Communications

The Formation of Spiro-β-lactams and Amides from Reaction of Cyclic Ketenes with Imines

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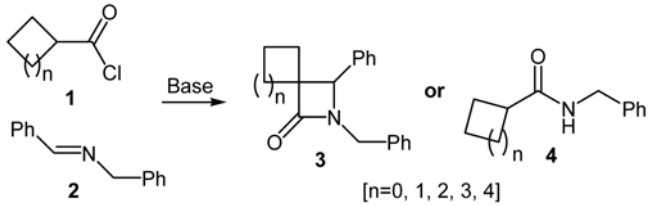
Spiro-β-lactams are interesting compounds due to their antiviral,[1] and antibacterial properties,[2] ability to inhibit cholesterol absorption,[3] and the enzymes responsible for the cleavage of the amyloid precursor protein.[4]

Most synthetic efforts to form spiro-β-lactams utilize cycloaddition reactions. The cycloaddition usually uses ketene-imine.[5]

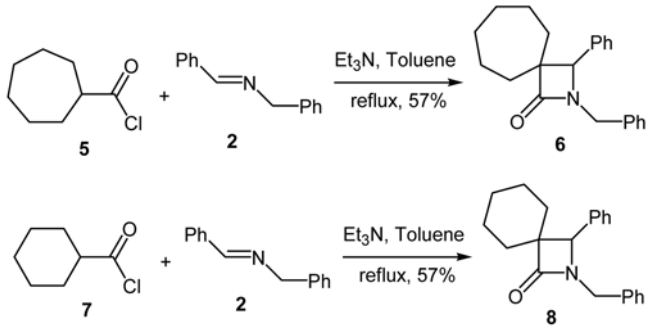
In this paper, we present a novel synthesis of spiro-β-lactam derivatives **3** and amide derivatives **4**, from cyclic acid chloride **1** with imine **2** (Scheme 1). We will describe the effects which govern selectivity in the formation of **3** and **4**, and show that the size of the ring in **1** has the largest influence in this process.

The spiro-β-lactams **6** and **8** were prepared by reaction of either cycloheptyl acid chloride **5** or cyclohexyl acid chloride **7** with imine **2**, respectively (Scheme 2). In a typical procedure, the acid chloride was added to a stirred, refluxing solution of the imine and triethylamine in toluene. After refluxing the solution overnight and an aqueous work-up, spiro-β-lactams **6** and **8** were obtained in moderate yields and trash amount of side products were detected in TLC. The spiro-β-lactams **6** and **8** are the expected products of the [2+2] cycloadition reaction of imine **2** with the cyclic ketenes intermediate.

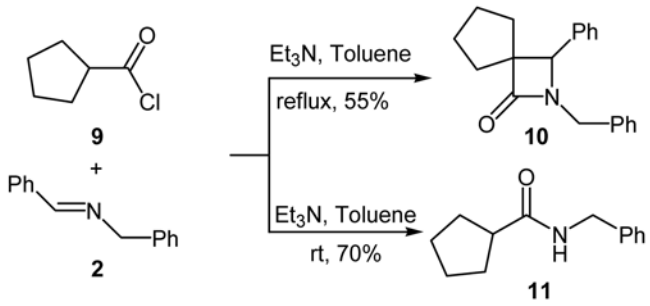
We next examined the formation of spiro-β-lactams **10**, from the reaction of cyclopentyl acid chloride **9** and imine **2**. Under the same reaction conditions described above, spiro-β-lactams **10** was obtained in 55% yield and small amount of side products were observed in TLC. On the other hand, the amide **11** was obtained when the reaction was performed



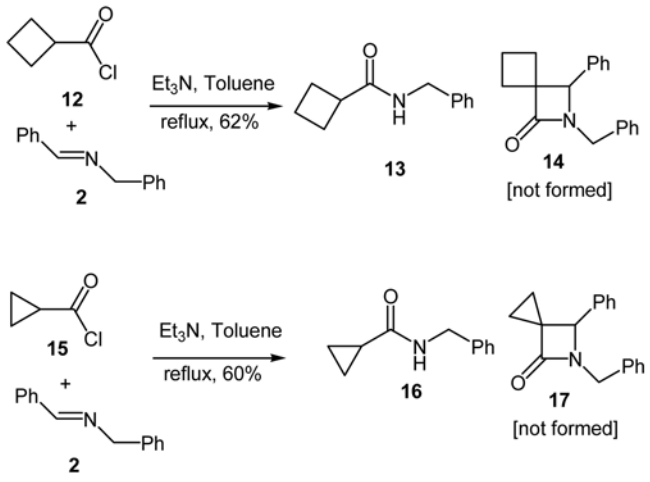
Scheme 1. The formation of spiro β-lactam or amide derivatives.



