Tetrahedron Letters, Vol. 34, No. 1, pp. 27-30, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

[2+2] Cycloaddition Reaction of Cyclic Enecarbamates and Enamides With Ketenes. A Short and Efficient Synthesis of the Geissman-Waiss Lactone.

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Abstract: *The synthesis of several 2-aza-bicyclo[3.2.0]heptan-6-ones has been achieved in a regiospecific manner through a [2+2] cycloaddition reaction between five-membered cyclic enecarbamates and enamides and free ketenes. The synthetic potential of this new methodology has been demonstrated by a concise synthesis of the Geissman-Waiss lactone in 62% overall yield.*

[2+2] Cycloaddition of ketenes with double bonds to produce cyclobutanone derivatives has been a pivotal reaction in organic chemistry. The excellent work of Ghosez, Snider and Brady, among others,[1] has added a new dimension in the use of cyclobutanone adducts in organic synthesis making them valuable intermediates in the preparation of a large number of natural and unnatural compounds.[2] The mechanistic aspects of this [2+2] cycloaddition has also attracted much attention allowing one nowadays to rationalize the concertedness levels of this reaction, as well as, the peri-, stereo-, and regiochemical bias involved in the process.[3] Although a large number of [2+2] cycloadditions of ketenes with compounds containing a double bond are known, the use of enecarbamates and enamides as ketenophiles is virtually unexplored.[4] In view of the fact that reactions leading to α-nitrogen functionalization play a decisive role in alkaloid syntheses, the cyclic enecarbamates and enamides having a strategically placed double bond next to a nitrogen atom seem to be appropriate starting materials in the synthesis of many classes of alkaloids (scheme I).

In this communication we disclose our preliminary results regarding a [2+2] cycloaddition reaction of free ketenes and a number of 5-membered cyclic enecarbamates and enamides as ketenophiles (Table I).[5] Furthermore, the potential of this methodology is demonstrated by a concise synthesis of the Geissman-Waiss lactone, a key precursor in the synthesis of some pyrrolizidine alkaloids such as retronecine,[6] from the 2-aza-bicyclo[3.2.0]heptan-6-one **10**.

Scheme 1

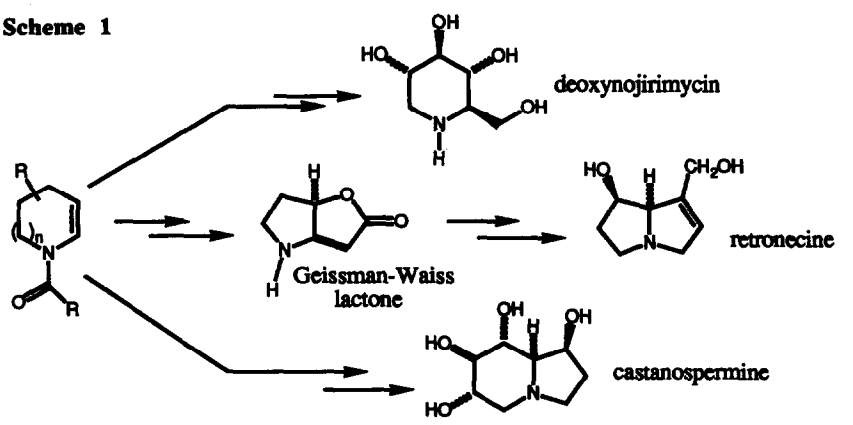
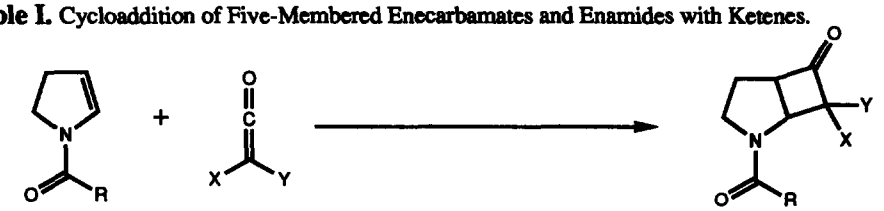
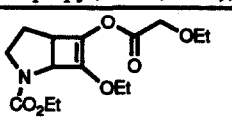
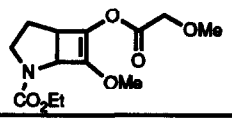


Table I. Cycloaddition of Five-Membered Enecarbamates and Enamides with Ketenes.



