Tetrahedron Letters, Vol. 33, No. 39, pp. 5717-5720, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SYNTHESIS OF γ- AND δ-LACTAMS BY AN INTRAMOLECULAR ENE REACTION OF AZO COMPOUNDS

Margherita Scartozzi, Ronald Grondin and Yves Leblanc*

Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec, H9H 3L1, Canada

Key-words: Lactams, Ene Reaction, Azo

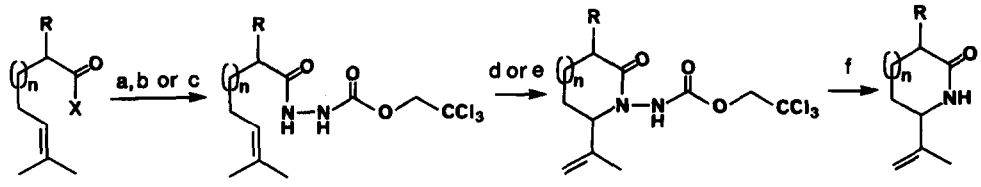
Summary: γ- and δ-lactams were efficiently prepared from the intramolecular ene reaction of azodicarbonyl species.

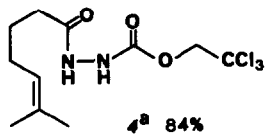
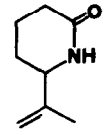
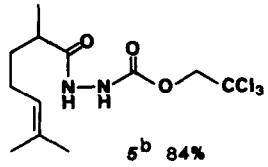
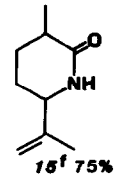
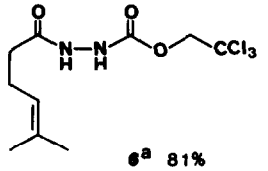
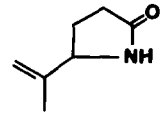
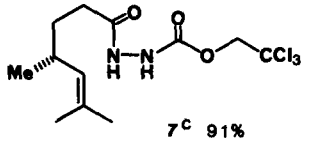
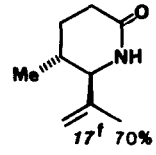
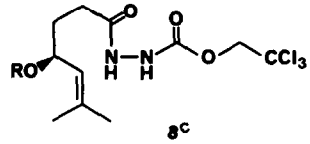
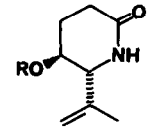
Azodicarboxylates are effective sources of electrophilic nitrogen.[1] We have demonstrated that the electronic nature of the ester groups affects their reactivities.[2,3] Thus, replacement of the ethyl esters of diethyl azodicarboxylate (DEAD) by 2,2,2-trichloroethyl esters (BTCEAD) accelerates both the bimolecular ene reaction with alkenes[2] and the [4+2] cycloaddition reaction with glycals.[3]

Substituted γ- and δ-lactams are useful molecules as they were used as precursors in alkaloid syntheses.[4] Such molecules were prepared by Keck's group[5] via an intramolecular ene reaction of acyl nitroso compounds. The degradation of acyl nitrosos and ene adducts under the conditions used to oxidize the precursor hydroxamic acids, however, requires the trapping of the acyl nitroso compound as a Diels-Alder adduct with 9,10-dimethylanthracene. The ene reaction then takes place after pyrolysis of the adduct. In a subsequent report, Vedejs and Meier showed one example of the synthesis of a γ- and δ- lactam via an intramolecular ene reaction of azodicarbonyl species.[6] The oxidation of the diacylhydrazines to the azo intermediates was accomplished with a 20-30 mole excess of manganese dioxide. As for the acylnitroso method, the ene adducts were converted to their corresponding lactams in a two step reduction sequence. Considering the mild conditions available to oxidize diacylhydrazines to azodicarbonyl species,[7] we envisioned that lactams could be formed at non-pyrolytic temperatures via an intramolecular variation of our ene reaction using stoichiometric amount of an oxidizing agent. In addition, the conditions developed in our laboratories for the conversion of 2,2,2-trichloroethyloxyhydrazides to free amines should allow the transformation of the ene adducts to the parent lactams in a single operation.[2]

