Synthesis of Large-Ring Lactams by a Carbene-Anion Bond Forming Reaction

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Treatment of large-ring lactams **1** with potassium *t*-butoxide results in the formation of bicyclic structures **2**. Evidence was obtained to support the formation of **2** through a carbene-anion coupling. The structures of a series of bicyclic lactams **2** have been rigorously defined.

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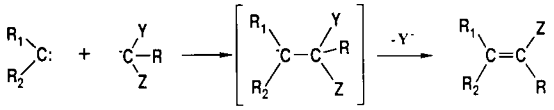
Introduction.

Several examples exist where the reaction between a carbene and an anion is the basis of a carbon-carbon bond forming reaction [1]. Generally speaking, these are reactions between a carbenic substrate and a carbanion which possesses groups Y and Z (Scheme 1). The functional group, Z, can stabilize the anionic charge, and Y acts as a leaving group which is eliminated yielding an olefin as the product. If the carbene and the carbanion are part of the same molecule then a ring is formed.

Scheme 1



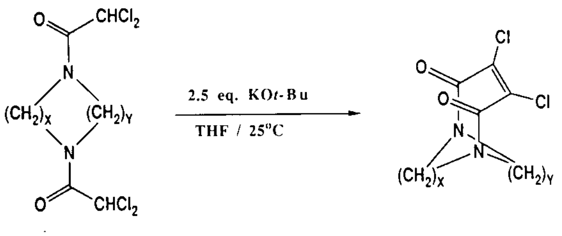
We report a new variation of the above scheme where a dichloroacetamide function serves as both the carbene and carbanion partner in a bond forming reaction. With our examples, both dichloroacetamide functions are a part of the same molecule resulting in lactam products.

Results and Discussion.

Bis-amide Intramolecular Reactions.

When a mixture of bis-amide **1** and 2.5 equivalents of potassium *t*-butoxide is stirred at 0° for several hours, the bicyclic bis-lactam **2** is isolated from the reaction in a 67% yield (Scheme 2). This reaction is successful with many large-ringed bis-amides from ring size seven to eleven (Table 1). Yields range from poor (4%) with the eleven-membered ring compound to good (68%) with a nine-membered example. In cases where the yield is poor the majority of the reaction mass is high molecular weight materials. These materials probably result from intermolecular polymerization reactions. That intermolecular reactions happen is not surprising. Over the course of the reaction the concentration of the bis-amides varies from 0.2 to 0.4*M* - not what one would consider to be high dilution conditions. We have not carried our experiments involving high dilution conditions, but would assume higher dilution may attenuate the formation of the high molecular weight materials.

Scheme 2



1, x,y = 4,3

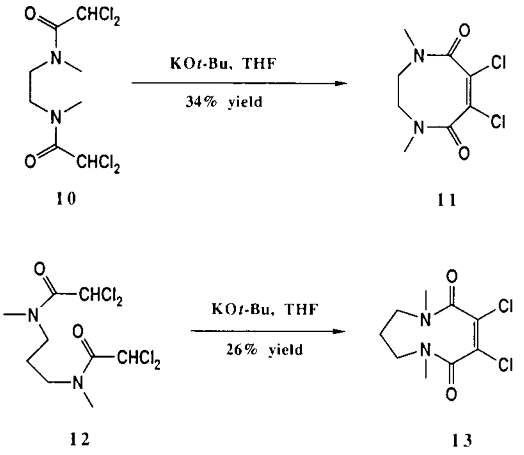
2, x,y = 4,3

Table 1

Product ID	3	4	5	6	2	7	8	9
X,Y	3,2	4,2	3,3	5,2	4,3	6,2	5,3	6,3
Yield	46%	59%	57%	68%	67%	60%	33%	4%

Limited success has also been obtained with acyclic substrates (Scheme 3). The bis-amide **10** prepared from *N,N'*-dimethylethylene diamine cyclized to give the eight-membered bis-lactam **11** in a modest 34% yield. The homolog bis-amide **12**, likewise, produced the nine-membered bis-lactam **13** in a 26% yield. The yields in these two cases have suffered from the formation of high molecular weight materials, similar to the poorer yielding examples in Table 1.

