hold some promise for supramolecular catalysis. The high polarity of water as well as the high ionic strength around the charges will decrease the favorable electrostatic interactions; in addition, the necessary desolvation of both host and nucleophile or base will limit the achievable catalytic efficiency.

Experimental Section

Complexation constants with CP66 were determined as described previously[2] using NMR titrations in D_2O at pH = 7.0, 300 ± 5 K, with guest compounds 1–7 usually starting with concentrations of $[G] = 1.0 \times 10^{-3}$ M and $[CP66] = 8.8 \times 10^{-3}$ M. The equilibrium constants K (in 10^{-3} M^{-1} units) were as follows (before/after correction for ionic strength): 1 (7.0/8.2); 2 (0.21/0.32); 3 (0.78/1.05); 4 (0.51/0.71); 6 (0.36/0.53); 7 (0.51/0.72). The titrations were performed by adding the host CP66 solution in usually six to eight increments; the nonlinear least-squares curve fitting[2] of the observed ^{1}H NMR shifts gave K and CIS values (Chart I) which agreed within usually ±5% (in K) for each measurement.

The salt effects on the complexation constant K for 1 with CP66 (Figure 1) were obtained from single measurements at concentrations appropriate for higher complexation degrees[2] by comparing the observed shift changes to the CIS values which were determined independently once for a given salt concentration, assuming a negligible CIS dependence on salt concentration. The ionic strength term calculated from [CP66] and added sodium chloride (see below) varied as follows: 0.09, 0.16, 0.20, 0.22, 0.25, 0.33, 0.41, 0.48; the corresponding K values (in 10^{-3} M^{-1} units) were: 5.97, 4.71, 4.13, 3.80, 3.45, 2.65, 2.06, 1.63. The ionic strength term $\sqrt{I}/(1+\sqrt{I})$ of the Debye–Hückel eq 1 was calculated for the sum of the ionic host CP66, the guest G, and the added electrolyte NaCl concentrations with $I = 0.5\sum_i c_i z_i^2$. For the free host H = CP66 (z = 4) we arrive at $I = 10[H]$; for the complex $H{\cdot}G$ (z = 3) at $I = 6[H{\cdot}G]$.

Kinetic Measurements. The reactions of 1-chloro-2,6-dinitrobenzoate (2) with either OH^- or NO_2^- were monitored by recording the UV extinction of the resulting phenoxide at 428 nm (Kontron Uvikon 860 UV/vis spectrometer, data registration, and procession with Apple and PC-compatible computers with suitable programs[16]. The temperature was kept constant (±0.02°) by thermostated cells; the compounds were added with syringes from stock solutions. The reactions were usually followed up to 10 half-lives and showed clean (pseudo-)first-order kinetics (with 2 + NO_2 after a 20-min induction period, see above). The elimination reaction from 8 was followed by the UV absorptions at 304.9 nm; independent measurements yielded the extinction coefficients = 3403 M^{-1} cm^{-1} for 8 and 7504 M^{-1} cm^{-1} for the product nitrostyrene; the Lambert–Beer measurements between 1 and 3 [IO^3M^{-1}] showed linear correlations coefficients of $r >$ 0.99.

Compounds were either prepared as described earlier (CP66[17]) or were commercially available (2–7) and recrystallized if their spectroscopic purity (NMR) was found to be <95%. The ester 8 was obtained from 2-(p-nitrophenyl)ethanol and methanesulfonyl chloride in pyridine using standard procedures.

Acknowledgment. This work was financially supported by the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt.

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Multipath Reactions between Intramolecularly Formed Oxazolium Salts and Nucleophiles[†,1]

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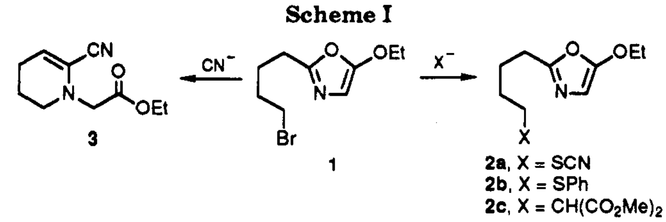
Reaction of 2-(4′-bromobutyl)-5-ethoxyoxazole (1) with nucleophiles led either to S_N2 substitution products or to products with a piperidine skeleton. The latter were shown to arise from an intramolecular ring closure to an oxazolium salt 7, which was faster in the presence of a catalytic amount of NaI and in a polar solvent and for which NMR evidence is presented. The further transformation of 7 to 3–6 apparently involves addition of nucelophiles to 7 to produce 4-oxazoline 8 which opens to azomethine ylide 9. Neutralization of the latter occurred either via a proton shift, an alkyl shift, or via trapping by a dipolarophile (electron poor or electron rich). FMO calculations explain the preferred regiochemistry observed during trapping of ylide **9b**.

