determined from 27 centered reflections within 17.9° ≤ 2θ ≤ 22.5°. The data collection range of *hkl* was 0 ≤ *h* < 18, 0 ≤ *k* ≤ 19, 0 ≤ *l* ≤ 23, with $[(\sin\theta)/\lambda]_{max}$ = 0.595. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±1.5% during the data collection. A set of 1280 reflections was collected in the θ/2θ scan mode, with scan width [2θ(Kα$_1$) − 0.4]° to [2θ(Kα$_2$) + 0.4]° and a constant ω scan rate of 15.63 deg/min. There were 1167 unique reflections, and 923 were observed with $F_o > 3\sigma(F_o)$. The full-matrix least-squares refinement varied 241 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms and atom coordinates for the two amino hydrogen atoms. All CH hydrogen atoms were included by using a riding model (coordinate shifts of C applied to attached H atoms, C–H distances set to 0.96 Å, H angles idealized). The U_{iso}(H) were set to 1.1 × U_{eq}(neighboring atom). The final residuals were *R* = 0.051 and *wR* = 0.043 with final difference Fourier excursions of 0.36 and −0.36 e Å^{-3}.

***cis-syn-cis*-2,6-Dioxo-1,4,7,8-tetranitrodecahydro-1*H*,5*H*-diimidazo[4,5-*b*:4′,5′-*e*]pyrazine (5b)**: $C_6H_6N_{10}O_{10}$, FW = 378.2, monoclinic space group $P2_1/n$, *a* = 8.5114 (14) Å, *b* = 12.259 (3) Å, *c* = 24.952 (7) Å, β = 97.30 (2)°, *V* = 2582.4 (1.1) Å^3, *Z* = 8, ρ_{calcd} = 1.945 mg mm^{-3} at −50 °C (1.930 at 20 °C), λ(Cu Kα) = 1.541 84 Å, μ = 1.579 mm^{-1}, *F*(000) = 1536, *T* = 223 K.

A translucent, colorless 0.04 × 0.08 × 0.25 mm crystal, in the shape of a lath, was used for data collection. Lattice parameters were determined from 25 centered reflections within 36.3° ≤ 2θ ≤ 93.9°. The data collection range of *hkl* was −9 ≤ *h* ≤ 8, 0 ≤ *k* ≤ 13, 0 ≤ *l* ≤ 26, with $[(\sin\theta)/\lambda]_{max}$ = 0.531. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.5% during the data collection. A set of 3985 reflections was collected in the θ/2θ scan mode, with scan width [2θ(Kα$_1$) − 0.5]° to [2θ(Kα$_2$) + 0.5]° and ω scan rate (a function of count rate) from 12.0 to 30.0 deg/min. There were 3230 unique reflections, and 2342 were observed with $F_o > 3\sigma(F_o)$. The full-matrix least-squares refinement varied 506 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms and atomic coordinates for the hydrogen atoms (the U_{iso}(H) were set to 0.05 Å^2). The final residuals were *R* = 0.081 and *wR* = 0.080 with final difference Fourier excursions of 0.52 and −0.47 e Å^{-3}.

1,4-Diformyl-2,3,5,6-tetraacetoxypiperazine (9): $C_{14}H_{18}N_2O_{10}$, FW = 374.3, monoclinic space group $P2_1/n$, *a* = 7.905 (2) Å, *b* = 25.691 (4) Å, *c* = 13.536 (2) Å, β = 98.69 (1)°, *V* = 2717.2 (7) Å^3, *Z* = 6 (1.5 mol/asymmetric unit), ρ_{calcd} = 1.372 mg mm^{-3}, λ(Cu Kα) = 1.541 84 Å, μ = 0.983 mm^{-1}, *F*(000) = 1176, *T* = 293 K.

A clear, colorless 0.12 × 0.14 × 0.27 mm crystal, in the shape of a prism, was used for data collection. Lattice parameters were determined from 25 centered reflections within 40° ≤ 2θ ≤ 57°. The data collection range of *hkl* was 0 ≤ *h* ≤ 8, 0 ≤ *k* ≤ 28, −14 ≤ *l* ≤ 14, with $[(\sin\theta)/\lambda]_{max}$ = 0.547. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.5% during the data collection. A set of 4327 reflections was collected in the θ/2θ scan mode, with scan width [2θ(Kα$_1$) − 0.5]° to [2θ(Kα$_2$) + 0.5]° and ω scan rate (a function of count rate) from 8.0 to 29.3 deg/min. There were 3738 unique reflections, and 2606 were observed with $F_0 > 3\sigma(F_o)$. The full-matrix least-squares refinement varied 398 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms and atomic coordinates for all (nine) non-methyl hydrogen atoms. Eighteen methyl H atoms were included as rigid rotatable groups (C–H distances set to 0.96 Å, H angles idealized). The U_{iso}(H) were set to 0.050 or, if methyl, 0.075 Å^2. The final residuals were *R* = 0.066 and *wR* = 0.059 with final difference Fourier excursions of 0.31 and −0.26 e Å^{-3}.

There are two independent molecules in the asymmetric unit of this crystal, one sitting on a crystallographic center of symmetry and the other in a general position. The conformations of both are identical (to within experimental error); the molecules are somewhat flattened chair forms (alternating ring torsions of ca. ±45° rather than ±60°), and each has four axial acetoxy substituents.

Acknowledgment. This work was supported by the Offices of Naval Research, Mechanics Division, Code 1132P, and Naval Technology (Explosives and Undersea Warheads Block) and by the Australian Defence Science and Technology Organization.

Supplementary Material Available: Tables of atomic coordinates and equivalent isotropic displacement coefficients, bond lengths and angles, anisotropic displacement coefficients, and H-atom coordinates and isotropic displacement coefficients for compounds **5a**, **5b**, and **9**, Supplementary Figure 5 showing the numbering scheme for the second molecule of **5b**, and Supplementary Figure 6 showing the numbering scheme for the second molecule of **9** (13 pages). Ordering information is given on any current masthead page.

Novel Heterocycles by Bis Heteroannulation of Oxazoles[1]

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We report the first examples of intramolecular Diels–Alder addition of heterodienophiles N=N, C=N, C=O, C=S to oxazoles. The required 5-ethoxy- and 5-phenyloxazoles were synthesized bearing a side chain of variable length on C-2 to which the different heterodienophiles are attached. The products of the thermal bis heteroannulation are 3-triazolines, imidazolines, oxazolines, or thiazolines fused to a five- to six-membered ring. Relative reactivities were established and the mechanism is discussed.

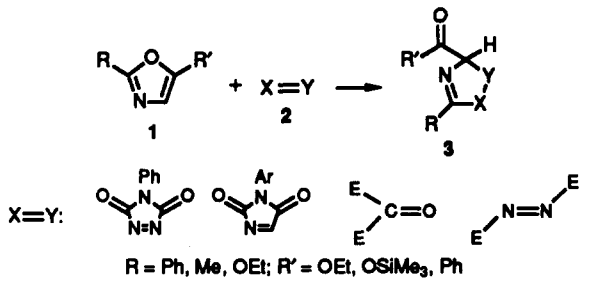
Introduction

In a previous paper[2] we reported the results of intermolecular cycloaddition of different oxazoles with heterodienophiles (Scheme I). These reactions were HOMO diene controlled since they required the normally electron poor azadiene to bear electron-donating groups (OEt, $OSiMe_3$) at C-2 or C-5. The heterodienophiles **2** were electron poor: PTAD, DEAD, dehydrohydantoin, and diethyl ketomalonate. The thermal reactions (in the dehydrohydantoin and diethyl ketomalonate cases, BF_3·etherate was needed to facilitate the reaction) led to 3-triazolines (**3**; X, Y = N), imidazolines (**3**; X = C, Y =

(1) Cycloadditions 48. For paper 47, see: Hassner, A.; Dehaen, W. *Chem. Ber.*, in press.
(2) Hassner, A.; Fischer, B. *Tetrahedron* **1989**, *45*, 3535.