Entry: enamide or enecarbamate	2. Ketene[a]	Reaction conditions	Cycloadduct; yield[b]
1. **1a**(R= OCH_3)	X= Y= Cl	hexane, rt	**3a**(R= OCH_3, X= Y= Cl); **50%**
2. **1b**(R= OEt)	X= Y= Cl	Hexane, rt	**3b**(R= OEt, X= Y= Cl); **92%**
3. **1c**(R= CH_3)	X= Y= Cl	Hex/CH_2Cl_2(1:1), rt	**3c**(R= CH_3, X= Y= Cl); -[c]
4. **1d**(R=$C(CH_3)_3$)	X= Y= Cl	Hexane, 15°C	**3d**(R= $C(CH_3)_3$, X= Y= Cl); **77%**
5. **1e**(R= n-propyl)	X= Y= Cl	Benzene, rt or reflux[d]	**3e**(R= n-propyl, X= Y= Cl); -[c]
6. **1b**	X= Cl, Y= H	Hexane, -78°C to rt	ketene polymerization
7. **1b**	X= Br, Y= CH_3	Hexane, 15°C	**4b**(R= OEt, X= Br, Y= CH_3); **85%**[e]
8. **1d**	X= Br, Y= CH_3	Hexane, 15°C	**4d**(R=*tert*-Bu, X=Br, Y=CH_3); **70%**[f]
9. **1e**	X= Br, Y= CH_3	THF, reflux	Decomposition of starting material
10. **1b**	X= Br, Y= H	CH_2Cl_2, -78°C to rt	ketene polymerization
11. **1b**	X= Et, Y= H	Hexane, reflux	**5b**(R= OEt, X= Et, Y= H); **60%**[g]
12. **1e**	X= Et, Y= H	Benzene, reflux	**5e**(R= n-propyl, X=Et, Y=H); **30%**[h]
13. **1b**	X= OEt, Y= H	Hexane, 80°C[i]	**6b**  **39%**
14. **1d**	X= OEt, Y= H	Hexane, 80°C[i]	**6d**(R=*tert*-Bu, X= OEt, Y= H); **0%**
15. **1b**	X= OMe, Y= H	Hexane, 80°C[i]	**7b**  **77%**
16. **1b**	X= CH_2CH_2Cl Y= H	Hexane, reflux	**8b**(R= OEt, X= 2-Cl-Et, Y=H); **50%**[j]
17. **1b**	X= ϕ, Y= H	Hexane, rt or reflux	Recovery of starting material
18. **1e**	X= ϕ, Y= H	Benzene, reflux	Decomposition of starting material

a. Ketenes were generated *in situ* from Et_3N and the corresponding acid chloride. Substrate to ketene ratio: 1:1; b. Yields refer to isolated and purified products (flash chromatography on silica gel); c. Cycloadducts decomposed during isolation; d. Enamide was insoluble in hexane; e. Endo/exo (methyl) mixture (2:1); f. Endo/exo (methyl) mixture (1.7:1); g. Endo/exo mixture(1:1) as determined by ^{1}H NMR (360 MHz, CD_3CN, 67 °C); h. Endo/exo mixture (1:2) as determined by ^{1}H NMR (360 MHz, CD_3CN, 67 °C); i. Oil bath temperature; j. Endo/exo mixture (2:1) as determined by ^{1}H NMR (300MHz, CD_3CN, 57 °C).

The feasibility of cyclic enecarbamates and enamides **1a-1e**[7] to act as ketenophiles and perform [2+2] cycloadditions was examined towards several different ketenes. The results obtained are shown on Table I.

The enecarbamate **1a** and **1b** reacted smoothly with dichloroketene to provide the corresponding aza-bicyclic cyclobutanones **3a** and **3b** (entries 1 and 2) in 50% and 92% yield respectively.[8] In both cases reactions occur under very mild conditions with a single cycloadduct being produced almost instantaneously at room temperature. Among the cyclic enamides tested with dichloroketene (**1c**, **1d** and **1e**; entries 3, 4 and 5) only the N-pivaloyl-2-pyrroline **1d** afforded the expected dichloro-aza-cyclobutanone (**3d**, 77% yield).

[2+2] Cycloaddition of enecarbamate **1b** and enamide **1d** with methylbromoketene (entries 7 and 8) were clean reactions providing the aza-cyclobutanone **4b** in 85% yield (endo:exo/2:1) and **4d** in 70% isolated yield (endo:exo/1.7:1).