Oxazolium salts are useful precursors to azomethine ylide intermediates[2,3] and have been generated by intermolecular alkylation of oxazoles. Intramolecular generation of oxazolium salts had not been reported until this study.[4] Although azomethine ylides have not been isolated to date, they are useful synthetic intermediates formed either by elimination of a positively charged group at the α-position of immonium salts or by tautomerization of isolable valence isomers of azomethine ylides.[5] Thus, conventional methods utilize immonium salts,[6] *N*-oxides of tertiary amines,[7] triazolines,[8] or aziridines[9] as azomethine ylide precursors.

Results

In the course of our studies on intramolecular Diels–Alder cycloadditions of heterodienophiles to oxazoles,[10] we prepared the 5-ethoxyoxazole 1 possessing an ω-bromoalkyl side chain in the 2-position. Such a compound is a potential starting point for intramolecular alkylation of the

Scheme I



† Dedicated to Albert I. Meyers on the occasion of his 60th birthday.

(1) Cycloadditions 50. For paper 49 see: Hassner, A.; Murthy, K.S.K. *Isr. J. Chem.* 1991, *31*, 239. Based in part on the Ph.D. thesis of B.F. at Bar-Ilan University.
(2) (a) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* 1986, *108*, 6433. (b) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* 1988, *110*, 3238. (c) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* 1988, *53*, 1876.
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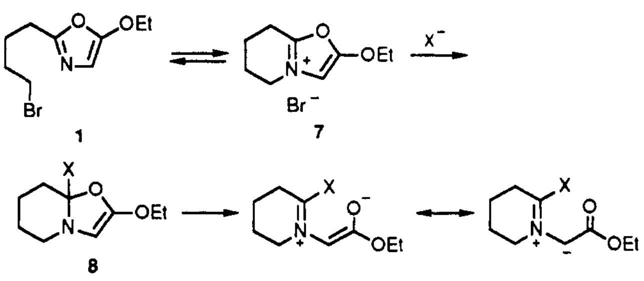
Scheme II



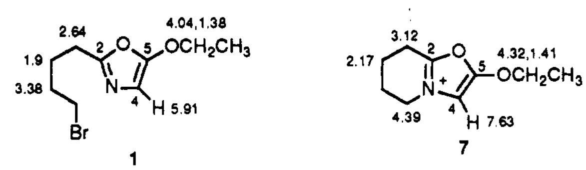
9a, X = CN
9b, X = pyrrolidine
9c, X = CH_2NO_2

oxazole nitrogen[11] leading to a bicyclic oxazolium salt, which should be trappable by nucleophiles. Our initial attempts in this direction were not very promising. Thus, heating of **1** with KSCN or with thiophenolate (thiophenol and triethylamine) in acetone in the presence of NaI led in good yield to the substitution products **2a** and **2b**, respectively (H-4 singlet at 5.94 and 5.93 ppm). The stronger nucleophiles, sodium or potassium dimethyl malonate, the former in DMF at 25 °C and the latter in THF at 56 °C, also afforded only substitution product **2c** in low yield (Scheme I).

However, when 2-(4′-bromobutyl)oxazole **1** was heated for 18 h with NaCN in acetone with a catalytic amount of NaI, an unexpected product was isolated in 90% yield. Although the mass spectrum showed the anticipated MH^+ peak as mass 195 and a cyano function was evident from IR (2220 cm^{-1}) and CMR (115.5 ppm), the other spectral data were inconsistent with an ethoxyoxazole or oxazoline structure and indicated the formation of 1-(carbethoxymethylene)-2-cyano-1,4,5,6-tetrahydropyridine.

The transformation of the ethoxyoxazole **1** to the cyano-1,4,5,6-tetrahydropyridine **3** is consistent with an intramolecular alkylation of the relatively nucleophilic oxazole nitrogen[11] by the bromoalkyl side chain to produce an oxazolium salt **7**. This is probably followed by a nucleophilic attack by cyanide ion to give the 4-oxazoline **8**. Ring opening of the latter, assisted by the unshared electron pair on nitrogen, leads to the carbonyl stabilized ylide **9**, which undergoes internal neutralization by transfer of the relatively acidic proton α to the immonium ion (Scheme II). The lower homologue 2-(3′-bromopropyl)-5-ethoxyoxazole did not undergo either intramolecular cyclization or trapping by nucleophiles and was recovered unchanged when heated with NaCN–NaI in acetone for 24 h.