0022-3263/91/1956-3419$02.50/0

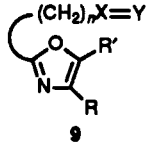
Scheme I



N), or 3-oxazolines (**3**; X = C, Y = O; plus 2-oxazolines). Among the oxazoles studied 5-ethoxy- and 5-siloxyoxazoles proved to be most reactive, while 2-ethoxyoxazoles were far less reactive and nonactivated oxazoles (e.g. 2-methyl-5-phenyloxazole) were not reactive at all. The reactivity difference between 2-ethoxy- and 5-ethoxyoxazoles was probably due to the better ability of the latter to provide increased electron density to the ring. Generally, formation of the products may be explained by formation of a Diels–Alder adduct **4** (either via a concerted or stepwise mechanism a or b), which undergoes ring opening to **5** followed by rearrangement to **6** and closure to an azole (Scheme II). We couldn't exclude, in some cases, nucleophilic attack from C-4 of the oxazole onto the dienophile (**1** → **7**) followed by ring opening and intramolecular cycloaddition leading to the product **3** (pathway c). Path d is an option proceeding via nitrilium ylid, **8**.

The intramolecular Diels–Alder reaction of oxazoles with C–C dienophiles has been applied by Weinreb[3] and Jacobi[4] to the total synthesis of various natural products. By contrast, intramolecular cycloaddition of oxazoles using heterodienophiles remained virgin territory. Hence, it was of interest to extend our study of Diels–Alder type reactions of oxazoles with heterodienophiles to intramolecular systems. Our goals were to examine the scope of the reaction as an entry to novel heterocycles by bis heteroannulation[4d] and to compare it with the corresponding intermolecular reaction (mechanism, reactivity of diene and dienophile).

Synthesis of Systems Containing Oxazoles and Heterodienophiles. Based on our former studies, in which 5-ethoxyoxazoles proved to be reactive substrates in intermolecular cycloadditions, our target molecules in the present study were 5-ethoxyoxazoles **9** bearing at C-2



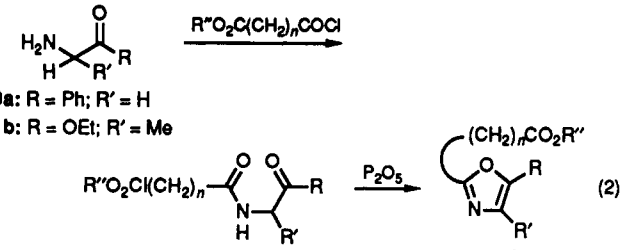
(1)

9

R = H, Me
R = Ph, OEt
X=Y = N=N, C=O, C=N, C=S
n = 2, 3, 4

a side chain which contained a heterodienophile. Our synthetic strategy involved formation of the oxazole with the desired tether length, via an amido ketone Robinson–Gabriel synthesis,[5] (see **11** → **12**) followed by elaboration of the necessary X=Y functional group. This strategy was found to be superior to combining fragments bearing the desired functional groups or to ring closure with the desired functional groups present. On the other hand, ring closure to an oxazole at an early stage limits elaborating certain functional groups. For instance, it was found difficult to introduce a carboxylic acid function in 5-ethoxyoxazoles due to their sensitivity to both acids and neutral ester cleaving agents (e.g. TMSI); in such a case an alternative system bearing a 5-phenyl substituent was synthesized (see **12a**).

Oxazoles **12** were synthesized by starting with ethyl glycinate **10b** or 2-aminoacetophenone **10a** and the appropriate acid chloride to form first the α-amido ketone (or ester) **11** followed by dehydration using P_2O_5.[4b]



In the 5-phenyloxazole series (**12**, R = Ph) an N=N heterodienophile (cf. **15**) was formed in situ by the following steps: the ester **12** was subjected to TMS-I (3 equiv) in refluxing acetonitrile for 20 h to yield the acid **13** in ca. 80% yield[6] (Scheme III). Hydrazide **14** was isolated in relatively low yields from a one pot reaction of the acid **13** with thionyl chloride/pyridine at 0 °C followed by addition of ethyl carbazate and DMAP (at 0 °C and then at rt overnight)[7] or, alternatively, in a better yield (65%) by condensing acid **13** with ethyl carbazate in the presence of DCC at room temperature. The desired azo function (**15**) was revealed by oxidation with iodobenzene diacetate in refluxing benzene.[8] Oxidation was very rapid (5 min) and **15** was not isolated but underwent intramolecular cycloaddition under those conditions.

In the 5-ethoxyoxazole series, C=O, C=S, and C=N, functions were elaborated from the ester **12** (R = OEt). Aldehyde **16** was obtained in 80% yield after DIBAL-H reduction of **12**.[4b] Thioaldehyde **17** resulted by treating aldehyde **16** with hexamethyldisilathiane and a catalytic amount of BuLi in dry THF at 0 °C and then at 20 °C overnight.[9] The thioaldehyde wasn't isolated but reacted in situ. Imine **18** was likewise formed in situ, from reaction of **16** with ethyl carbamate and a catalytic amount of *p*-TsOH, in refluxing benzene.

The reactivity of a heterocumulene in these reactions was studied on thiocyanate **20**. Reaction of 5-bromovaleronitrile with ethyl diazoacetate in the presence of BF_3-etherate afforded the substituted 5-ethoxyoxazole **19**,[11]

(3) (a) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580. (b) Levin, J. I.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325. (c) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397.

(4) (a) Jacobi, P. A.; Kaczmarek, S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, *25*, 4859. (b) Jacobi, P. A.; Craig, T. A.; Walker, P. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (c) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (d) Jacobi, P. A.; Craig, T. A. *J. Am. Chem. Soc.* **1978**, *100*, 7748.

(5) Turchi, I. J. Oxazoles. *Heterocyclic Compounds*; John Wiley: New York, 1986; Vol. 45, pp 3–6.

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(9) Murai, S.; Ryu, I.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1988**, *110*, 1976.

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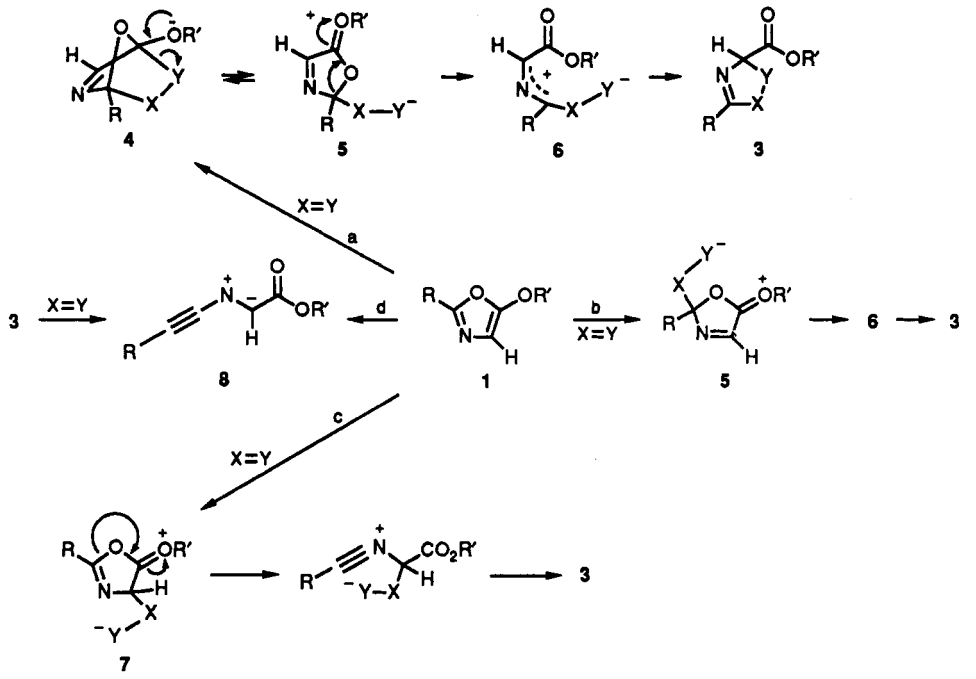
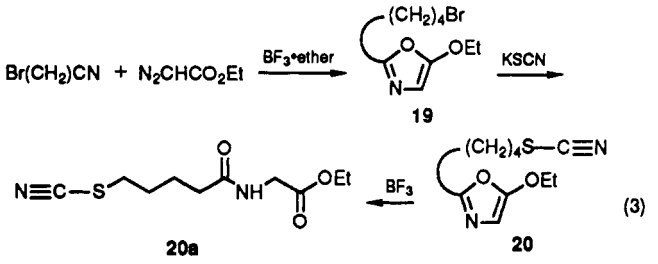
(11) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.

