivities of simple β-thiolactones and β-lactones toward nucleophilic ring opening reactions.



Scheme 1 Formation and opening of the β-lactone **3**.

Results and discussion

Treatment of commercial 2,2-bis(hydroxymethyl)butyric acid **1** with mesitylenesulfonyl chloride and triethylamine in dichloromethane at −20 °C enabled isolation of the β-lactone **2** in 34% yield (Scheme 1). Mitsunobu reaction with thioacetic acid,[34,35] diethyl azodicarboxylate, and commercial 4-(heptadecafluorodecyl)phenyl diphenylphosphine[36,37] then led to the thioester **3** in 59% yield. Treatment of **3** with hydrazine in acetonitrile enabled selective cleavage of the thioester and resulted in the isolation of the mercaptomethyl-β-lactone **4** in 87% yield (Scheme 1).

Treatment of the acetylthiomethyl-β-lactone **3** with hot 6 N HCl, following a literature precedent for opening of β-lactones under acidic conditions,[57] enabled isolation of the hydrolysis product **5** in 31% yield in a process complicated by nucleophilic ring opening by chloride anion. The use of 48% tetrafluoroboric acid in place of 6 N HCl resulted in a cleaner reaction mixture and enabled isolation of **5** in 71% yield (Scheme 1).

In a series of experiments intended to probe the relative kinetics of ring closure of β-lactones and β-thiolactones, the hydroxymercapto acid **5** was exposed to a variety of typical condensation reagents and the crude reaction mixtures examined for the formation of **4** and/or **7** (Scheme 2) by both IR and NMR spectroscopy. In all cases the reaction mixtures were complex, showing, in addition to the β-thiolactone **7** (C=O stretch 1730 cm^{-1}), traces of the lactone **4** (C=O stretch 1810 cm^{-1}) and a number of other products which rendered isolation difficult. Eventually, careful purification of the crude reaction

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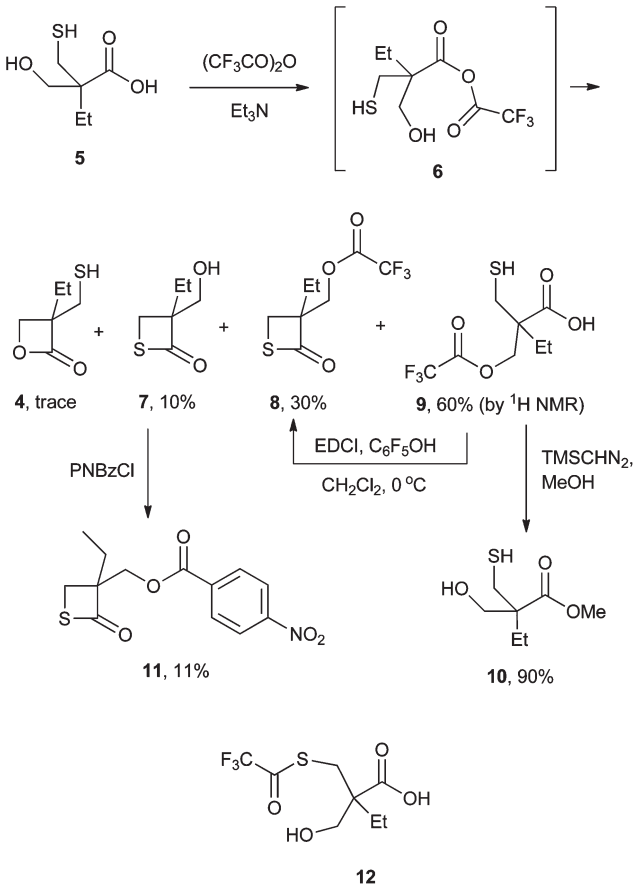
†Electronic supplementary information (ESI) available: Full experimental details, characterization data and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c2ob25640a



Scheme 2 Cyclization of the hydroxymercapto acid **5** with trifluoroacetic anhydride.