Evidence for Oxazolium Salt Formation. In order to obtain further information about a possible intramolecular alkylation of **1** to generate an oxazolium salt **7**, we examined the PMR spectrum of **1** in $CDCl_3$, which confirmed a slow conversion of **1** to oxazolium salt **7**. Thus, after 48 h at 25 °C a new set of downfield peaks was present in addition to the peaks of **1** (see major chemical shift differences indicated on the structures below).



The intramolecular alkylation was followed kinetically in deuterioacetone or in deuterioacetonitrile (by integration of the PMR singlets of H-4 at 5.91 ppm for **1** and 7.63 ppm for **7**) in order to illuminate the role of NaI, the effect of solvent polarity and to obtain activation parameters. The results shown in Figures 1 and 2 and Table I indicate a first order reaction in the presence of a catalytic amount of NaI, with a half-life of 19 min at 78.3 °C. In the absence of NaI (half-life of 27 min), mixed first- and second-order kinetics apply (Figure 1), suggesting involvement of a species such as **10** (intermolecular alkylation). It is clear that NaI has an accelerating effect as does the more polar acetonitrile over acetone (Figure 2). Activation parameters, calculated using the Eyring equation, show a $\Delta G^\ddagger$ of approximately 25 kcal/mol. The greater stabilization of the

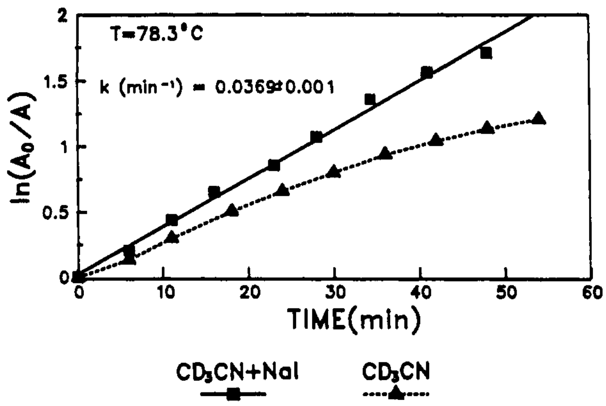


Figure 1.

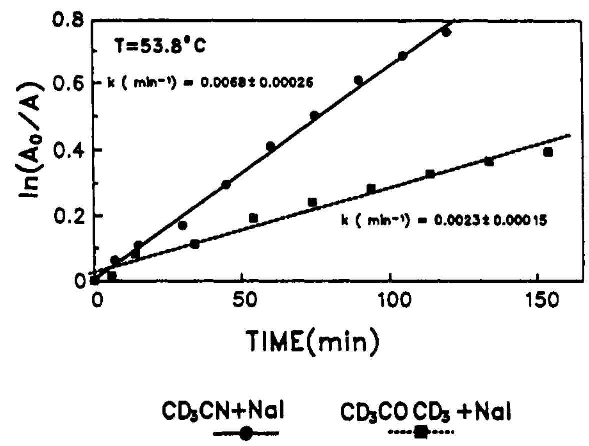


Figure 2.

Table I. Rate Constants and Activation Parameters for Intramolecular Alkylation 1 → 7

solvent	T (°C)	k (s^{-1})	$t^{1/2}$ (min)	ΔG^* (cal/mol^{-1})	ΔS^* (cal/mol^{-1}·K)
CD_3COCD_3	53.8 ± 0.5	3.8×10^{-5}	301	25.81 ± 0.06	
CD_3CN	53.8 ± 0.5	1.13×10^{-4}	102	25.10 ± 0.08	
CD_3CN	78.3 ± 0.5	6.2×10^{-4}	19	25.85 ± 0.06	-31 ± 6

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(6) (a) Huisgen, R.; Grashey, T.; Steingruber, E. *Tetrahedron Lett.* **1963**, 1441. (b) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4067. (c) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941. (d) Vedejs, E.; Dax, S.; Martinez, G. R.; McClure, C. K. *J. Org. Chem.* **1987**, *52*, 3470.
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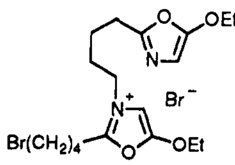
(10) Hassner, A.; Fischer, B. *J. Org. Chem.* **1991**, *56*, 3419.
(11) There are very few examples reported for intramolecular reactions of oxazoles in which the nitrogen serves as a nucleophile. See for instance: (a) Kjellin, G.; Sandström, J. *Acta Chem. Scand.* **1969**, *23*, 2879. (b) Corbett, D. F. *Chem. Commun.* **1981**, 803.



10

almost fully charged transition state in acetonitrile as compared to acetone is reflected by an almost 1 kcal difference of their $\Delta G^{\ddagger}$. The very negative entropy of activation (−31 cal/mol·K) may indicate that ring closure and charge development are almost completed in the transition state (Table I).