Scheme II



which upon substitution with potassium thiocyanate yielded **20**.



Results and Discussion

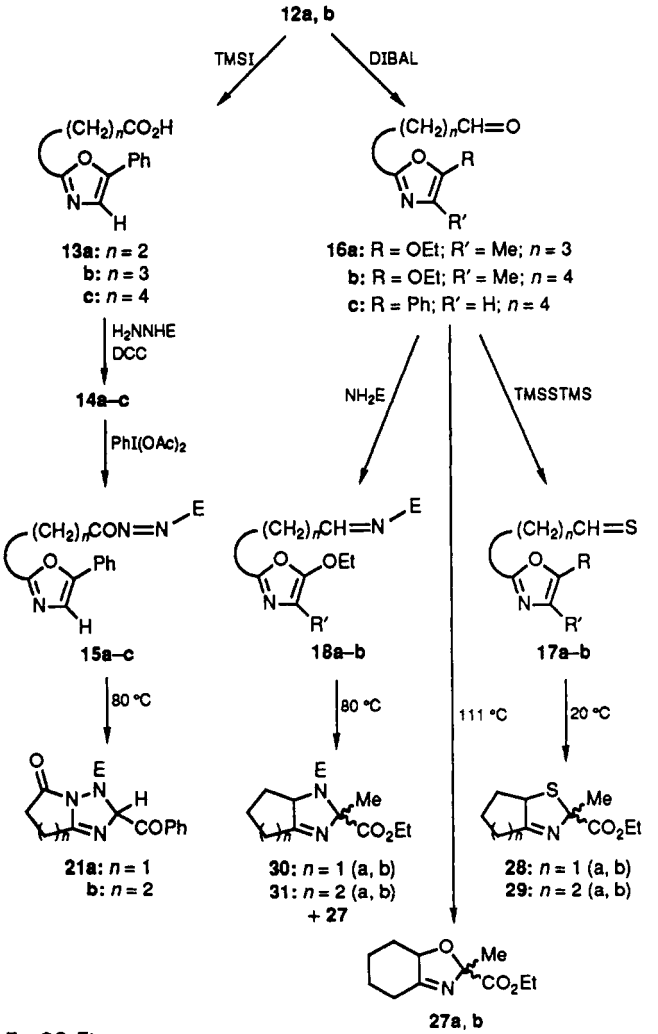
The Cycloaddition. A. The N=N Dienophile. The azo compounds **15a,b** were prepared in situ when the hydrazine **14a** or **14b** was heated with iodobenzene diacetate[8] for 2 h. Within 5 min no starting material was left and intramolecular reaction of the azo function provided the triazolines **21a** and **21b** in 40% and 57% yield, respectively. The structure of **21** was assigned on the basis of ^{1}H NMR, ^{13}C NMR, IR, and MS data, including 2D NMR studies. ^{1}H NMR spectra for **21a,b** showed typical features. Due to the proximity to the chiral center at C-2, the ester's methylene appears as an AB quartet of quartets and C-5 (or C-6) methylene appears as an AB quartet or doublet of doublets. Elongation of the side chain by one more methylene, **15c**, didn't lead to the corresponding seven-membered ring under the reaction conditions but rather to a complex mixture of products.

It is noteworthy that the 5-phenyloxazoles **15** underwent intramolecular cycloaddition with the azo function while intermolecular Diels–Alder reaction with an azo function required a 5-ethoxy or 2-ethoxy substituent for activation.[2] As expected, entropy and proximity factors overcame the low reactivity of the 5-phenyloxazoles.

Formation of the fused 1,2,4-triazolines **21** can be explained by an intramolecular Diels–Alder addition followed by a ring opening as shown in Scheme IV.

While C=C dienophiles, which reacted with oxazoles, led to zwitterions **25** that underwent elimination and aromatization of **26** to pyridines (Scheme V),[10] zwitterion

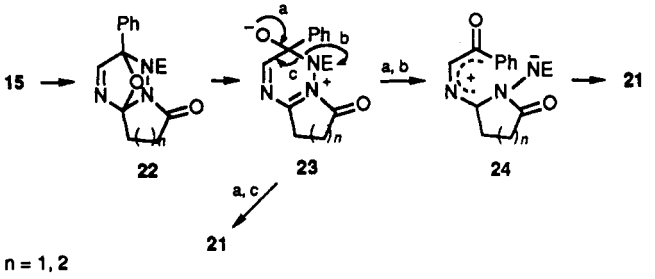
Scheme III



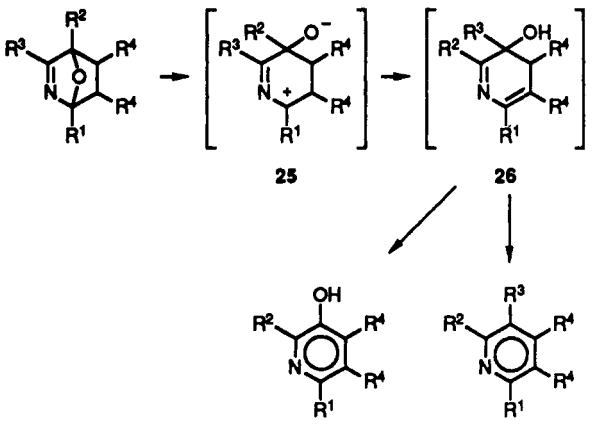
E = CO_2Et

23, derived from the N=N dienophile, had no elimination alternative and therefore underwent either ring opening to **24** (path a, b) followed by intramolecular cyclization to

Scheme IV



Scheme V



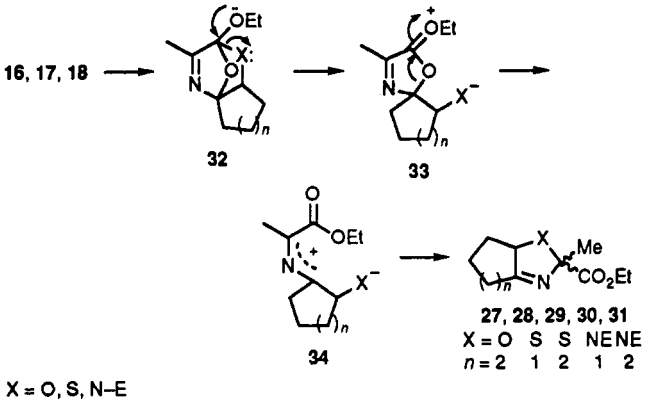
produce triazoline **21**, or a one-step Pinacol-type rearrangement (path a, c).

B. The C=O Dienophile. The 5-ethoxyoxazole **16b**, containing the aldehyde function attached to a 4-carbon tether, underwent cycloaddition upon heating for 5 h at 110 °C to produce the 2,5-dihydrocyclohexano(d)oxazole **27** in 78% yield. The product was isolated as a mixture of two stereoisomers in a ratio of ca. 2:1. Whereas, in the intermolecular Diels–Alder reaction an activated C=O dienophile (diethyl ketomalonate) and catalysis by BF_3·etherate were required,[2] in the intramolecular case even the plain aldehyde **16b** reacted in the absence of catalyst and at lower temperature. The lower homologue **16a**, with a three methylene tether, did not, however, form a cycloadduct even in refluxing toluene for 10 h and led only to starting material, while refluxing in xylene led to brown tar. Neither did cycloaddition take place in the 5-phenyloxazole series **16c** in refluxing toluene or xylene. In refluxing toluene starting material remained as such, while refluxing in xylene led to brown tar.

C. The C=S Dienophile. Both thioaldehydes **17a,b** obtained in situ from the corresponding aldehydes **16**[11] and bearing a three- or four-carbon tether, underwent cycloaddition readily at room temperature. The products were **28** and **29**, respectively. These S analogues of **27** were also obtained as a mixture of two stereoisomers (**a** and **b** in a ratio of 1:1), which were separated by chromatography in the case of **28**. In spite of the high reactivity of the thioaldehyde function in these cycloadditions,[12] no adduct formed when the corresponding 5-phenyloxazole **16c** was subjected to the reaction conditions.