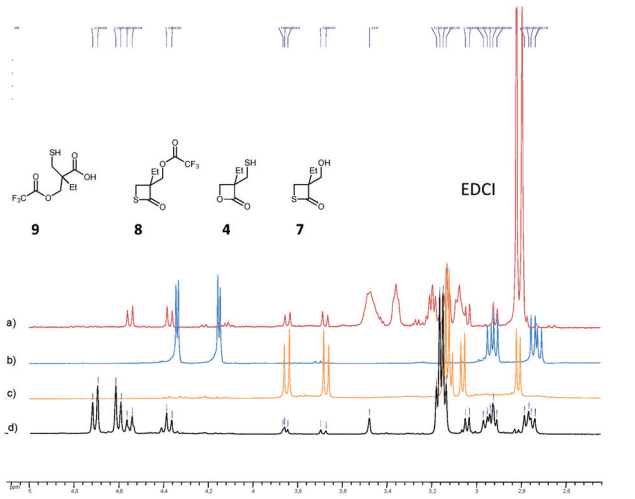
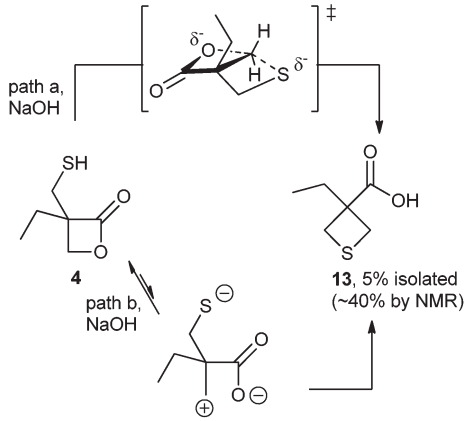


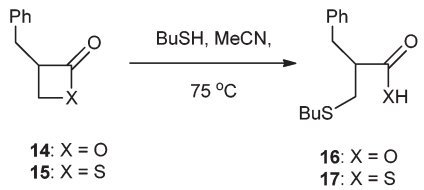
Fig. 1 The cyclization of **5** with trifluoroacetic anhydride. (a) ^{1}H NMR of **8** (crude product), (b) ^{1}H NMR of **4**, (c) ^{1}H NMR of **7**, (d) ^{1}H NMR of the crude reaction mixture.

mixture arising from cyclization with trifluoroacetic anhydride and triethylamine enabled the isolation of the β-thiolactone **7** in 10% yield (Scheme 2) along with the trifluoroacetyl ester **9** of the starting hydroxymercapto acid **5**, which could not be isolated pure, but which was identified following esterification and loss of the trifluoroacetyl group to give **10**. The trifluoroacetylated β-thiolactone **8** was tentatively identified in the crude cyclization reaction mixture as a major product (Scheme 2, Fig. 1). The identity of this trifluoroacetyl-β-thiolactone **8** was confirmed when treatment of a crude isolate of mercaptoacid **9** was cyclized with EDCI and pentafluorophenol (Scheme 2). When a crude reaction mixture from the cyclization of **5** with trifluoroacetic anhydride was treated with 4-nitrobenzoyl chloride, the β-thiolactone derivative **11** was isolated in 11% yield (Scheme 2), somewhat consistent with the 10% yield of **7**. Evidently, the 4-*exo*-trig cyclization of the initial mixed anhydride **6** to give ultimately either the β-lactone **4** or the β-thiolactone **7** is relatively slow due to the highly sterically hindered nature of the carboxyl group. A competing 6-*exo*-trig cyclization leading to the transfer of the trifluoroacetyl group and formation of the acid **9** was observed as the major pathway. Activation of this acid with further trifluoroacetic anhydride then provides the esterified β-thiolactone **8**. While the chemistry is exemplified for cyclization with trifluoroacetic anhydride, similar problems were encountered with other dehydration reagents, including sulfonyl chlorides. Indeed, the low yield of the β-lactone **2** (Scheme 1) can be accounted for in part by competing sulfonylation of a hydroxyl group that is best explained by an intramolecular transfer from a carboxyl/sulfonyl mixed anhydride. While quantitative results could not be obtained from these reaction mixtures, inspection of the IR and NMR spectra of the crude reaction mixtures nevertheless leads us to the reasonable conclusion that in activated forms of **5**, such as the mixed anhydride **6**, 4-*exo*-trig cyclization to form the β-thiolactone **7** is faster than that to form the β-lactone **4**. Conversely, 6-*exo*-trig cyclization from **6** appears to be faster for the harder alcohol than for the softer thiol. We can not completely rule out the possibility that the 6-*exo*-trig trifluoroacetyl transfer process is also more rapid at sulfur, giving the thioester **12** (Scheme 2), and that this is then followed by a second acyl shift to the alcohol giving ester **9**. However, the lack of evidence for the formation of **12** combined with Occam's razor leads us to prefer the direct transfer of the trifluoroacetyl group from **6** to the alcohol giving **9**.