Scheme 3



10

11

12

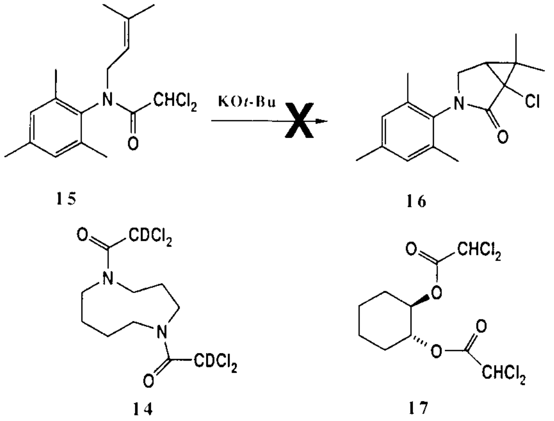
13

Reaction Mechanism.

Knowing that SN2 displacements of halogens *alpha* to carbonyls can be facile processes, we did not rule out the possibility of this being the mechanism for our cyclization. After the initial cyclization, the elimination of hydrogen chloride to give the olefin would be rapid. Strong evidence against the SN2 displacement came when bis-amide **1** was deprotonated with 2.1 equivalents of lithium diisopropyl amide and allowed to stand at room temperature for one hour. Under these conditions the bis-lactam **2** was formed as the major product. If the reaction is quenched at −78° with deuterium chloride in deuteriomethanol, the dideuterated bis-amide **14** can be isolated. These experiments prove that the product (**2**) forms from the dianion of **1**.

Armed with this information, the most plausible mechanism is through the decomposition of one anion to a carbene followed by coupling of this carbene with the remaining anion. The resulting anion would then rapidly eliminate chloride to give the olefinic product. This mechanism is similar to the coupling reactions of bis-thioacetals as reported by Cohen, *et al.* [2]. This report mentioned that the formation of the carbene was, in a number of cases, induced by the presence of a proximal carbanionic center. In other words, the repulsion between two carbenoid carbanions provides the driving force causing decomposition of one anion resulting in production of a carbene. To test if this type of induction was necessary in our case, we prepared a test substrate **15** (Scheme 4). If the anion of **15** were to form a carbene then insertion of the electron poor carbene into the electron rich intramolecular olefin should be facile to give lactam **16** [3]. When **15** was treated with an excess of potassium *t*-butoxide, no lactam **16** was produced. This result supports the carbene induction theory. It appears that dichloroacetamide anions are stable, and only form carbenes when induced by anions in close proximity.

Scheme 4

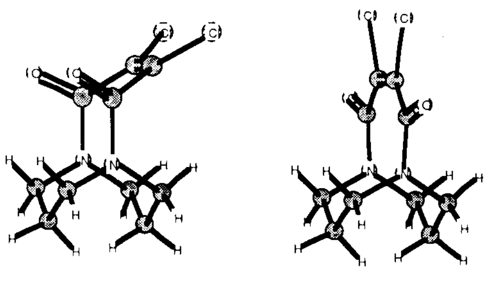


To extend this reaction to other functionalities, we prepared the bis-dichloroacetate **17** and subjected it to the same basic reaction conditions. No coupled product was isolated from this reaction. Anions of dichloroacetates are presumably more stable than those of dichloroacetamides. Clearly, they are too stable to be induced to form carbenes under our conditions. It is known that the anion of chloroform rapidly produces a carbene. The stability of a dichloroacetamide anion lies somewhere between that of a chloroform and a dichloroacetate anion. It seems to be only at this intermediate level of stability where the anionic induction of carbenes comes into play.

Structures of Bicyclic Bis-Lactams.