A reaction similar to that with CN^- was observed when 1 was heated with nitromethane–Et_3N in the presence of NaI. The structure of the product was deduced as the piperidine derivative 4 from spectral data. In this case transfer of the more acidic proton from **9c** led to an exocyclic double bond. The *E*-stereochemistry of the double bond was established by an NOE experiment (8% enhancement between the vinylic and carbethoxy methylene protons). Reaction of 1 with aqueous Na_2CO_3 in acetone led to the known[12] piperidone ester 5. The latter product also resulted when 1 was heated with EtOH–Et_3N and NaI catalyst. With 1 molar equiv. of NaI in refluxing acetone the product was 2-oxo-1-piperidineacetic acid (6).[13] In both of the latter cases small amounts of water apparently added to a primarily formed azomethine ylide, thus affording a piperidone; in the presence of a large amount of NaI hydrolysis of the ethyl ester 5 to the carboxylic acid 6 also took place.

Why Is a 4-Oxazoline Not Detected? Addition of nucleophiles (CN^-, nitromethide, hydroxide, ethoxide) onto the immonium carbon of the oxazolium salt 7 is expected to generate a 4-oxazoline 8. This can be followed by ring opening to an azomethine ylide 9. Such intermediates (8 and 9) were neither isolated nor detected when the reaction was followed by NMR. 4-Oxazolines are often unstable compounds, and those isolated in other studies have been heavily substituted by an electron-withdrawing group at either C-4,[14] C-5, or C-2[15]; their relative stability probably stems from a lowered basicity of the ring nitrogen. Indeed, our 4-oxazoline intermediates 8 possess an activating ethoxy group and neither an electron-withdrawing group nor a C-4 substituent and are therefore expected to undergo facile ring opening.

Trapping Azomethine Ylide Intermediates. Evidence for the existence of azomethine ylides was obtained in the past from trapping with dipolarophiles. Additions to carbonyl stabilized azomethine ylides were considered to be restricted to electron-deficient dipolarophiles.[2] In the case of 9, we were able to trap the dipole with both electron-poor (dimethyl acetylenedicarboxylate, DMAD) and electron-rich (acetone enamine) dipolarophiles. For instance, reaction of 1 with NaCN in the presence of DMAD afforded the fused pyrrole 11 in high yield. The formation of 11 can be explained as a result of a 1,3-dipolar cycloaddition which proceeds with loss of hydrogen cyanide (Scheme IV). Similarly, heating of 1 with pyrrolidine–acetone (in situ formation of acetone enamine) gave the pyrrole 12 according to Scheme V involving addition and formation of ylide **9b** and elimination of pyrrolidine. The structures of 11 and 12 are based on PMR and CMR spectra and in the case of 12 also on hetero COSY experiments.

FMO Calculations and the Regiochemistry of Trapping Ylide 9b with an Enamine. In order to ex-

(12) Hardegger, E.; Rostetter, C.; Seres, J.; Andreatta, R. *Helv. Chim. Acta* **1969**, *52*, 873.

(13) Engelsma, J. W.; Van der Meulen, J. D.; Slump, P.; Haagsma, N. *Lebebsm.-Wiss. Technol.* **1979**, *12*, 203.

(14) Vaultier, M., Mullick, G.; Carrié, R. *Can. J. Chem.* **1979**, *57*, 2876.

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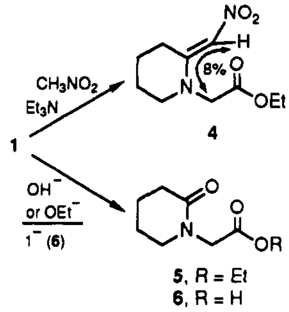
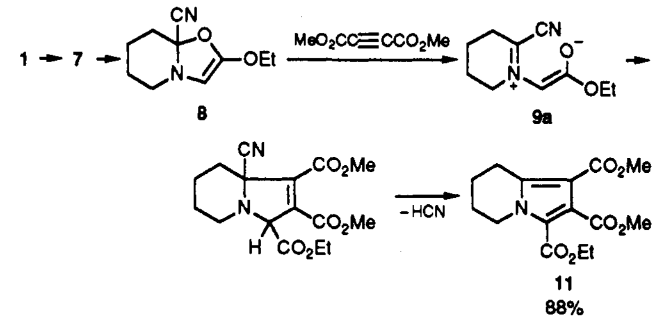
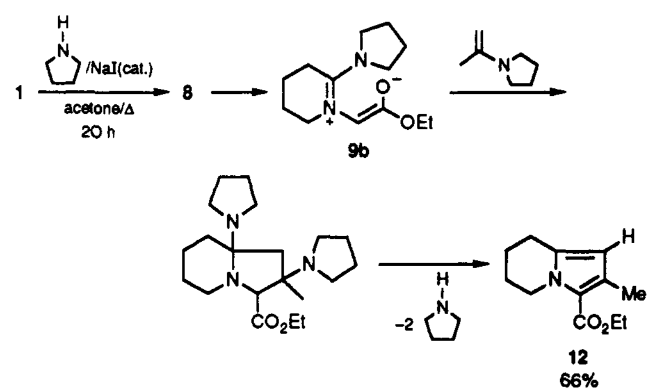
Scheme III