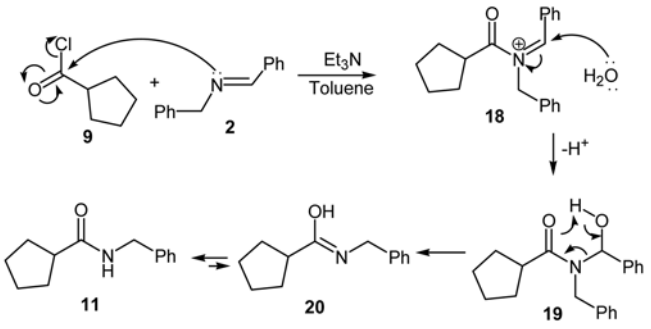
Scheme 2. The formation of spiro β-lactams.



Scheme 3. The limitation of spiro β-lactam and amino formation.



Scheme 4. The amide formation.



Scheme 5. Prposed mechanism for amide formation.

at room temperature (Scheme 3). These results indicate that the reaction conditions play a critical role in the product distribution of the 5-membered ring acid chloride.

Given the above results, we sought to determine whether the size of the ring in the precursor acid chloride had any effect on the product distribution, or whether the selectivity for one product over the other was solely a function of the reaction conditions. Thus we examined the reactions of cyclobutyl acid chloride **12** and cyclopropyl acid chloride **15**, with imine **2**. Upon treatment with TEA in refluxing touene, the amide was observed as the only product in each of the reactions shown in Scheme 4. The inability of the cyclopropyl and cyclobutyl acid chloride **12**, **15** to undergo reaction with TEA and imine **2** to generate a spiro-β-lactams **14**, **17** could be the result of two factors. These include difficulty in forming the ketene intermediate or ring strain associated with the spirocyclic system.

In order to explain amide formation, we propose the mechanism depicted in Scheme 5. Initial formation of amide **19** occurs by acylation of imine **2** at room temperature to give iminium ion **18**, which in turn undergoes nucleophilic attack of H_2O on the iminium carbon. The final product amide **11** was generated by elimination of **19** and tautomerization of **20** (Scheme 5).

We have examined the reaction of acid chlorides with TEA and imine to form either spiro-β-lactams or amides. It was determined that the ring size of the acid chloride dictates the mechanistic course of the reaction, and thus the product distribution. We are currently engaged in the preparation of spiro-γ-lactams from other spiro-β-lactams through the ring expansion method[6] which was developed in these laboratories. This should prove useful in the preparation antibiotic compounds.

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7. *General experimental*: A solution of the acid chloride (1.2 equiv.) and triethylamine (1.2 equiv.) in toluene was added to a solution of the imine (1.0 equiv.) in toluene. The imine solution was used in situ without purification. After refluxing the reaction mixture for 24 h water was added and the product extracted with EtOAc. After columm chromatography, the pure spiro β-lactam or amide derivative was obtained. (**a**) Spirocyclic β-lactam **6**: IR (neat): 1749 (s); ^{1}H NMR ($CDCl_3$): δ 1.20-1.88 (m, 12H), 3.82 (d, J = 15.0 Hz, 1H), 4.17 (s, 1H), 4.91 (d, J = 15.0 Hz, 1H), 7.11-7.40 (m, 10H). (**b**) Spirocyclic β-lactam **8**: IR (neat): 1740 (s); ^{1}H NMR ($CDCl_3$): δ 1.02-2.14 (m, 10H), 3.11 (d, J = 8.4 Hz, 1H), 4.97 (d, J = 8.4 Hz, 1H), 6.15 (s, 1H), 7.02-7.57 (m, 10H). (**c**) Spirocyclic β-lactam **10**: IR (neat): 1751 (s); ^{1}H NMR ($CDCl_3$): δ 1.10-2.16 (m, 8H), 3.85 (d, J = 15.0 Hz, 1H), 4.25 (s, 1H), 4.92 (d, J = 15.0 Hz, 1H), 7.11-7.42 (m, 10H). (**d**) *N*-benzylcyclopentane carboxamide **11**: IR (KBr): 3293 (s), 1639 (s); ^{1}H NMR ($CDCl_3$): δ 1.25-1.89 (m, 8H), 2.48-2.59 (m, 1H), 4.44 (d, J = 5.9 Hz, 2H), 5.74 (s, 1H), 7.25-7.59 (m, 5H). (**e**) *N*-benzylcyclobutane carboxamide **13**: IR (KBr): 3289 (s), 1632 (s); ^{1}H NMR ($CDCl_3$): δ 2.17-2.32 (m, 6H), 3.02 (m, 1H), 4.44 (d, J = 5.5 Hz, 2H), 7.27-7.36 (m, 5H). (**f**) *N*-benzylcyclopropane carboxamide **16**: IR (KBr): 3285 (s), 1632 (s); ^{1}H NMR ($CDCl_3$): δ 0.72-0.79 (m, 2H), 0.97-1.05 (m, 2H), 1.28-1.38 (m, 1H), 4.46 (d, J = 5.7 Hz, 2H), 7.25-7.38 (m, 5H).