For each of the bicyclic bis-lactams in Table 1, there exists several possible conformations. The first conformational question is regarding the orbital overlap of the carbonyls. It is possible for the carbonyl π orbitals to overlap with either the olefinic π orbitals or the nitrogen lone pairs, but not both simultaneously. When the symmetrical bis-lactam **5** was analyzed by nmr it was clearly evident that the carbonyls were not overlapped with the olefin, but were in resonance with the nitrogens. The preferred conformation places the carbonyls in resonance with the nitrogens resulting in non-equivalent three-membered bridges (Scheme 5). One can observe four distinct carbon nmr signals for the saturated bridges; whereas, in a structure where the olefin overlaps with the carbonyls one would expect to see only two signals resulting from the C_{2v} symmetry of this conformation.

Scheme 5

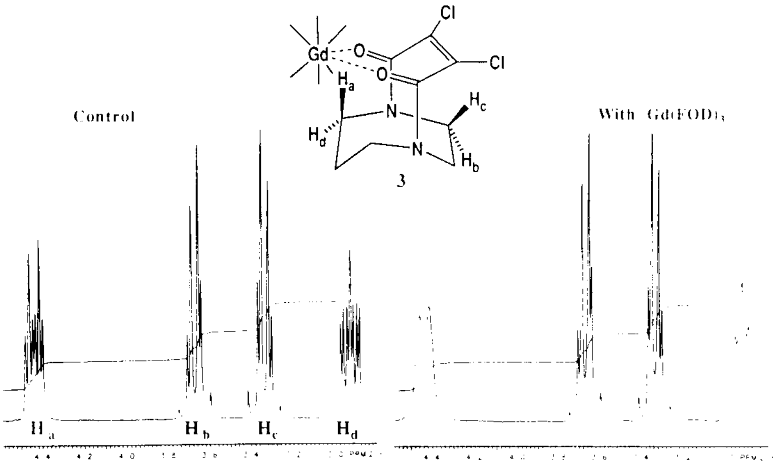


3-D Depiction of compound 5 with amide resonance (l) and carbonyl and olefin overlap (r)

Having a conformation with the carbonyls in amide resonance left us with a series of structures each having two possible isomers, with regards to the *E*/*Z* stereochemistry of the amides. In all cases, only one isomer was isolated from the reaction. If one builds models of both the *E* and *Z* isomers of any of the bis-lactams from Table 1, it becomes obvious more strain exists in the *E* amide isomer than the *Z* amide isomer. The strain arises from a twisting of the amide carbonyls out of resonance with the nitrogens when the smaller saturated bridge is *cis* with the carbonyl oxygens.

To determine if we had the *E* or *Z* isomer for the compounds in Table 1, we resorted to a nmr analysis using tris-

Scheme 6



(6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) gadolinium (GdFOD) as a line broadening agent [4]. The Lewis acid gadolinium would be expected to bind to the carbonyls of the amides and exert its effect on the protons in the closest proximity (Scheme 6). By assigning the protons on the saturated bridges we could observe which protons were in close proximity to the carbonyls. At a ratio of 1000:1 of substrate to gadolinium in deuterated chloroform line broadening was evident for one set of protons adjacent to the amide nitrogens. In every case, the isomer derived from the reaction was the *Z* (less strained) amide isomer.

As a result of forming only one of the two possible isomers, we wondered if we had formed the kinetic or thermodynamic product, and whether it was possible to interconvert the isomers. Interconversion of the isomers is theroretically possible through a concurrent isomerization of both amides. Studying this matter, we took the symmetrical bis-lactam **5** to 160° in DMSO in a nmr experiment. If the two isomers were interconvertable, then one would expect to see a coalescence of the proton signals between the *E* and *Z* bridges, since the two isomers of **5** are degenerate. We could not observe any coalescence up to the 160° experiment temperature. We have surmised that the products formed are, indeed, the kinetic products of the reaction. It is reasonable the kinetic product would also be the thermodynamic product since the transition state for the carbon-carbon bond forming step would be very product-like due to the geometrical requirements of the reaction.