The ^1H NMR spectra of both 3-oxazoline (**27**) and thiazoline (**28, 29**) derivatives exhibited typical patterns. For instance, the peak of the ester methylene appears as an AB quartet of quartets (see **21**). The equatorial hydrogen on C-4 appears as a doublet of multiplets (dm)

Scheme VI



shifted relatively downfield (2.8 ppm) due to the anisotropic effect of the C=N cis to it. The cis (H, Me) isomer **28a**, separated chromatographically from the trans isomer **28b**, exhibited a simpler pattern for both the carbethoxy methylene (quartet) and H-4 (multiplet).

D. The C=N Dienophile. The *N*-carbethoxyimine **18a**, formed in situ by heating the aldehyde **16a** with ethyl carbamate in the presence of *p*-toluenesulfonic acid catalyst in benzene, cycloadded with formation of the fused imidazoline **30**, isolated as a mixture of four isomers (two sets of rotamers) in 43% yield. The typical patterns in PMR spectra mentioned above for the oxazoline and thiazoline cases were distorted in the case of the imidazoline products. The typical sharp dd's for H-6(7), appear in this case as sixteen peaks (four dd's) broad due to the nitrogen effect. Considerable line broadening is pronounced in the other peaks as well. The unique pattern for the carbethoxymethylene is not seen in this case.

With the four carbon tether, there was a competitive reaction between cycloaddition of the starting aldehyde **16b** to produce **27** and formation of the imine **18b**, which underwent cycloaddition to yield **31** as a mixture of four isomers. The ratio of **27**:**31** was 82:18, as indicated by GC/MS.

E. Heterocumulene SCN. The thiocyanate function proved to be a poor dienophile since **20** did not cycloadd even at 140 °C in the presence of BF_3·etherate but instead underwent acid-catalyzed ring-operning reaction to **20a**.

F. Reaction Pathways. Formation of cycloadducts **27–31** is best explained as derived from a Diels–Alder adduct **32**. This tricyclic intermediate is unstable and undergoes cleavage; either a one-step rearrangement or a three-step cleavage–recyclization (via **33**, **34**, see Scheme VI) analogous to **23**. In these reactions Diels–Alder addition with formation of a six-membered ring is geometrically less strained than fusion to a five-membered ring. Hence, the latter is only observed in the case of the more reactive C=S and C=NCO_2Et dienophiles but not in the C=O case. The pathway described in Scheme VI also accounts for formation of stereoisomers in near equal ratio.

Among the four possible pathways mentioned in Scheme II for the cycloaddition of 5-ethoxyoxazoles with heterodienophiles, Diels–Alder reaction (path a indistinguishable at this time from the two-step path b) appears the most attractive. Our results eliminate pathway d, since opening of an ethoxyoxazole to a nitrilium ylid **8** requires heat,[13] while the C=S addition took place at room temperature. Path c, nucleophilic attack from C-4 of the oxazole onto the dienophile, also appears unlikely since it requires as

(12) The first report of a thioaldehyde serving as a heterodienophile in *intermolecular* Diels–Alder reactions with oxazoles is by: Vedejs, E.; Fields, S. *J. Org. Chem.* **1988**, *53*, 4663.

(13) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, 181.

the first step a very strained bicyclic transition state violating Bredt's rule.

Conclusion

While intramolecular cyclizations between oxazoles and olefins or acetylenes led to ring systems fused to pyridines[3] or furans,[4] the use of heterodienophiles prove to be an entry to a variety of fused five-membered ring heterocycles.

We have shown that bis heteroannulation of 2-substituted 5-ethoxyoxazoles with C=O, C=S, C=N, N=N functions proceeds readily with ultimate formation of novel five-membered ring heterocycles fused to a six-membered ring. With shorter three atom tethers only the N=N, C=S, and C=N functions underwent cycloaddition.

Among the dienophiles studied, the azo system proved to be the most reactive, cycloadding even to a nonactivated oxazole. The thioaldehyde group reacted only with 5-ethoxyoxazoles, however, without need of heating. The C=NCO$_2$Et dienophile reacted with 5-ethoxyoxazoles only upon heating and plain aldehydes reacted only in the case of a four-methylene tether. Thiocyanate **20** proved unreactive even upon heating in the presence of BF$_3$-etherate.

In general, as expected, the intramolecular systems reacted either under less drastic conditions or with less activated dienophiles than the corresponding intermolecular reactions.

Out of the four possible mechanisms for the cycloaddition (see Scheme II), the most probable is formation of a Diels–Alder adduct which undergoes ring opening to **24** or **34** followed by closure to the bicyclic products **21**, **27–31**.

Experimental Section

General. The NMR spectra were recorded on Bruker AM-300 and Bruker AC-200 spectrometers using CDCl$_3$ as a solvent (unless otherwise indicated). IR spectra were recorded on Nicolet 60 SXB FT-IR spectrometer and on a Perkin-Elmer Model 457 instrument. Mass spectra were obtained on a Finnigan 4021 instrument. Silica gel (Merck 9385) was used for chromatography. The following abbreviations for NMR spectra were used: o = ortho, p = para, m = meta, i = ipso. In the ^{13}C spectra superscripts a and b refer to uncertainty in peak assignment to specific carbons. HRMS of products **21**, **27**, **28**, **30** showed M – CO$_2$Et due to their aromatization in the spectrometer. Compound **16a** was synthesized according to literature.[4b] Compounds **11b**, **12b**, **16b** (n = 4) were synthesized according to Jacobi's procedure[4b] with the modifications indicated below.

Ethyl *N*-(5-Carbethoxypentanoyl)alaninate (11b, n = 4). The reaction was performed with 5.53 g (28 mmol) of adipoyl chloride monoethyl ester. Yield: 88% (6.73 g) of a colorless oil. ^{1}H NMR: δ 6.16 (NH, br s, 1 H), 4.55 (CH, quintet, J = 7 Hz, 1 H), 4.18, 4.10 (2 CO$_2$C*H*$_2$CH$_3$, 2 q, 4 H), 2.30 (CH$_2$, m, 2 H), 2.21 (CH$_2$, m, 2 H), 1.65 (CH$_2$CH$_2$, m, 4 H), 1.38 (CH$_3$, d, J = 8 Hz, 3 H), 1.28, 1.23 (2 CO$_2$CH$_2$C*H*$_3$, 2 t, 6 H), MS (m/e): 274 (MH$^+$), 228 (MH$^+$ – EtOH), 200 (MH$^+$ – HCO$_2$Et).

2-(4-Carbethoxybutyl)-4-methyl-5-ethoxyoxazole (12b, n = 4). The reaction was carried out on 8.75 mmol (2.4 g of **11b**) for 9 h, as indicated for **12a**. Yield: 92% (2.05 g) of light yellow oil. ^{1}H NMR: δ 4.09, 4.07 (2CO$_2$C*H*$_2$CH$_3$, 2 q, 4 H), 2.58 (CH$_2$, t, J = 7 Hz, 2 H), 2.29 (CH$_2$, t, J = 7 Hz, 2 H), 1.96 (CH$_3$, s, 3 H), 1.7 (CH$_2$CH$_2$, m, 4 H), 1.31 (OCH$_2$C*H*$_3$, t, 3 H), 1.22 (CO$_2$CH$_2$C*H*$_3$, t, 3 H). ^{13}C NMR: δ 173.31 (CO$_2$Et), 155.08 (C-2), 153.46 (C-5), 112.40 (C-4), 70.20 (O*C*H$_2$CH$_3$), 60.25 (CO$_2$*C*H$_2$CH$_3$), 33.86, 28.11, 26.27, 24.33 (4, CH$_2$), 14.94, 14.17 (2 CO$_2$CH$_2$*C*H$_3$), 9.95 (CH$_3$). MS (m/e): 256 (MH$^+$), 128 (MH$^+$ – CH$_3$-(CH$_2$)$_3$CO$_2$Et).