Scheme IV



Scheme V



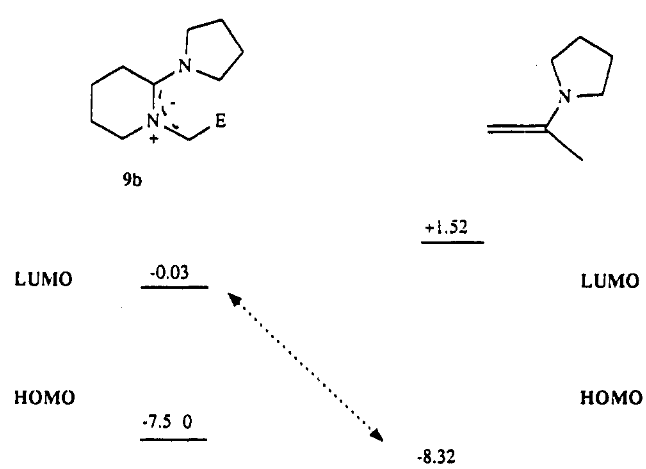


Figure 3.

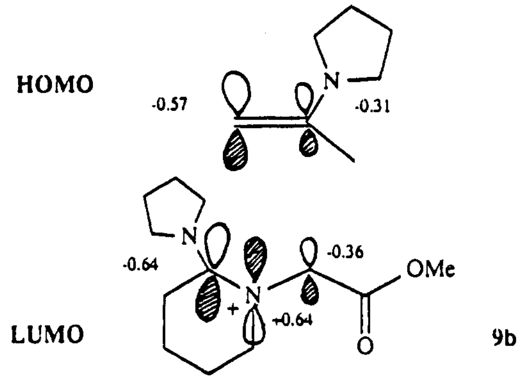
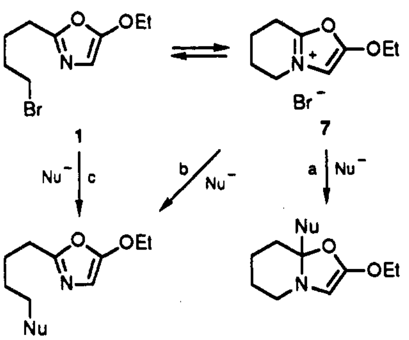


Figure 4.

Scheme VI

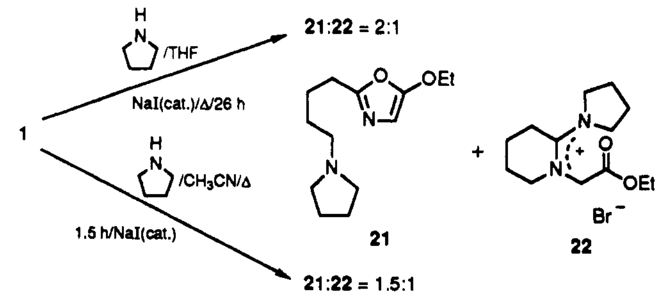


plain the observed regiochemistry of the dipolar cycloaddition of ylide **9b** with acetone enamine, we carried out FMO calculations at the AM1 level[16] for the S-dipole (*E*, *Z*)[17] and the enamine dipolarophile.

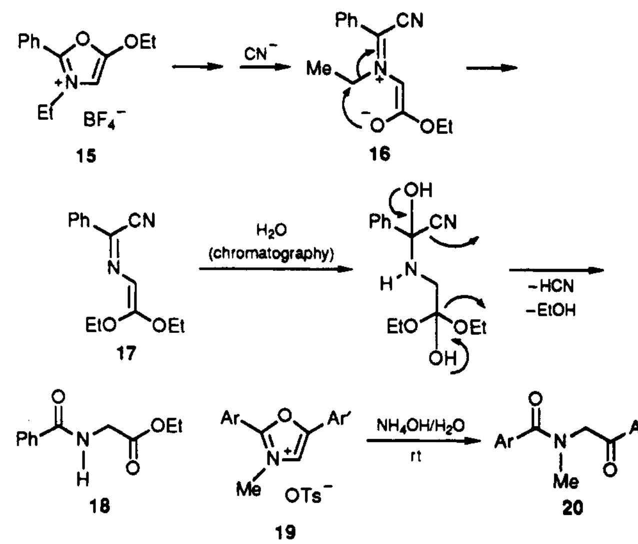
The reaction was found to be LUMO–dipole controlled as shown by its correlation diagram (Figure 3). The frontier molecular orbital interaction between dipole and dipolarophile is indicated in Figure 4, in which the largest lobe in the HOMO of the electron-donor dipolarophile interacts with the largest lobe in the LUMO of the dipole (electron acceptor), which is consistent with the experimentally observed regiochemistry.