In conclusion, we've discovered a new version of an induced carbene-anion coupling which produces large-ring lactams in moderate yields. Structural studies of the novel bicyclic lactams indicate that their structures are very rigid, showing no evidence of amide isomerization.

EXPERIMENTAL

General Methods.

The ^{1}H nmr spectra were recorded at 300 MHz on a Varian XL-300 spectrometer. ^{13}C nmr spectra were recorded at 90 MHz on a Bruker WM-360 instrument. Chemical shifts are reported in ppm downfield from the reference TMS at 0.00 ppm with either TMS or the deuterated solvent serving as the internal standard. Melting points were determined on a Mel-Temp (Laboratory Devices, Inc.) apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Inc.

All reagents and solvents were used as purchased. Anhydrous solvents were purchased as anhydrous grade and used as such. Yields are unoptimized and were derived from the recovery of analytically pure isolated products. The dichloroacetamides were obtained by the reaction of the amines with dichloroacetyl chloride under Schotten-Baumann conditions. The large-ringed diamines were prepared by reduction of bicyclic amidines using a literature procedure [5].

General Procedure for the Preparation of Bis-lactams (Entries 2-9 Table 1).

(*exo, exo*)-9,10-Dichloro-1,7-diazabicyclo[5.4.2]tridec-9-ene-8,11-dione (**6**).

To a solution of 1,4-bis(dichloroacetyl)-1,4-diazacyclononane (4.5 g, 12.85 mmoles) in 30 ml of anhydrous tetrahydrofuran at 0° under nitrogen was added a solution of potassium *t*-butoxide (3.6 g, 32.14 mmoles) in 50 ml of anhydrous tetrahydrofuran over a ten minute period. The reaction was stirred for two hours at 0° followed by quenching with water. The mixture was diluted with 100 ml of ethyl acetate, and was washed with water then brine. After drying over anhydrous magnesium sulfate and filtration, concentration gave a brown solid. The crude product was recrystallized from methylene chloride-methylcyclohexane with the aid of decolorizing carbon. Isolated 2.41 g (68% yield) of **6** as fine white crystals, mp 222-224°; ^{1}H nmr (deuteriochloroform): 4.32 (2H, ddd, J = 14, 8, 4 Hz), 3.78 (2H, m), 3.42 (2H, m), 2.79 (2H, ddd, J = 14, 7, 4 Hz), 1.82-1.98 (2H, unresolved m), 1.46-1.72 (3H, unresolved m), 1.28-1.42 (1H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 162.6 (1C), 127.1 (2C), 47.5 (2C), 47.1 (2C), 23.1 (2C), 21.1 (1C) ppm.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.67; H, 5.09; Cl, 25.58; N, 10.11. Found: C, 47.74; H, 5.09; Cl, 25.53; N, 10.10.

(*exo, exo*)-3,4-Dichloro-1,6-diazabicyclo[4.3.2]undec-3-ene-2,5-dione (**3**).

Compound **3** was purified by recrystallization from methylene chloride-methylcyclohexane with the aid of decolorizing carbon to give 2.87 g (46% yield) as fine cream colored crystals, mp 238-240°; ^{1}H nmr (deuteriochloroform): 4.44 (2H, dt, J = 14, 5 Hz), 3.67 (2H, m), 3.34 (2H, m), 2.93 (2H, ddd, J = 14, 10, 4 Hz), 1.97-2.15 (1H, unresolved m), 1.44-1.64 (1H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 164.1 (2C), 127.7 (2C), 48.7 (2C), 46.0 (2C), 18.7 (1C) ppm.

Anal. Calcd. for $C_9H_{10}Cl_2N_2O_2$: C, 43.40; H, 4.05; Cl, 28.47; N, 11.25. Found: C, 43.42; H, 4.10; Cl, 28.38; N, 11.21.