2-(5-Oxopentyl)-4-methyl-5-ethoxyoxazole (16b, n = 4). The reaction was performed on a 5.1-mmol scale (1.3 g of **11b**). Workup by addition of 3 mL of EtOH followed by 7 mL of saturated solution of sodium potassium tartarate. After 1 h at room temperature, the reaction mixture was extracted with ethyl acetate (6 × 30 mL). The crude residue, obtained after drying and evaporation of the solvent, was chromatographed (ethyl acetate) to yield **16b** (n = 4) as a yellowish oil (85%, 0.96 g). ^{1}H NMR: δ 9.76 (CHO, t, J = 1.5 Hz, 1 H), 4.10 (OC*H*$_2$CH$_3$, q, 2 H), 2.63 (CH$_2$, t, J = 7 Hz, 2 H), 2.47 (CH$_2$, dt, J = 7, 1.5 Hz, 2 H), 1.99 (CH$_3$, s, 3 H), 1.7 (CH$_2$CH$_2$, m, 4 H), 1.34 (OCH$_2$C*H*$_3$, t, 3 H). ^{13}C NMR: δ 201.84 (CHO), 154.89 (C-2), 153.53 (C-5), 112.44 (C-4), 70.24 (O*C*H$_2$CH$_3$), 43.42, 28.18, 26.28, 21.47 (4 CH$_2$), 15.00 (OCH$_2$*C*H$_3$), 9.99 (CH$_3$). MS (m/e): 212 (MH$^+$).

General Procedure. *N*-(3-Carbethoxypropanoyl)-ω-aminoacetophenone (11a, n = 2). A solution of 2-aminoacetophenone hydrochloride (2 g, 11.6 mmol) in dry pyridine (12 mL) was stirred at 0 °C in a flame-dried three-neck flask under Ar. An equivalent amount of glutaric acid mono acid chloride monoethyl ester was added dropwise during 25 min. The ice bath was removed, and the solution was stirred at 25 °C for 3–4 days. A white precipitate had formed in the brownish solution. Chloroform (20 mL) was added to the solution followed by water (4 mL). The precipitate dissolved, and the aqueous layer was extracted with CHCl$_3$ (2 × 20 mL). The combined organic phases were washed with 5% aqueous NaHCO$_3$ (to pH = 8) and dried. The pyridine was removed under high vacuum at 70 °C, affording a brownish solid (92%). Crystallization from ethanol/ether yielded colorless needles, mp 77 °C. ^{1}H NMR: δ 7.96 (Ph-*o*, 2 H), 7.60 (Ph-*p*, 1 H), 7.48 (Ph-*m*, 2 H), 6.82 (br s, NH), 4.75 (CH, d, J = 4 Hz, 1 H), 4.13 (CO$_2$C*H*$_2$CH$_3$, q, J = 7 Hz, 2 H), 2.66 (CH$_2$CH$_2$, m, 4 H), 1.23 (CO$_2$CH$_2$C*H*$_3$, t, J = 7 Hz, 3 H). MS (m/e): 264 (MH$^+$), 246 (MH$^+$ – H$_2$O), 218 (MH$^+$ – EtOH).

***N*-(4-Carbomethoxybutanoyl)-2-aminoacetophenone (11a, n = 3):** 94% yield. Crystallization from CHCl$_3$/petroleum ether (40–60 °C) yielded white feathers, mp 64–5 °C. ^{1}H NMR: δ 6.64 (br s, NH), 4.76 (CH, d, J = 4.5 Hz, 1 H), 3.68 (MeO, s, 3 H), 2.41 (CH$_2$, t, J = 7.5 Hz, 2 H), 2.37 (CH$_2$, t, J = 7.5 Hz, 2 H), 2.01 (CH$_2$, quintet, J = 7.5 Hz, 2 H). MS (m/e): 264 (MH$^+$ – H$_2$O), 232 (MH$^+$ – MeOH). Anal. Calcd for C$_{14}$H$_{17}$NO$_4$: C, 63.86; H, 6.51. Found: C, 63.59; H, 6.45.

General Procedure. 2-(3-Carbomethoxypropyl)-5-phenyloxazole (12a, n = 3). A solution of keto amide (**11a**, n = 3) (3.3 g, 12.5 mmol) and P$_2$O$_5$ (4 equiv) in dry CHCl$_3$ (25 mL) in a flame-dried three-neck flask under Ar was heated under reflux for 2 days. Ice was added to the cold solution followed by neutralization with 10% aqueous NaHCO$_3$. The aqueous phase was extracted with CHCl$_3$ (3 × 20 mL) and dried, and the solvent was removed. The oily residue was chromatographed (ethyl acetate/hexane, 1:1) to afford a solid product (2.84 g, 92%). Crystallization from EtOH yielded **12a** as a white solid, mp 53 °C. ^{1}H NMR: δ 7.61 (Ph-*o*, 2 H), 7.41 (Ph-*m*, 2 H), 7.30 (Ph-*p*, 1 H), 7.22 (CH, s, 1 H), 3.69 (OMe, s, 3 H), 2.91 (CH$_2$, t, J = 7.5 Hz, 2 H), 2.48 (CH$_2$, t, J = 7.5 Hz, 2 H), 2.17 (Ch$_2$, quintet, J = 7.5 Hz, 2 H). MS (m/e): 245 (M$^+$), 214 (M – OMe), 186 (M – CO$_2$Me), 172 (M – CH$_2$CO$_2$Me). Anal. Calcd for C$_{14}$H$_{15}$NO$_3$: C, 68.55; H, 6.16. Found: C, 68.85; H, 5.97.

2-(2-Carbethoxyethyl)-5-phenyloxazole (12a, n = 2) was obtained as a colorless oil, yield 76%. ^{1}H NMR: δ 7.60 (PH-*o*, 2 H), 7.40 (Ph-*m*, 2 H), 7.30 (Ph-*p*, 1 H), 7.21 (CH, s, 1 H), 4.18 (CO$_2$C*H*$_2$CH$_3$, t, 3 H), 3.16 (CH$_2$, t, J = 7 Hz, 2 H), 2.86 (CH$_2$, t, J = 7 Hz, 2 H), 1.26 (CO$_2$CH$_2$C*H*$_3$, t, 3 H). ^{13}C NMR: δ 171.86 (CO$_2$Et), 162.68 (C-2), 151.21 (C-5), 128.81 (Ph-*m*), 128.17 (Ph-*p*), 124.01 (Ph-*o*), 121.82 (C-4), 60.71 (CO$_2$*C*H$_2$CH$_3$), 31.09, 23.58 (CH$_2$CH$_2$), 14.13 (CO$_2$CH$_2$*C*H$_3$). MS (m/e): 246 (MH$^+$), 200 (MH$^+$ – EtOH).

General Procedure. 3-(5′-Phenyl-2′-oxazolyl)propanoic Acid (13a, n = 2). A solution of oxazole **12a** (n = 2) (1.65 g, 6.7 mmol) and TMSI (3 equiv) in dry acetonitrile (20 mL) in a flame-dried three-neck flask was heated under reflux in an inert atmosphere for 22 h. The reddish solution was poured on water (3 mL) at 0 °C. Sodium thiosulfate was added till the disappearance of the red color. The aqueous solution was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried and the solvent was removed to yield **13** (n = 2) as a beige solid (1.21 g, 83%). The product was crystallized from CHCl$_3$ to give colorless cubic crystals (mp 152–153 °C). ^{1}H NMR: δ 7.53 (Ph-*o*, 2 H), 7.34 (Ph-*m*, 2 H), 7.26 (Ph-*p*, 1 H), 7.19 (CH, s, 1 H), 3.11 (CH$_2$, t, J = 6.5 Hz, 2 H), 2.81 (CH$_2$, t, J = 6.5 Hz, 2 H). ^{13}C NMR: δ 175.54 (CO$_2$H), 162.76 (C-2), 151.42 (C-5), 128.85 (Ph-*m*), 128.40 (Ph-*p*), 127.79 (Ph-*i*), 124.09 (Ph-*o*), 121.30 (C-4), 30.79 (CH$_2$), 23.80 (CH$_2$). IR (KBr pellet): ν max 2900–2500 (OH), 1700 (C=O), 1540(C=N) cm^{-1}. MS (m/e): 218 (MH$^+$),

200 ($MH^+ - H_2O$). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10. Found: C, 66.02; H, 4.87.

4-(5′-Phenyl-2′-oxazolyl)butanoic acid (13b, *n* = 3): yield 86%. Crystallization from $CHCl_3$/petroleum ether, mp 168 °C. ^1H NMR: δ 7.61 (Ph-*o*, 2 H), 7.42 (Ph-*m*, 2 H), 7.35 (Ph-*p*, 1 H), 7.27 (CH, s, 1 H), 2.97 (CH_2, t, J = 7 Hz, 2 H), 2.50 (Ch_2, t, J = 7 Hz, 2 H), 2.17 (CH_2, quintet, J = 7 Hz, 2 H). MS (*m/e*): 232 (MH^+), 214 ($MH^+ - H_2O$).