The Fate of the Azomethine Ylide in the Absence of a Transferable Proton. In all the above cases studied in the absence of a trapping agent, the azomethine ylide underwent a fast internal neutralization by transfer of a proton α to the immonium carbon or of another acidic proton. Precedents for proton transfer by "enolizable" methyl groups in azomethine ylides are documented.[18] However, when we examined a system in which such a proton was not available, i.e., 5-ethoxy-3-ethyl-2-phenyloxazolium tetrafluoroborate (**15**), prepared from the corresponding oxazole with triethyloxonium tetrafluoroborate, we found that the reaction with NaCN in acetone led unexpectedly to the deethylated product **18**. The loss of the ethyl group from the immonium ion was indeed surprising, since in a related reaction (**19** → **20**) there was no loss of the alkyl substituent.[19] One possible explanation

Scheme VII



for the deethylation process may be formation of the cyanoazomethine ylide **16** which, in the S-conformation and in the absence of neutralization by proton transfer, undergoes neutralization via an ethyl transfer from nitrogen to oxygen, followed by hydrolysis of the ketene acetal and of the cyanoimine moieties of **17** on chromatography. That alkyl transfer did not occur in the case of **19** is most likely due to attack by excess OH^- on the oxazolium salt followed by neutralization via proton transfer from the OH function.



A Mixed Case. Formation of Both Oxazole and Piperidine Derivatives. A good explanation why certain nucleophiles attack the bromide on the side chain (Scheme VI, path c), or may be the methylene group in the oxazolium ion **7** (path b), in preference to the immonium ion (path a), is still lacking. Possibly softer nucleophiles (SPh, SCN, malonate ions) prefer to react via an S_N2 process, while harder nucleophiles (OH, CN, nitromethide ions) attack at the immonium carbon, though a good distinction is not available. Another possibility is that step a becomes reversible when Nu^- is a good leaving group (^-SPh, ^-SCN, malonate) thus permitting competitive attack on **1** (step c).

We did find a mixed case in which both pathways a and b or c operated, leading to a substitution product and to a piperidine derivative. The reaction of pyrrolidine with **1** in the absence of a dipolarophile led to an inseparable mixture of **21** and **22**, identified by NMR. The reason why **21** was not observed when the reaction was carried out in the presence of a dipolarophile (acetone enamine) (see Scheme IV) may be due to the existence of an equilibrium between the oxazolium ion **7** and the ylide **9b**, which in the presence of the dipolarophile gets trapped in a fast reaction but in its absence is capable of undergoing either proton transfer to afford **22** or an S_N2-type attack by pyrrolidine to produce **21**.

(16) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(17) Calculations (reported elsewhere) for the U-dipole and S-dipole conformations show a definite preference for the latter.

(18) (a) Achenson, R. M.; Bailey, A. S.; Selby, I. A. *J. Chem. Soc., Chem. Commun.* **1966**, 835. (b) Schmidt, G.; Stracke, H.-U.; Winterfeldt, E. *Chem. Ber.* **1970**, *103*, 3196. (c) Dowd, P.; Kang, K. *J. Chem. Soc. Chem. Commun.* **1974**, 258. (d) Padwa, A.; Dean, D.; Oine, T. *J. Am. Chem. Soc.* **1975**, *97*, 2822.

(19) Ott, D. J.; Hayes, F. N.; Kerr, V. V. *J. Am. Chem. Soc.* **1956**, *78*, 1941.

In conclusion, we have shown that intramolecular alkylation of oxazoles is possible with a tether leading to formation of a six-membered-ring fused oxazolium salt **7**. The alkylation was studied kinetically; rate constants were established, and activation parameters were calculated.