Although alkyl ketenes are notoriously inefficient for intermolecular [2+2] cycloadditions,[1d] ethylketene reacted well with the cyclic enecarbamate **1b** and enamide **1e** furnishing the 7-ethyl-aza-cyclobutanone **5b** (endo:exo, 1:1) in 60%, non-optimized yield (entry 11) and **5e** (endo:exo/1:2) in somewhat lower yield (30%, entry 12) due to partial decomposition of the starting material. Further demonstration that intermolecular cycloaddition of enecarbamates and alkylketenes can be a synthetically useful process came from the cycloaddition of enecarbamate **1b** with β-chloro-ethylketene to give the aza-cyclobutanone **8b** (endo:exo/2:1) in 50% yield (entry 16). Compound **8b** is an attractive intermediate for the synthesis of pyrrolizidine alkaloids.[9]

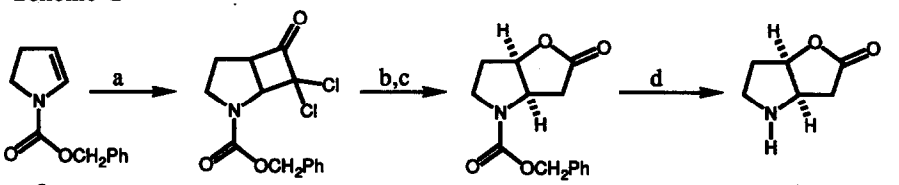
Surprisingly, [2+2]cycloaddition of enecarbamate **1b** with ethoxy- or methoxyketenes provided the aza-bicyclo-cyclobutenes **6b** and **7b** (Entries 13 and 15). These cycloadducts probably resulted from enolization of the expected aza-alkoxy-cyclobutanones followed by O-acylation by the alkoxyketene at the rather vigorous conditions usually employed to effect this type of cycloaddition (sealed tube, 80°C). Cycloaddition of enamide **1d** failed to yield the expected aza-cycloadduct **6d** (Entry 14) probably because of its greater thermo-instability when compared to enecarbamate **1b**.

Finally, no reaction is observed with enecarbamate **1b** and enamide **1e** and phenylketene (entries 17 and 18). Monochloroketene (entry 6) and monobromoketene (entry 10) showed a great tendency to polymerize before cycloaddition and no cycloadducts were observed.

The results presented above indicate that *cyclic enecarbamates and enamides are reactive ketenophiles in [2+2] cycloaddition reactions*, which permits to prepare a number of aza-bicyclo-cyclobutanones as potential intermediates in the synthesis of alkaloids. As expected, a single aza-bicyclo-cyclobutanone regioisomer was observed in all successful cycloadditions.

To illustrate the synthetic potential of the above protocol we report herein a short and effective synthesis of the Geissman-Waiss lactone **12** in 62% overall yield starting from the 7,7-dichloro-2-aza-bicyclo[3.2.0]heptan-6-one **10** obtained from the [2+2] cycloaddition reaction involving the cyclic enecarbamate **9** and dichloroketene.

Scheme 2



Reagents and Conditions: (a) $Cl_2CHCOCl$, Et_3N, Hex., rt (90%); (b) Zn, AcOH, rt, 0.5 h (89%); (c) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 0.5 h (90%); (d) H_2, Pd/C, HCl, MeOH (91%).

As shown in scheme 2, cycloaddition of cyclic enecarbamate **9** with dichloroketene proceeded smoothly in hexane at room temperature to give the aza-bicyclo-cyclobutanone **10** in 91% isolated yield. Dechlorination of the dichlorocyclobutanone **10** was accomplished under standard conditions (Zn, AcOH, rt., 0.5 h) to provide

the corresponding aza-bicyclo-cyclobutanone in 89% yield. Next, ring expansion of the cyclobutanone ring to a γ-lactone was best carried out using MCPBA (CH_2Cl_2, $NaHCO_3$, rt., 0.5 h) to afford the bicyclic carbamate lactone **11** in 90% isolated yield. Then, hydrogenolysis of the benzyloxycarbonyl moiety provided the Geissman-Waiss lactone **12** in 91% yield as the only product. The spectroscopic data of the resulting aza-lactone **12** were identical to those reported in the literature.[6]

We are presently exploring the above protocol in the total synthesis of some pyrrolizidine and indolizidine alkaloids. Results regarding these studies will be reported in due course.

Acknowledgments. We thank the Brazilian National Research Council(CNPq) and the International Foundation for Science(IFS), Sweden, for financial support of this work. We also thank Prof. Joseph P. Marino(The University of Michigan, USA), the State University of Campinas, Brazil, for variable temperature NMRs and Profs. R. H. Wightman(Heriot-Watt University, Edinburgh) and J. G. Buchanan(University of Bath, England) for kindly providing us with copies of spectra of some Geissman-Waiss lactone derivatives.