In order to facilitate the present study, an efficient method for the preparation of the hydrazides **4** to **8** was required. The peptidic bond formation was accomplished in the last step of the synthesis using the monoprotected hydrazine as the amine source. Therefore, the acids **1**[8] and **3**[9] were condensed with 2,2,2-trichloroethyloxycarbonylhydrazine (**20**)[10] in CH_3CN in the presence of 2-chloro-1-methylpyridinium iodide as an activator to provide the hydrazides **4** and **6** (Scheme 1). On the other hand, the hydrazide **5** was prepared from the acyl chloride **2**.[8] Treatment of the hydrazides **4** and **5** with [bis(trifluoroacetoxy)iodo]benzene (1.1 equiv.) in CH_2Cl_2 at 0°C allowed the formation of the corresponding cyclic hydrazides **9** and **10**, in good yield, presumably via the azo compounds.[11]

Scheme 1

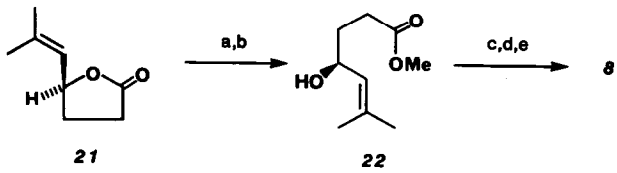


HYDRAZIDE	ENE ADDUCT	LACTAM
 **4**[a] 84%	**9**[d] 75%	 **14**[f] 93%
 **5**[b] 84%	**10**[d] 71% 3/1 TRANS/CIS	 **15**[f] 75%
 **6**[a] 81%	**11**[e] 81%	 **16**[f] 83%
 **7**[c] 91%	**12**[e] 80% 90% de	 **17**[f] 70%
 **8**[c] R = t-BuPh$_2$Si-	**13**[e] 86%	 **18**[f] 97% → **19** R=Ac

a) 2-CHLORO-1-METHYLPYRIDINIUM IODIDE 2.0 EQUIV., Et_3N 2 EQUIV., $H_2NNHCO_2CH_2CCl_3$ ***(20)*** 1.3 EQUIV., CH_3CN, 0°C TO R.T.; b) ***20*** 1.2 EQUIV., Et_3N EXCESS, CH_2Cl_2, 0° TO R.T.; c) SEE e) SCHEME 2 d) [BIS(TRIFLUOROACETOXY)IODO] BENZENE 1.1 EQUIV., CH_2Cl_2, 0°C 2.5 h; e) $Pb(OAc)_4$ 1.2 EQUIV., CH_2Cl_2, -20°C 30 MIN. TO 0°C 30 MIN.; f) Zn DUST 3 EQUIV. BY WEIGHT OVER 12 h, ACETIC ACID–ACETONE (3/1), R.T.

For the hydrazide **6**, better results were obtained when lead tetraacetate (1.2 equiv.) in CH_2Cl_2 at -20°C to 0°C was used as oxidizing agent which afford the ene adduct **11** in 81% yield.

Scheme 2



a) K_2CO_3, MeOH, H_2O, R.T.; b) REMOVE MeOH FROM (a) THEN H_2O WAS ADDED FOLLOWED BY AcOH (pH 5.5), CH_2N_2, Et_2O (89%); c) + Ph_2SiCl, Et_3N, DMAP, CH_2Cl_2, 0°C TO R.T. (94%); d) LiOH, THF, H_2O, 50°C (94%); e) *20* 2 EQUIV., DMAP 2 EQUIV., 1-HYDROXYBENZOTRIAZOLE 2 EQUIV., 1-(-3-DIMETHYLAMINOPROPYL)-3-ETHYLCARBODIIMIDE•HCl 2 EQUIV., CH_2Cl_2, R.T. (80%)

Hydrazide **5**, which bears a methyl group adjacent to the carbonyl moiety, afforded a 3/1 trans:cis mixture of the cyclic hydrazide **10**. Greater diastereoselectivity was anticipated from a substrate having a stereogenic center adjacent to the forming asymmetric center. Towards this end, the optically active hydrazide **8** was prepared from lactone **21**[12] (Scheme 2). First, the lactone was converted to the hydroxy acid under basic conditions followed by an esterification with diazomethane to provide the hydroxy ester **22**. After silylation of the alcohol and hydrolysis of the ester, the hydrazide **8** was formed by activation of the acid with 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide•HCl in the presence of 1-hydroxybenzotriazole and **20**. Treatment of **8** with $Pb(OAc)_4$ in CH_2Cl_2 (-20°C to 0°C) smoothly provided the trans ene adduct **13** in high yield, as a single diastereoisomer.[13] High induction was still observed with a methyl group contiguous to the olefin (**7**).[14] In this case the ene adduct was isolated in 80% yield with a 90% diastereomeric excess. The trans selectivity observed in the last two cases suggests a chair-like arrangement of the chain in the transition state with the allylic substituent in an equatorial orientation as proposed by Tietze[15] for the ene reaction of 1,7-dienes.