(*exo, exo*)-3,4-Dichloro-1,6-diazabicyclo[4.4.2]dodec-3-ene-2,5-dione (**4**).

Compound **4** was purified by recrystallization from methylene chloride-methylcyclohexane to give 3.72 g (59% yield) as fine white needles, mp 241-242°; ^{1}H nmr (deuteriochloroform): 4.37 (2H, ddd, J = 14, 8, 4 Hz), 3.74 (2H, m), 3.32 (2H, m), 2.66 (2H, ddd, J = 14, 7, 3 Hz), 1.58-1.92 (4H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 162.8 (2C), 127.3 (2C), 47.7 (2C), 45.6 (2C), 25.4 (2C) ppm.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.65; H, 4.60; Cl, 26.95; N, 10.65. Found: C, 45.73; H, 4.65; Cl, 27.01; N, 10.61.

3,4-Dichloro-1,6-diazabicyclo[4.3.3]dodec-3-ene-2,5-dione (**5**).

Compound **5** was purified by recrystallization from methylene chloride-methylcyclohexane with the aid of decolorizing carbon to give 3.60 g (57% yield) as cream colored crystals, mp 229-230°; ^{1}H nmr (deuteriochloroform): 4.23 (2H, ddd, J = 14, 4, 2 Hz), 3.79 (2H, ddd, 16, 14, 4 Hz), 3.31 (2H, ddd, 16, 5, 2 Hz), 3.07 (2H, ddd, J = 14, 4, 2 Hz), 2.69-2.90 (1H, unresolved m), 2.09-2.30 (1H, unresolved m), 1.46-1.66 (1H, unresolved m), 1.14-1.28 (1H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 161.1 (2C), 127.8 (2C), 47.8 (2C), 43.9 (2C), 18.8 (2C), 15.8 (2C) ppm.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.65; H, 4.60; Cl, 26.95; N, 10.65. Found: C, 45.73; H, 4.62; Cl, 27.04; N, 10.64.

(*exo, exo*)-3,4-Dichloro-1,6-diazabicyclo[4.4.3]tridec-3-ene-2,5-dione (**2**).

Compound **2** was purified by recrystallization from methylene chloride-methylcyclohexane to give 10.56 g (67% yield) as cream colored crystals, mp 201.5-202.5°; ^{1}H nmr (deuteriochloroform): 4.40 (2H, ddd, J = 14, 9, 4 Hz), 3.93 (2H, m), 3.34 (2H, m), 2.66 (2H, ddd, J = 14, 7, 3 Hz), 2.01-2.36 (3H, unresolved m), 1.73-1.90 (2H, unresolved m), 1.53-1.67 (1H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 161.9 (2C), 127.1 (2C), 49.0 (2C), 46.1 (2C), 26.5 (2C), 23.2 (1C) ppm.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.67; H, 5.09; Cl, 25.58; N, 10.11. Found: C, 47.59; H, 5.13; Cl, 25.53; N, 10.08.

(*exo, exo*)-10,11-Dichloro-1,8-diazabicyclo[6.4.2]tetradec-10-ene-9,12-dione (**7**).

Compound **7** was purified by washing through silica gel (ethyl acetate eluent) and recrystallization from methylene chloride-methylcyclohexane to give 4.80 g (60% yield) as pale yellow crystals, mp 184-185°; ^{1}H nmr (deuteriochloroform): 4.39 (2H, ddd, J = 14, 12, 4 Hz), 3.71 (2H, m), 3.49 (2H, m), 2.81 (2H, ddd, J = 14, 4, 3 Hz), 1.46-1.80 (8H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 163.1 (2C), 126.5 (2C), 47.1 (2C), 45.0 (2C), 23.7 (2C), 21.0 (2C) ppm.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_2$: C, 49.50; H, 5.54; Cl, 24.35; N, 9.62. Found: C, 49.39; H, 5.55; Cl, 24.42; N, 9.57.