Rearrangement of mercaptomethyl-β-lactone **4** to the corresponding hydroxymethyl-β-thiolactone **7** was attempted under a variety of conditions to no avail. However, treatment of **4** with a mixture of 1 M aqueous sodium hydroxide and THF gave a crude reaction mixture whose ^{1}H NMR spectrum was devoid of signals arising from **4** or **7**, but which contained a major product, formed in approximately 40% yield. Extractive work up and acidification enabled isolation of this product, albeit only in 5% yield, and its identification as 3-ethylthietan-3-carboxylic acid **13** (Scheme 3), with the low yield reflecting difficulties in isolation. In view of the fact that thiolates are well-known to open β-lactones by S_N2 attack at the β-position, this remarkable reaction might be viewed as an intramolecular S_N2-like process involving a bicyclo[2.2.0]hexane-like transition state made possible by the relatively long C–S bonds, both existing and incipient (Scheme 3, path a). Alternatively, taking note of the widely accepted stepwise zwitterionic intermediate model for the extrusion of CO_2 from β-lactones,[38–48] it may be considered as arising from trapping of a transient zwitterionic form of the lactone



Scheme 3 Possible mechanisms for the formation of thietanecarboxylic acid **13**.



Scheme 4 Opening of β-lactone **14** and β-thiolactone **15** with butanethiol.

(Scheme 3, path b). While the elucidation of the mechanism of formation of **13** from **4** must await further work, the formation of **13** serves to underline the preference of β-lactones toward nucleophilic ring opening at the β-position by soft nucleophiles[49–56] even though the nucleophile is ideally placed for attack on the carbonyl centre. The attempted conversion of the hydroxymethyl-β-thiolactone **7** to the mercaptomethyl-β-lactone **4** under a variety of basic and Lewis acidic conditions was not productive.

We next turned our attention to intermolecular competition reactions for the opening of β-lactones and β-thiolactones by simple nucleophiles. Thus, an equimolar mixture of 3-benzyl-2-oxetanone **14**[58] and its thio analog **15**[12] in acetonitrile was heated to 75 °C in the presence of 10 equivalents of butanethiol and the progress of the reactions monitored by LC-MS. Separate experiments demonstrated both substrates to react with the thiol cleanly in the S_N2-like mode and provided authentic samples of the respective products **16** and **17** (Scheme 4). Plotting of the concentrations of **14**–**17** against time for the competition reaction (Fig. 2) and standard data analysis according to a pseudo-first order kinetic scheme revealed the β-thiolactone **15** to be cleaved to **17** with a half-life of 5.6 h, under conditions when the conversion of the β-lactone **14** was essentially zero.

A similar competition between **14** and **15** for reaction with isobutylamine was complicated by the parallel existence of the S_N2 and acylation pathways for the opening of the β-lactone by the amine to give **18** and **19** in 27 and 71% yield, respectively, consistent with literature precedents (Scheme 5).[59,60] The β-thiolactone **15** followed a unique reaction path with the amine leading to the formation of the amide **20**, again consistent with