***N′*-Carbethoxy-3-(5′-phenyl-2′-oxazolyl)propanoic Hydrazide (14b, *n* = 3)**. A suspension of the acid **13b** (*n* = 3) (0.1 g, 0.47 mmol) in dry CH_2Cl_2 (3.5 mL) in a flame-dried three-neck flask was stirred in an inert atmosphere at 0 °C. Dry pyridine was added (0.04 mL, 1 equiv) followed by slow dropwise addition of $SOCl_2$ (0.058 mL, 1.6 equiv). The solution turned clear during the addition. The solution was stirred at 0 °C for 15 min. Dry ethyl carbazate (0.052 g, 1 equiv) and DMAP (0.055 g, 0.9 equiv) were added. The ice bath was removed, and the reaction was left overnight at rt. After removal of the solvent the mixture was chromtographed (ethyl acetate and then ethyl acetate/hexane/methanol, 2:1:1) to yield product **14**, *n* = 3, as a colorless oil (0.023 g, 15%). ^1H NMR: δ 8.65 (NH, br s), 7.58 (Ph-*o*, 2 H), 7.39 (Ph-*m*, 2 H), 7.32 (Ph-*p*, 2 H), 7.19 (CH, s, 1 H), 7.16 (NH, br s), 4.18 ($NCO_2CH_2CH_3$, q, 2 H), 2.96 (CH_2, t, J = 6.5 Hz, 2 H), 2.38 (CH_2, t, J = 6.5 Hz, 2 H), 2.16 (CH_2, quintet, J = 6.5 Hz, 2 H), 1.24 ($NCO_2CH_2CH_3$, t, 3 H). ^{13}C NMR: δ 172.24 (NHC=O), 163.51 (C-2), 156.59 ($HNCO_2Et$), 151.22 (C-5), 128.83 (Ph-*m*), 128.28 (Ph-*p*), 124.74 (Ph-*o*), 121.50 (C-4), 62.16 ($CO_2CH_2CH_3$), 32.53, 26.72, 22.69 ($CH_2CH_2CH_2$), 14.54 ($CO_2CH_2CH_3$). MS (*m/e*): 318 (MH^+), 272 (MH^+ – EtOH).

***N′*-Carbethoxy-2-(5′-phenyl-2′-oxazolyl)ethanoic Hydrazide (14a, *n* = 2)**. To a solution of acid **13a** (*n* = 2) (0.217 g, 1 mmol) and ethyl carbazate (0.104 g, 1 mmol) in freshly distilled acetonitrile, an equivalent amount of DCC (0.206 g) was added at room temperature. A thick white precipitate was formed within $^1/_2$ h. After 4 h no starting material was left. The white precipitate was filtered and washed with chloroform. After removal of the solvent the solid residue was chromatographed (ethyl acetate) to yield product **14a** (*n* = 2) as a white solid (0.182 g, 65%). Further purification by crystallization from ethyl acetate or by sublimation (150 °C (0.02 mmHg)) gave **14**, mp 136 °C. ^1H NMR: δ 8.69 (NH, br s), 7.57 (Ph-*o*, 2 H), 7.39 (Ph-*m*, 2 H), 7.30 (Ph-*p*, 1 H), 7.10 (NH, br s), 4.17 ($NCO_2CH_2CH_3$, q, 2 H), 3.20 (CH_2, t, J = 6.5 Hz, 2 H), 2.81 (CH_2, t, J = 6.5 Hz, 2 H), 1.25 ($NCO_2CH_2CH_3$, t, 3 H). ^{13}C NMR: δ 171.35 (NHCO), 162.96 (C-2), 156.65 (NCO_2Et), 151.36 (C-5), 128.81 (Ph-*m*), 128.31 (Ph-*p*), 127.74 (Ph-*i*), 124.00 (Ph-*o*), 121.33 (C-4), 62.12 ($CO_2CH_2CH_3$), 30.22 (CH_2), 23.36 (CH_2), 14.31 (CH_3). MS (*m/e*): 304 (MH^+). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.30 H; 5.65. Found: C, 58.39; H, 5.48. IR (KBr pellet): ν max 3281, 3211 (NH), 1721 ($NHCO_2Et$), 1697 (NHC=O), 1697 (C=N) cm^{-1}.

General Procedure. 2,3,5,6-Tetrahydro-5-oxo-2-benzoyl-3-carbethoxy-1,2,4-triazolo[2,3-*a*]pyrrole (21a, *n* = 1). A solution of hydrazide **14a** (*n* = 1) (0.07 g, 0.23 mmol) and (diacetoxyiodo)benzene (0.074 g, 0.23 mmol) in dry benzene (2 mL) was heated under reflux for 2 h. Removal of the solvent and chromatography (ethyl acetate) afforded the product **21a** (*n* = 1) as a colorless oil (0.028 g, 40%). ^1H NMR: δ 8.17 (Ph-*o*, 2 H), 7.65 (Ph-*p*, 1 H), 7.53 (Ph-*m*, 2 H), 7.24 (CH, t, J = 1.5 Hz, 1 H), 4.31 ($NCO_2CH_2CH_3$, AB q split into q, J = 10, 7 Hz, 2 H), 3.13, 2.93 ($COCH_2$, AB q split into dd, J = 18.75, 8.75, 3.75 Hz, 2 H), 2.90–2.84 (CH_2C=N, m, 2 H), 1.32 ($NCO_2CH_2CH_3$, t, 3 H). ^{13}C NMR: δ 189.76 (C=O), 164.19 (NC=O), 163.23 (C=N), 156.39 (NCO_2Et), 134.18 (Ph-*p*), 133.69 (Ph-*i*), 129.35 (Ph-*o*), 128.86 (Ph-*m*), 93.99 (CH), 64.14 ($NCO_2CH_2CH_3$), 32.97 (CH_2CO), 19.27 (CH_2C=N), 14.25 ($NCO_2CH_2CH_3$). IR: ν max (neat) 1699 (NC=O), 1652 (C=N) cm^{-1}. MS (*m/e*): 302 (MH^+), 230 (MH^+ – HCO_2Et). HRMS: calcd for $C_8H_{10}N_3O_3$ (M – PhCO) 196.0719, found 196.0731.

2,3,5,6,7,8-Hexahydro-5-oxo-2-benzoyl-3-carbethoxy-1,2,4-triazolo[2,3-*a*]pyridine (21b, *n* = 2). The product was obtained as a colorless oil (61% yield). ^1H NMR: δ 8.18 (Ph-*o*, 2 H), 7.64 (Ph-*p*, 1 H), 7.52 (Ph-*m*, 2 H), 6.94 (CH, s, 1 H), 4.29 ($NCO_2CH_2CH_3$, AB q split to q, J = 10, 7 Hz, 2 H), 2.90–2.81 (H_2CC=N, m, 2 H), 2.79 (CH, ddd, J = 11, 6, 3.5 Hz, 1 H), 2.62 (CH, ddd, J = 11, 4.2, 3.5 Hz, 1 H), 2.15–2.00 (CH_2, m, 2 H), 1.30 ($NCO_2CH_2CH_3$, t, 3 H). ^{13}C NMR: δ 190.06 (C=O), 164.79 (NC=O), 157.08 (C=N), 156.76 (NCO_2Et), 134.12 (Ph-*p*), 133.83 (Ph-*i*), 129.35 (Ph-*o*), 128.83 (Ph-*m*), 84.36 (CH), 63.94 ($NCO_2CH_2CH_3$), 32.64 (CH_2CO), 25.22 ($CO_2CH_2CH_2$), 18.77 (CH_2C=N), 14.27 ($NCO_2CH_2CH_3$). IR: ν max (neat) 1717 br (C=O), 1640 (C=N). MS (*m/e*): 316 (MH^+), 244 (MH^+ – HCO_2Et). HRMS: calcd for $C_{13}H_{11}N_3O_2$ (M – HCO_2Et) 241.0853, found 241.0842.