The reaction of oxazolium salt **7** with a variety of N-C-O-, and S-nucleophiles was studied with a view to formation of 4-oxazoline species which are valence tautomers of azomethine ylides. Trapping experiments of these ylides were successful with either electron-rich or electron-poor dipolarophiles. This is probably due to the narrow HOMO–LUMO gap of the ylides (as was found by STO-3G calculations for ylides **9a** and **9b**). The regiochemistry of the 1,3-dipolar cycloaddition (with acetone enamine) was analyzed by FMO theory. FMO energies were calculated (at AM1 and STO-3G levels) for both dipole **9b** and acetone enamine. The correlation diagram and the interactions between the appropriate FMO's of the reactants are in complete agreement with experimental results.

In the absence of external dipolarophiles, the fate of the extremely reactive ylide intermediates was neutralization to produce a stable species by internal shift of an acidic proton or by an alkyl shift.

No nucleophilic addition unto the immonium moiety of oxazolium salt **7** was observed with NCS^-, PhS^-, and $(MeCO_2)_2CH^-$, but rather nucleophilic displacement of the bromide at the end of the side-chain oxazole **1**.

Experimental Section

General. For spectral data details see ref 10. For ethyl groups the J values were 7 ± 0.5 Hz. Solvents were purified and dried as follows: acetone, distilled over K_2CO_3 and stored over 4-Å molecular sieves; acetonitrile, distilled over P_2O_5; THF, distilled over Na; DMF, passed through basic alumina column and stored over 4-Å molecular sieves; EtOH, distilled over Mg. NaI was dried by high vacuum at 80 °C for 4 h.

2-(4′-Bromobutyl)-5-ethoxyoxazole (1). To a mixture of 5-bromovaleronitrile (2 g, 12.3 mmol) and BF_3•etherate (1.23 mL, 10 mmol) in a flame-dried system under Ar was added dropwise ethyl diazoacetate (1.14 g, 10 mmol) at 0–5 °C. The mixture turned dark red on stirring at room temperature for 12 h. One equiv of triethylamine was added, and this mixture was chromatographed on silica gel. Elution with EtOAc–hexane (1:3) yielded the product **1** as an orange oil (0.74 g, 30%): ^{1}H NMR δ 5.91 (H-4, s, 1 H), 4.04 (OEt, q, 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, 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/z 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 (2a). A solution of **1** (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. The thick white precipitate that formed was filtered, and the solid was washed with acetone and chloroform. The filtrates were concentrated and purified by chromatography (EtOAc) to yield the product **2a** as a yellowish oil (0.12 g, 88%): ^{1}H 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=C=S—), 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/z 227 (MH^+), 200 (MH^+ – HCN), 168 (MH^+ – HSCN); HRMS calcd for $C_{10}H_{14}N_2O_2S$ 226.0773, found 226.0748.

2-(4′-(Phenylthio)butyl)-5-ethoxyoxazole (2b). (2b). A solution of **1** (0.1 g, 0.4 mmol) and equivalent amounts of thiophenol (0.041 mL) and triethylamine (0.056 mL) in the presence of a catalytic amount of NaI (0.01 g) in dry acetone (3 mL) was heated under reflux for 18 h. The white precipitate that formed was filtered, and the filtrate was evaporated and separated on a column (EtOAc–hexane (1:4)). Product **2b** was obtained as a yellow oil (0.08 g, 73%): ^{1}H NMR δ 7.28 (Ph-*o* + Ph-*m*, 4 H), 7.16 (Ph-*p*, 1 H), 5.93 (H-4, s, 1 H), 4.05 (OEt, q, 2 H), 2.93 (SCH_2, t, 2 H), 2.64 (CH_2-oxazole, t, 2 H), 1.8 (CH_2CH_2, m, 4 H), 1.40 (OEt, t, 3 H); ^{13}C NMR δ 159.41 (C-5), 155.00 (C-2), 136.48 (Ph-*i*), 129.14 (Ph-*o*), 128.84 (Ph-*m*), 125.83 (Ph-*p*), 98.75 (C-4), 67.88 (OEt) 33.20 (CH_2-oxazole), 28.21 (CH_2S), 27.73, 25.96 (CH_2CH_2), 14.51 (OEt); MS (CI) m/z 278 (MH^+, 100), 168 (MH^+ – PhSH, 25). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.96; H, 6.91. Found: C, 64.70; H, 6.96.

2-(5′,5′-Dicarbomethoxypentyl)-5-ethoxyoxazole (2c). NaH/DMF Procedure. Sodium hydride (0.012 g, 0.24 mmol) was washed three times with pentane in a dry system under Ar. The traces of pentane were evaporated with Ar, and dry DMF (1 mL) was added. The flask was cooled in an icebath, and an equimolar amount of dimethyl malonate (0.028 mL) was added. The ice bath was removed, and the solution was stirred at 25 °C for 10 min. A solution of **1** (0.06 g, 0.24 mmol) and a catalytic amount of NaI in DMF (1 mL) was added dropwise. The mixture was stirred at 25 °C for 20 h, extracted with ether, and washed with water. The aqueous phase was extracted with ether (4 × 2 mL). The ethereal phase was washed with saturated NaCl solution. The residue obtained after solvent evaporation was chromatographed (EtOAc–hexane (1:15)) to give the product **2c** as a colorless oil (0.015 g, 21%).