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2. Bellus, D.; Ernst, B. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 797-839.
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4. Enamides have a rich chemistry in both ground and excited state, for reviews see: (a) Lenz, G. R. *Synthesis* **1978**, 489-518., (b) Campbell, A.; Lenz, G. R. *Synthesis* **1987**, 421-451. To the best of our knowledge the only other work dealing with [2+2] cycloaddition of enecarbamates and enamides (but not cyclic derivatives) were recently reported by Hegedus (Soderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364-4374 and Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923-927) in which photolysis of chromium-alkoxy-carbene complexes (Fischer carbenes) in the presence of an excess of an enecarbamate or enamide produced cyclobutanones. However, as stated by the authors, no free ketenes seem to be involved in the process.
5. Taken from the M.Sc. Thesis of Antônio R. de Faria, NPPN-UFRJ, August 1992. Part of this work was presented at the XIV Annual Meeting of the Brazilian Chemical Society (SBQ), May 1991, Caxambu, Minas Gerais, Brazil, abstract QO-176.
6. (a) Geissman, T. A.; Waiss Jr., A. C. *J. Org. Chem.* **1962**, *27*, 139-142. (b) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans I* **1987**, 2377. For a recent chiral synthesis see: Wistrand, L. G.; Thaning, M. *J. Org. Chem.* **1990**, *55*, 1406-1408 and references cited therein.
7. Prepared according to: Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791-4792
8. All new compounds gave satisfactory spectroscopic data. Representative data for selected compounds; For **3b**: ^{1}H NMR (360 MHz, CD_3CN, 67°C) δ: 4.85 (d, J =7.5 Hz, 1 H), 4.40 (br. t, 1H), 4.20 (q, J = 7 Hz, 2H), 3.90 (ddd, J = 11; 8.5; 2 Hz, 1H), 3.30 (dt, J = 11; 7. 2 Hz, 1H), 2.25 (dd, J =13; 7 Hz,1H), 2.10 (m, 1H), 1.27 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 50°C) δ: 196.3, 154.3, 88.3, 64.8, 61.8, 60.9, 46.4, 25.9, 14.3; IR (CH_2Cl_2): 1810, 1700, 812 cm^{-1}; HRMS: calc. for $C_9H_{11}NO_3Cl_2$; 251.01159, found; 251.01259. For **3d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.25 (d, J = 7.6 Hz, 1H), 4.20 (m, 2H), 3.45 (dt, J =11; 6.1 Hz,1H), 2.35 (dd, J =12; 6.1 Hz, 1H), 2.10 (m, 1H), 1.30 (s, 9H); IR (neat): 1810, 1640, 812 cm^{-1}. MS (m/z): 265, 263, 181, 179, 123, 85, 69, 57(100%). For **4b** (endo): Rf = 0.4 (hex./AcOEt, 8:2); ^{1}H NMR (360 MHz, CD_3CN, 63 °C) δ: 4.74 (d, J = 7.4 Hz, 1H), 4.33 (br t, 1H), 4.15 (q, J = 7 Hz, 2H), 3.87 (m, 1H), 3.30 (m, 1H), 2.15 (dd, J = 12.9; 6.2, 1H), 2.05 (m, 1H), 1.60 (s, 3H), 1.27 (t, J = 7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers, characteristic peaks, δ: 204.3, 154.2 and 154.8, 69.0, 61.6 and 60.4, 17.3, 14.4; IR (neat): 1790, 1700, 770 cm^{-1}; HRMS: calc. for $C_{10}H_{14}NO_3Br$; 275.015705, found; 275.017258; For **4b** (exo): Rf = 0.2 (hex/AcOEt, 8:2); ^{1}H NMR (200 MHz, $CDCl_3$) mixture of rotamers, characteristic peaks, δ: 4.50 and 4.35 (2 d, J = 7.4 Hz, 1H), 4.30-3.80 (m, 4H), 3.4 (m, 1H), 2.25 (dd, J =12.9; 6.2, 1H), 2.00-1.90 (overlap of s, 3H and m, 1H), 1.30 (2 t, J = 7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 206.4 and 206.1, 154.9 and 154.4, 71.5, 59.6, 58.5, 23.8, 14.4; IR (neat): 1790, 1700, 700 cm^{-1}.
9. A short total synthesis of the pyrrolizidine alkaloid (+/-)-Platynecine was recently accomplished in our laboratories from the aza-cyclobutanone **8b**. A full account of this work will be published elsewhere.

(Received in USA 3 August 1992; accepted 1 October 1992)