2-(4′-Bromobutyl)-5-ethoxyoxazole (19). To a mixture of 5-bromopentanenitrile (2 g, 12.3 mmol) and BF_3·ether (1.23 mL, 10 mmol) in a flame-dried system under Ar was added dropwise ethyl diazoacetate (1.14 g, 10 mmol) at 0 °C (maximum solution temperature was 5 °C). The ice bath was removed, and the reaction mixture was stirred at room temperature for 20 h at which time the mixture became dark red. An equivalent of triethylamine was added. This mixture was loaded on a column and separated by ethyl acetate/hexane (1:3) to yield **19** as an an orange oil (0.74 g, 30%). ^1H NMR: δ 5.91 (H-4, s, 1 H), 4.04 (OEt, q, J = 7 Hz, 2 H), 3.38 (CH_2Br, t, J = 7 Hz, 2 H), 2.64 (CH_2-oxazole, t, J = 7 Hz, 2 H), 1.9 (CH_2CH_2, m, 4 H), 1.38 (OEt, t, J = 7 Hz, 3 H). ^{13}C NMR: δ 159.30 (C-5), 154.52 (C-2), 98.69 (C-4), 67.80 (OEt), 32.86 (CH_2Br), 31.72 (CH_2-oxazole), 27.17, 25.19 (CH_2CH_2), 14.39 (OEt). MS (*m/e*): 250, 248 (MH^+), 168 (MH^+ – HBr). Anal. Calcd for $C_9H_{14}NO_2Br$: C, 43.54; H, 5.65. Found: C, 43.80; H, 5.81.

2-(4′-Thiocyanatobutyl)-5-ethoxyoxazole (20). A solution of **19** (0.15 g, 0.6 mmol), dry KSCN (0.058 g, 0.6 mmol), and a catalytic amount of NaI (0.008 g) in dry acetone (3 mL) was heated under reflux for 2.5 h under Ar atmosphere. A thick white precipitate formed. The solution was filtered, and the solid was washed with acetone and chloroform. Purification by chromatography (ethyl acetate/hexane, 1:2) yielded the product as a yellowish oil (0.12 g, 88%). ^1H NMR: δ 5.94 (H-4, s, 1 H), 4.07 (OEt, q, J = 7 Hz, 2 H), 2.95 ($NCSCH_2$, br t, J = 6 Hz, 2 H), 2.69 (CH_2-oxazole, br t, J = 6 Hz, 2 H), 1.9 (CH_2CH_2, m, 4 H), 1.41 (OEt, t, J = 7 Hz, 3 H). ^{13}C NMR: δ 159.72 (C-5), 154.28 (C-2), 111.94 (N=CS), 99.00 (C-4), 68.05 (OEt), 33.60 (CH_2-oxazole), 29.66 ($NCSCH_2$), 27.38, 24.99 (CH_2CH_2), 14.51 (OEt). MS (*m/e*): 227 (MH^+), 200 (MH^+ – HCN), 168 (MH^+ – HSCN). HRMS: calcd for $C_{10}H_{14}N_2O_2S$ 226.0776, found 226.0748. Heating oxazole **20** (0.043 g, 0.2 mmol) in dry toluene (1 mL) in the presence of BF_3·etherate (0.005 mL, 0.04 mmol) for 7 h yielded after chromatography (ethyl acetate/hexane, 1:1) **ethyl *N*-(5-thiocyanatopentanoyl)glycinate (20a)** as a yellow oil (0.023 g, 48%). ^1H NMR: δ 6.07 (NH, br s, 1 H), 4.22 (OEt, q, 2 H), 4.03 (CH, d, J = 5.25 Hz, 1 H), 2.98 ($NCSCH_2$, t, 2 H), 2.32 (CH_2, t, 2 H), 1.85 (CH_2CH_2, m, 4 H), 1.30 (OEt, t, 3 H). MS (*m/e*): 244 (MH^+).

2-Methyl-2-carbethoxycyclohexa[*d*]-2,7a-dihydrooxazole (27). A solution of aldehyde **16b** (0.3 g, 1.42 mmol) in dry toluene (5 mL) in an inert atmosphere was heated under reflux for 3 h. The solvent was evaporated and the oily residue was chromatographed on silica gel (CH_2Cl_2/acetone, 20:1) to afford **27** as a colorless oil (0.23 g, 78%) as a mixture of two stereoisomers (~1:2). ^1H NMR: δ (major isomer) 4.61 (H-7a, dd, J = 10.5, 6.5 Hz, 1 H), 4.20, 4.18 ($CO_2CH_2CH_3$, AB q split into q, J = 10.5, 7 Hz, 2 H), 2.72 (H-4 eq, dm, J = 14.5 Hz, 1 H), 2.5–1.3 (H-4–H-7, m, 7 H), 1.57 (Me, s, 3 H), 1.27 ($CO_2CH_2CH_3$, t, J = 7 Hz, 3 H); (minor isomer) 4.66 (H-7a, dd, J = 10.5, 6.5 Hz, 1 H), 4.16, 4.14 ($CO_2CH_2CH_3$, AB q split into q, J = 10.5, 7 Hz, 2 H), 2.72 (H-4 eq, dm, J = 14.5 Hz, 1 H), 2.5–1.3 (H-4–H-7, m, 7 H), 1.67 (Me, s, 3 H), 1.25 ($CO_2CH_2CH_3$, t, J = 7 Hz, 3 H) ^{13}C NMR: δ (major isomer) 175.84 (C=N), 170.31 (CO_2Et), 108.28 (C-2), 85.26 (C-7a), 61.52 ($CO_2CH_2CH_3$), 34.71 (C-7), 29.99 (C-4), 26.41 (C-5),[a] 23.75 (CH_3), 22.57 (C-6),[a] 13.94 ($CO_2CH_2CH_3$); (minor isomer) 176.74 (C=N), 170.31 (CO_2Et), 108.08 (C-2), 85.43 (C-7a), 61.47 ($CO_2CH_2CH_3$), 35.34 (C-7), 29.94 (C-4), 26.18 (C-5),[b] 24.59 (CH_3), 22.45 (C-6),[b] 13.94 ($CO_2CH_2CH_3$). IR (neat): ν max 1735 (C=O), 1660 (C=N) cm^{-1}. MS (*m/e*): 212 (MH^+), 138 (MH^+ – HCO_2Et). HRMS: calcd for $C_8H_{12}NO$ (M – CO_2Et) 138.0919, found 138.0927. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 63.74; H, 8.27. Found: C, 62.44; H, 7.95.

2-Methyl-2-carbethoxycyclohexa[*d*]-2,7a-dihydrothiazole (29). A BuLi solution (1.6 M, 0.102 mL, 0.014 mmol) was added to a hexamethyldisilathiane[9] solution (0.2 g, 1.42 mmol) in freshly distilled THF (5 mL) in a flame-dried three-necked flask under Ar at 0 °C. The solution was stirred for 0.5 h at 0 °C, and aldehyde **16b** (0.3 g, 1.42 mmol) in THF (3 mL) was added. The mixture was stirred at 14–20 °C for 14 h, the solvent was evaporated, and

the oily residue was chromatographed (CH_2Cl_2/acetone, 25:1) to afford **29** as a colorless oil (0.16 g, 51%) as a mixture of two stereoisomers (~1:1). ^1H NMR: δ (isomer I) 4.19 (H-7a, dd, J = 12, 5.5 Hz, 1 H), 4.25, 3.97 ($CO_2CH_2CH_3$, AB q split into q, J = 10.5, 7 Hz, 2 H), 2.89 (H-4 eq, dm, J = 13.5 Hz, 1 H), 2.4–1.4 (H-4–H-7a, m, 7 H), 1.81 (Me s, 3 H), 1.27 ($CO_2CH_2CH_3$, t, J = 7 Hz, 3 H); (isomer II) 4.16 (H-7a, dd, J = 12, 5.5 Hz, 1 H), 4.21, 3.95 ($CO_2CH_2CH_3$, AB q split into q, J = 10.5 7 Hz, 2 H), 2.89, (H-4 eq, dm, J = 13.5 Hz, 1 H), 2.4-1.4 (H-4–H-7a, m, 7 H), 1.87 (Me, s, 3 H), 1.25 ($CO_2CH_2CH_3$, t, J = 7 Hz, 3 H). ^{13}C NMR (isomer I): δ 176.32 (C=N), 171.66 (CO_2Et), 86.61 (C-2), 61.60 ($CO_2CH_2CH_3$), 60.25 (C-7a), 37.61 (C-7), 32.64 (C-4), 27.76[a] (C-5), 26.76[a] (C-6), 25.14 (CH_3), 13.88 ($CO_2CH_2CH_3$); (isomer II) 176.43 (C=N), 172.03 (CO_2Et), 87.68 (C-2), 61.60 ($CO_2CH_2CH_3$), 59.78 (C-7a), 37.96 (C-7), 32.25 (C-4), 29.90[b] (C-5), 27.19[b] (C-6), 25.46 (CH_3), 13.88 ($CO_2CH_2CH_3$). IR (neat): ν max 1725 (C=O), 1665 (C=N) cm^{-1}. MS (m/e): 228 (MH^+), 154 (MH^+-HCO_2Et). HRMS: calcd for $C_9H_{12}NS$ (M – CO_2Et) 154.0690, found 154.0661. Anal. (mixture of isomers) Calcd for $C_{11}H_{17}NO_2S$: C, 58.13; H, 7.54. Found: C, 58.23; H, 7.48.