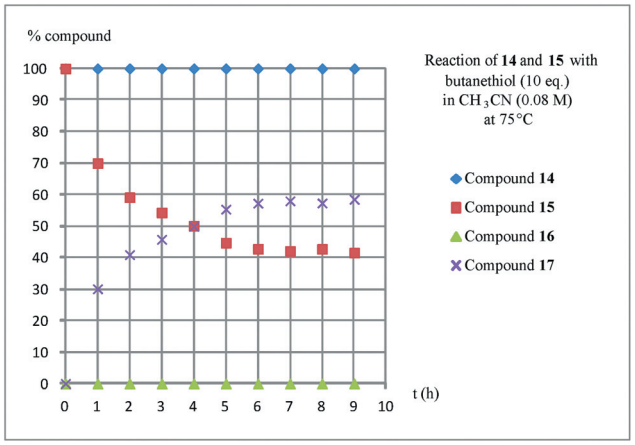
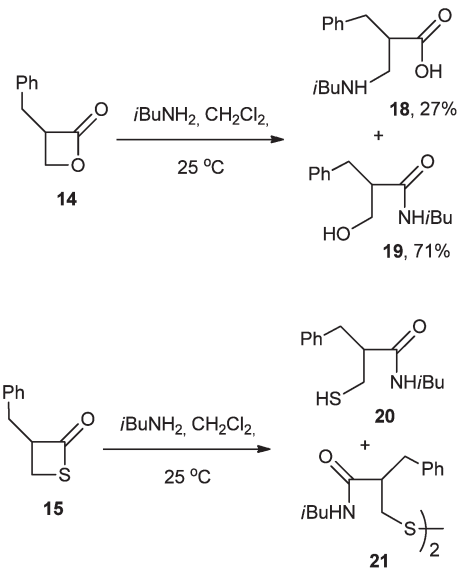


Fig. 2 Kinetic profile for the reaction of β-lactone **14** and β-thiolactone **15** with butanethiol.



Scheme 5 Opening of β-lactone **14** and β-thiolactone **15** with isobutylamine.

the literature precedents,[3,12] that was complicated only by subsequent disulfide formation to give **21** (Scheme 5).

Despite these complications, it proved possible to conduct competition experiments in dichloromethane at room temperature leading to the plots illustrated in Fig. 3 from which it is evident that the thiolactone **15** reacts ($t_{1/2}$ = 0.04 h) more rapidly with isobutylamine than lactone **14** ($t_{1/2}$ = 1.78 h) and, furthermore, that the two modes of reaction of the lactone **14** proceed with approximately equal rates. Unfortunately, attempts to perform similar competition experiments with methanol as the nucleophile have so far failed, owing to complications arising from slow reactions in the absence of catalysis or heat, and polymerization on heating or with catalysis by acid or base, consistent with earlier literature reports on the reactions of simple β-lactones with methanol.[61,62]

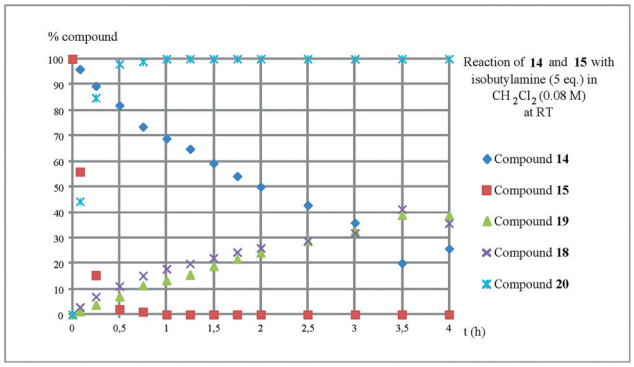


Fig. 3 Kinetic profile for the reaction of β-lactone **14** and β-thiolactone **15** with isobutylamine.

Conclusions

Comparisons of the reactivity of simple β-thiolactones and β-lactones for ring opening by simple nucleophiles reveal that the thiolactone is the more reactive of the two toward both a thiol and a primary amine, presumably reflecting the weakness of C–S as opposed to C–O bonds. The clear implication of this reactivity pattern is that β-thiolactones might be expected to be better inhibitors of cysteine protease enzymes than the corresponding β-lactones, as we have found in our exploratory work on their use in bioorganic chemistry.[1]

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