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A SHORT SYNTHESIS OF γ-LACTAMS VIA THE SPONTANEOUS RING EXPANSION OF β-LACTAMS

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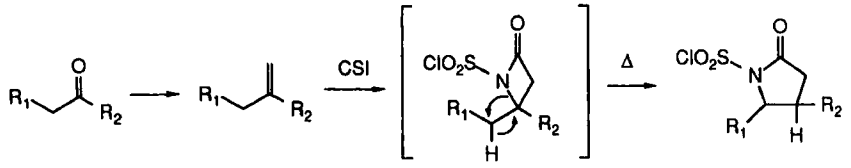
Abstract: β-Lactams, derived via the cycloaddition of chlorosulfonyl isocyanate to alkenes, undergo thermal rearrangement at room temperature to afford γ-lactams.

For some time, we have been interested in the exploitation of β-lactones as synthetic intermediates, and have determined that they are readily transformed into a variety of butyrolactones,[1] β,γ-unsaturated carboxylic acids,[2] or α-halo[3] or -alkyl[4] butenolides. These conversions are initiated by exposure of the appropriate β-lactones to catalysis by a Lewis acid (typically magnesium bromide or titanium tetrachloride); the acid effects ionization of the lactone, whereupon the carboxylate/carbocation intermediate undergoes further reactions to afford the products. It occurred to us that analogous transformations might be possible with β-lactams, allowing entry into the γ-lactam moiety so commonly encountered in naturally-occurring molecules. We herein report the results of preliminary studies, featuring an unanticipated thermal β- to γ-lactam ring expansion as the cornerstone event in the sequence.

Scheme I

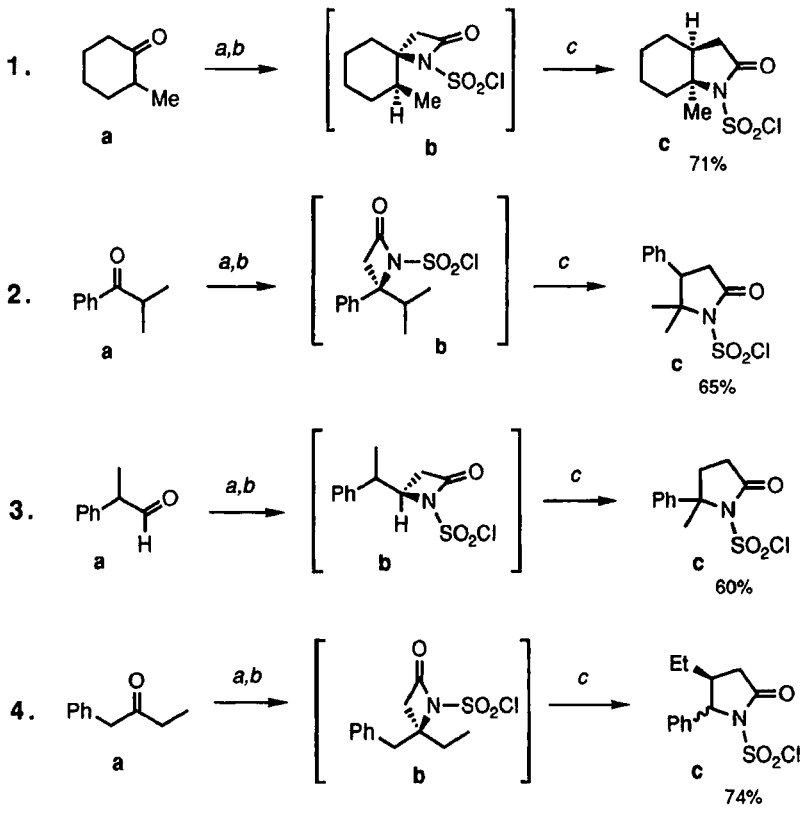


β-Lactams have been under investigation for years, and are available via a wide variety of synthetic methods.[5] For our purposes, the cycloaddition of chlorosulfonyl isocyanate (CSI) to alkenes[6] was chosen due to its operational simplicity and our need for only relatively unelaborated β-lactams. Furthermore, the alkene cycloaddition partners are easily acquired from carbonyl compounds via the Lombardo protocol.[7] The general overall sequence is depicted in Scheme I.

The initial experiments employed 1-methyl-2-methylenecyclohexane (derived from 2-methylcyclohexanone). Treatment of this alkene with two equivalents of CSI in ether led, after two hours, to the corresponding β-lactam as a crystalline material that precipitated out of solution. Our original intent was to isolate the product, reductively remove the chlorosulfonyl group, and investigate the capacity of various Lewis acids to effect ring expansion. However, when this mixture was allowed to stir overnight, a solution resulted from which the γ-lactam was isolated. The identity of the crystalline precipitate as the β-lactam was established by its later isolation and spectral characterization.

This γ-lactam annulation sequence has proven effective on a selection of substrates, listed in Scheme II. The primary structural requirement for

Scheme II



Reagents: a=CH_2I_2,Zn,$TiCl_4$; b=ClO_2SNCO; c=r.t., 12hr

success is that the carbonyl functionality be located adjacent to either a tertiary or benzylic carbon; this is in accord with our earlier lactone results in that rearrangement will only occur when a cation of equal (or lesser) energy to the nitrogen-bearing carbon atom is available adjacent to that atom. For instance, the β-lactam derived from methylenecyclohexane would not rearrange, and decomposed when heated to a temperature sufficient to effect reaction.

Further evidence for the importance of a stable cation target atom is provided by 1-phenyl-2-butanone (**4a**). Treatment with CSI and subsequent rearrangement afforded a 74% yield of γ-lactam **4c** as a mixture of stereoisomers, but uncontaminated by the regioisomer that would have resulted from expansion toward the non-benzylic carbon.

The synthesis of **1c** illustrates the technique. 1-Methyl-2-methylenecyclohexane (0.9 g, 8.0 mmol) was dissolved in anhydrous ethyl ether (20 mL), and chlorosulfonyl isocyanate (2.0 g, 14 mmol) was added slowly by syringe with stirring under nitrogen. The reaction mixture was allowed to stir at ambient temperature for 24 hr, whereupon removal of the ether and crystallization of the residue from 20% ethanol/hexane provided 1.5 g (75%) of the cis[8]-lactam as a white crystalline solid, mp 132-133 °C, displaying the following analytical data: IR (KBr) 2943, 1768, 1405, 1385, 1204, 1156, 955, 544 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.55(m, 2H), 2.20 (m, 1H), 2.08 (m, 2H), 1.77 (m, 1H), 1.68 (s, 3H), 1.41-1.63 (m, 5H) ppm; ^{13}C-NMR (300 MHz, $CDCl_3$) δ 172.80, 71.92, 38.95, 34.91, 33.40, 25.28, 24.45, 21.37, 20.75 ppm; Anal. calcd for $C_9H_{14}ClNO_3S$: C, 42.94; H, 5.61; N, 5.56. Found C, 43.08; H, 5.61; N, 5.51.

We are actively pursuing further applications of this interesting reaction, including a more refined definition of its structural requirements, with an eye toward application of the technique to more complex substrates. The facile removal of the N-chlorosulfonyl group,[9] allowing for subsequent N-functionalization, should allow for the facile synthesis of a variety of γ-lactams with varying substitution patterns.

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