2-Methyl-2-carbethoxycyclopenta[*d*]-2,6a-dihydrothiazole (28). Prepared from **16a**, n = 3, as described above. The two isomers were obtained as a colorless oil (42% yield, ratio ~1:1); after chromatography (ether/hexane, 6:1) each stereoisomer was isolated. ^1H NMR: δ (isomer I) 4.49 (H-6, dd, J = 11.5, 7 Hz, 1 H), 4.25 ($CO_2CH_2CH_3$, q, J = 7 Hz, 2 H), 2.5–2.0, 1.65–1.55 (H-4–H-6, m, 6 H), 1.83 (Me, s, 3 H) 1.30 ($CO_2CH_2CH_3$, t, 3 H). ^{13}C NMR: δ 185.68 (C=N), 172.04 (CO_2Et), 98.30 (C-2), 61.77 ($CO_2CH_2CH_3$), 60.41 (C-6a), 32.12 (C-6), 27.91 (C-4), 25.06 (C-5), 24.91 (CH_3), 14.06 ($CO_2CH_2CH_3$). ^1H NMR: δ (isomer II) 4.55 (H-6a, dd, J = 12, 7 Hz, 1 H), 4.20 ($CO_2CH_2CH_3$, AB q split into q, J = 11, 7 Hz, 2 H), 2.61 (H-4, eq, ddm, J = 17.5, 10 Hz, 1 H), 2.5–1.6 (H-4–H-6, m, 5 H), 1.92 (CH_3, s, 3 H), 1.28 ($CO_2CH_2CH_3$, t, J = 7 Hz, 3 H). ^{13}C NMR: δ 188.77 (C=N), 171.38 (CO_2Et), 95.71 (C-2), 62.42 (CO_2CHCH_3), 61.73 (C-6a), 32.10 (C-6), 27.25 (C-4), 25.60 (C-5), 25.12 (CH_3), 14.00 ($CO_2CH_2CH_3$). IR (neat): ν max 1725 br (C=O), 1655 br (C=N) cm^{-1}. MS (m/e): 214 (MH^+), 140 (MH^+ – HCO_2Et). HRMS: calcd for $C_7H_{10}NS$ (M – CO_2Et) 140.0534, found 140.0555.

2-Methyl-1,2-dicarbethoxycyclopenta[*d*]-2,6a-dihydroimidazole (30). A solution of aldehyde **16a** (0.14 g, 0.71 mmol), ethyl carbamate (0.15 g, 2.4 equiv), and a catalytic amount of p-toluenesulfonic acid (0.01 g) in benzene (6 mL) was heated under reflux in a Dean–Stark system for 2.5 h. The colorless solution turned black. The reaction mixture was filtered through basic alumina. The solvent was removed and the dark oil residue was sublimed to yield **30** as a thick yellow oil at 160 °C (2 mmHg) (0.082 g, 43%). The product was obtained as a mixture of four isomers. ^1H NMR: δ 4.86, 4.79, 4.70, 4.62 (H-6, four dd, J = 11, 7.5 Hz, 1 H), 4.15 ($CO_2CH_2CH_3$, m, 4 H), 2.50–2.10 ($CH_2CH_2CH_2$, m, 6 H), 1.91, 1.83, 1.77, 1.73 (Me, s, 3 H), 1.30 ($CO_2CH_2CH_3$, m, 6 H). ^{13}C NMR: δ 186.34, 184.74, 184.61 (C=N), 169.47, 169.20 (CO_2Et), 154.52, 152.76 (NCO_2Et), 126.32, 124.72 (C-2), 99.81, 99.14 (C-6a), 72.08, 70.97, 69.17, 68.44 ($NCO_2CH_2CH_3$), 61.76, 61.56, 61.33, 61.17 ($CO_2CH_2CH_3$), 30.80–21.11 ($CH_2CH_2CH_2$), 14.55–14.00 ($NCO_2CH_2CH_3$, $CO_2CH_2CH_3$). IR (neat): ν max 1747 (CO_2Et), 1709 (NCO_2Et), 1674 (C=N) cm^{-1}. MS: 269 (MH^+), 195 (MH^+ – CO_2Et). HRMS: calcd for $C_{10}H_{15}N_2O_2$ (M – CO_2Et) 195.1129, found 195.1196.

2-Methyl-1,2-dicarbethoxycyclohexano[*d*]-2,7a-dihydroimidazole (31). The product obtained, following the above procedure, was a mixture of **31** and **27** in a ratio of 18:82 according to GC/MS. Complete separation of **31** by flash chromatography was not successful. The data given below are for a mixture enriched in **31**. Total yield 41%. ^1H NMR: δ 4.48, 4.40, 4.33, 4.25 (H-7a, 4 dd, J = 1.1, 6 Hz, 1 H), 2.4–1.4 (H-4–H-7, m, 7 H), 1.82, 1.77, 1.71, 1.66 (Me, 4 s, 3 H), 1.25 ($CO_2CH_2CH_3$, $NCO_2CH_2CH_3$, m, 6 H). ^{13}C NMR: δ 176.89, 176.74 (C=N), 170.39 (CO_2Et), 108.45 (C-2), 67.51, 66.44, 66.42, 65.82 (C-7a), 61.72, 61.70, 61.27, 61.12 (CO_2Et, NCO_2Et), 35.42, 33.70, 32.71, 31.34, 26.61, 26.26, 24.67, 23.11, 22.53, 21.88 (C-7–C-4), 14.54, 14.37 (CO_2Et, NCO_2Et). MS (m/e): 283 (MH^+), 209 (MH^+ – HCO_2Et). IR (neat): ν max 1735 (CO_2Et), 1700 (NCO_2Et), 1655 (C=N) cm^{-1}.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **21a**, **21b**, **28a**, **28b**, and **30** (10 pages). Ordering information is given on any current masthead page.

Organoselenium- and Proton-Mediated Cyclization Reactions of Allylic Amides and Thioamides. Syntheses of 2-Oxazolines and 2-Thiazolines

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A variety of allylic amides and thioamides were treated with phenylselenenyl bromide in chloroform to give, via 5-exo cyclization, 2-oxazolines and 2-thiazolines, respectively, carrying a (phenylselenenyl)methyl substituent in the 5-position. In some cases (*N*-crotyl- and *N*-cinnamylamides/thioamides), dihydro-1,3-oxazines/-thiazines were formed via 6-endo cyclization. The phenylselenenyl group of the cyclofunctionalization products was slowly eliminated by treatment with *m*-chloroperbenzoic acid to introduce unsaturation in the resulting oxazoline/thiazoline. Reductive removal of the phenylselenenyl group was effected by treatment with triphenyltin hydride. This reaction was sometimes accompanied by a rearrangement of the heterocyclic ring. Proton-induced cyclizations of allylic thioamides to give 2-thiazolines was slowly but efficiently effected in boiling toluene containing a catalytic amount of *p*-toluenesulfonic acid.

Introduction

Organoselenium-mediated cyclization reactions have been very useful in organic syntheses over the last decade. Conceptually, the reactions involve addition of electrophilic selenium to an unsaturated site in the molecule, followed by intramolecular attack by a suitably positioned nucleophile. Cyclization of unsaturated alcohols, thiols, carboxylic acids, and amine derivatives are all well-represented in the literature. In addition, it is possible, with certain substrates, to form new carbon–carbon bonds in the reaction.[1]

Ethylurethanes of 4-pentenamines and 5-hexenamines, when treated with phenylselenenyl chloride, gave pyrrol-

(1) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; p 127.

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