(*exo, exo*)-9,10-Dichloro-1,7-diazabicyclo[5.4.3]tetradec-9-ene-8,11-dione (**8**).

Compound **8** was purified by washing through silica gel (ethyl acetate eluent) and recrystallization from methylene chloride-methylcyclohexane to give 1.32 g (33% yield) as fine white needles, mp 257-258°; ^{1}H nmr (deuteriochloroform): 4.18 (2H, ddd, J = 14, 7, 5 Hz), 3.89 (2H, dt, J = 15, 14 Hz), 3.31 (2H, dt, J = 15, 3 Hz), 2.76 (2H, ddd, J = 14, 7, 4 Hz), 2.20-2.44 (1H, unresolved m), 1.90-2.18 (2H, unresolved m), 1.42-1.70 (5H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 161.9 (2C), 126.5 (2C), 50.3 (2C), 47.0 (2C), 25.6 (2C), 24.1 (1C), 19.3 (1C) ppm.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_2$: C, 49.50; H, 5.54; Cl, 24.35; N, 9.62. Found: C, 49.60; H, 5.57; Cl, 24.26; N, 9.56.

(*exo, exo*)-3,4-Dichloro-1,6-diazabicyclo[6.4.3]pentadec-3-ene-2,5-dione (**9**).

Compound **9** was purified by chromatography on silica gel (ethyl acetate/hexanes = 1:1 eluent) and recrystallization from methylene chloride-methylcyclohexane to give 0.36 g (4% yield) as white flakes, mp 197-198°; ^{1}H nmr (deuteriochloroform): 4.45 (2H, m), 3.92 (2H, bt, J = 15 Hz), 3.35 (2H, dt, J = 15, 3 Hz), 2.80 (2H, dt, J = 14, 3 Hz), 2.40-2.60 (1H, m), 1.40-1.95 (9H, unresolved m) ppm; ^{13}C nmr (deuteriochloroform): proton decoupled, 162.1 (2C), 125.3 (2C), 50.4 (2C), 47.9 (2C), 28.6 (1C), 23.9 (2C), 13.7 (2C) ppm.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_2$: C, 51.16; H, 5.94; Cl, 23.23. Found: C, 51.27; H, 5.97; Cl, 23.28.

6,7-Dichloro-1,2,3,4-tetrahydro-1,4-dimethyl-1,4-diazocine-5,8-dione (**11**).

Compound **11** was purified by chromatography on silica gel (ethyl acetate/hexanes = 3:1 eluent) and recrystallization from methylene chloride-methylcyclohexane to give 1.84 g (34% yield) as light brown flakes, mp 148-152° dec; ^{1}H nmr (deuteriochloroform): 3.79 (2H, m), 3.42 (2H, m), 3.06 (6H, s) ppm.

Anal. Calcd. for $C_8H_{10}Cl_2N_2O_2$: C, 40.53; H, 4.25; Cl, 29.91; N, 11.82. Found: C, 40.56; H, 4.26; Cl, 29.99; N, 11.77.

7,8-Dichloro-2,3,4,5-tetrahydro-1,5-dimethyl-1*H*-1,5-diazonine-6,9-dione (**13**).

Compound **13** was purified by chromatography on silica gel (ethyl acetate/hexanes = 3:1 eluent) and recrystallization from methylene chloride-methylcyclohexane to give 1.90 g (26% yield) as light yellow crystals, mp 166-169°; ^{1}H nmr (deuteriochloroform): 3.77 (2H, m), 3.30 (2H, m), 2.95 (6H, s), 1.98-2.12 (1H, unresolved m), 1.50-1.60 (1H, unresolved m) ppm.

Anal. Calcd. for $C_9H_{12}Cl_2N_2O_2$: C, 43.05; H, 4.82; Cl, 28.24; N, 11.16. Found: C, 43.13; H, 4.83; Cl, 28.18; N, 11.14.

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REFERENCES AND NOTES

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