The ene adducts (**9-13**) prepared in the present study were then converted to their corresponding lactams (**14-18**) in high yields with zinc dust in acetic acid-acetone at room temperature.[2]

In summary, γ- and δ-lactams can be easily obtained from the intramolecular ene reaction of azodicarbonyl species. In addition to the mild conditions used for the ene reaction, the high selectivity observed with substrate **7** and **8** makes this method very attractive for the preparation of 5,6-disubstituted 2-piperidone and 4,5-disubstituted 2-pyrrolidone.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Ball for performing the X-ray crystallographic analysis on compound **19**, C. Li for recording mass spectra, M. Bernstein and L. Trimble for recording ^1H NMR spectra. We also wish to thank Marc Labelle and Peppi Prasit for helpful suggestions in the preparation of this manuscript.

REFERENCES

1. a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394-6395.
   b) Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397.
   c) Trimble, L.A.; Vederas, J.C. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399.
   d) Wilson, R.M.; Hengge, A. *Tetrahedron Lett.* **1985**, *26*, 3673-3676.
2. Leblanc, Y.; Zamboni, R.; Bernstein, M.A. *J. Org. Chem.* **1991**, *56*, 1971-1972.
3. a) Grondin, R.; Leblanc, Y.; Hoogsteen, K. *Tetrahedron Lett.* **1991**, *32*, 5021-5024.
   b) Leblanc, Y.; Fitzsimmons, B.J. *Tetrahedron Lett.* **1989**, *30*, 2889-2892.
4. a) Massiot, G.; Delaude, C. in *"The Alkaloids"*, Bossi, A. *Ed. Academic:* Orlando, Florida, **1986**; *Vol. 27*, Chapter 3.
   b) Strunz, G.M.; Findlay, J.A. in *"The Alkaloids"*, Bossi, A. *Ed. Academic:* Orlando, Florida, **1985**; *Vol. 26*, Chapter 3.
5. a) Keck, G.E.; Webb, R.; Yates, J.B. *Tetrahedron* **1981**, *37*, 4007-4016.
   b) Keck, G.E.; Webb, R. *Tetrahedron Lett.* **1979**, 1185-1186.
   c) Keck, G.E. *Tetrahedron Lett.* **1978**, 4767-4770.
6. Vedejs, E.; Meier G.P. *Tetrahedron Lett*, **1979**, 4185-4188.
7. Moriaty, R.M., Prakash, I.; Penmasta, R. *Synth. Commun.* **1987**, *17*, 409-413.
8. Mori, K.; Matsui, M. *Tetrahedron*, **1969**, *25*, 5013-5018.
9. The acid **3** was prepared using the same sequence as described for **1**[7].
10. 2,2,2-Trichloroethyloxycarbonylhydrazine (**20**) was obtained from the condensation of hydrazine and trichloroethyl chloroformate in chloroform at 0°C.
11. In all cases so far, the azo intermediate has never been observed. The mechanistic alternative to the ene reaction consisting of the activation of the double bond by [bis(trifluoroacetoxy)iodo]benzene followed by nucleophilic displacement by the hydrazide cannot therefore be excluded. See: Kahn, M.; Chrusciel, R.A.; Su T.; Xuan, T. *Synlett*, **1991**, *1*, 31-32.
12. Liu, Meng-Ying, L.; Silverstein, R.M. *Xuaxve Xvebao*, **1985**, *43*, 467-471.
13. The relative stereochemistry has been confirmed by X-ray crystallographic analysis of the derived lactam **19**.
14. The corresponding acid to hydrazide **7** was prepared, with minor modifications, as described in literature see: Randad, R.S.; Kwlkarni, G.H. *Indian J. Chem.* **1983**, *22B*, 795-801.
15. Tietze, L.F.; Belfuß, U. Liebigs *Ann. Chem.* **1988**, 321-329.

(Received in USA 2 June 1992)