***t*-BuOK/THF Procedure.** Dimethyl malonate (0.064 mL, 0.48 mmol) was added to a solution of *t*-BuOK (0.053 g, 0.48 mmol) in freshly distilled THF (4 mL). The solution was stirred at 25 °C for 10 min. A solution of an equimolar of **1** (0.12 g) in THF (1 mL) was added. The reaction mixture was heated under reflux for 28 h. After solvent removal the residue was chromatographed (EtOAc–hexane (1:15)) to give product **2c** as a colorless oil (0.024 g, 17%): ^{1}H NMR δ 5.93 (H-4, s, 1 H), 4.08 (OEt, q, 2 H), 3.73 (CO_2Me, s, 6 H), 3.36 (CH, *t*, J = 7 Hz, 1 H), 2.63 (CH_2, t, J = 7 Hz), 1.94 (CH_2, q, J = 7 Hz, 2 H), 1.75 (CH_2CH_2, m, 4 H), 4.41 (OEt, t, 3 H); ^{13}C NMR δ 169.70 (CO_2Me), 159.38 (C-2), 155.08 (C-5), 98.88 (C-4), 67.95 (OEt), 52.44 (CO_2Me), 51.52 (CH), 28.45, 27.95, 26.74, 26.40 (CH_2), 14.54 (OEt); IR 1733 (CO_2Me), 1686 (C=N) cm^{-1}; MS (CI) m/z 300 (MH^+, 100); HRMS calcd for $C_{14}H_{21}NO_6$ 299.1363, found 299.1133.

1-(Carbethoxymethyl)-2-cyano-1,4,5,6-tetrahydropyridine (3). A solution of **1** (0.172 g, 0.7 mmol), NaCN (0.034 g, 0.7 mmol), and NaI (0.008 g) in dry acetone (10 mL) was heated under reflux for 13 h. After filtration and solvent evaporation, the residue was chromatographed (EtOAc–hexane (1:4)) to give **3** as a colorless oil (0.12 g, 90%): ^{1}H NMR δ 5.42 (CH, t, J = 4.5 Hz, 1 H), 4.20 (OEt, q, 2 H), 3.85 (NCH_2E, s, 1 H), 3.11 (CH_2N, t, J = 6 Hz, 2 H), 2.15 (*C*H_2CH=, q, J = 6 Hz, 2 H), 1.88 (CH_2, quintet, J = 6 Hz, 2 H), 1.28 (OEt, t, 3 H); ^{13}C NMR δ 169.88 (CO_2Et), 120.81 (C=C), 115.56 (C≡N), 115.08 (C=CH), 61.06 (OEt), 53.76 (NCH_2E), 48.00 (CH_2N), 22.01, 21.11 (CH_2), 14.15 (OEt); MS (CI) m/z 195 (MH^+, 99), 121 (MH^+ – $EtCO_2H$, 100); IR (neat) ν_{max} 2220 (C≡N), 1745 (CO_2Et), 1615 (C=C) cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27. Found: C, 61.33; H, 7.30.

1-(Carbethoxymethyl)-2-(nitromethylene)piperidine (4). A solution of **1** (0.062 g, 0.25 mmol) and Et_3N (0.035 mL, 0.25 mmol) in freshly distilled nitromethane was heated under reflux for 4 h. After evaporation of the solvent, the residue was chromatographed (EtOAc–hexane (1:1)) to yield product **4** as a yellow solid. Crystallization from EtOAc–ether yielded yellow needles, mp 117 °C (0.036 g, 63%): ^{1}H NMR δ 6.60 (CH, br s, 1 H), 4.25 (OEt, q, 2 H), 3.92 (NCH_2E, s, 2 H), 3.43 (CH_2N, t, J = 6 Hz, 2 H), 3.30 (CH_2C=C, br t, J = 6 Hz, 2 H), 1.88 (CH_2, m, 2 H), 1.78 (CH_2, m, 2 H), 1.32 (OEt, t, 3 H); ^{13}C NMR δ 167.00 (CO_2Et), 161.71 (C=C), 112.73 (C=CH), 62.13 (OEt), 54.29 (NCH_2E), 52.25 (CH_2N), 27.73 (CH_2C=C), 22.27, 18.61 (CH_2), 14.11 (OEt); MS (CI) m/z 229 (MH^+, 100), 182 (MH^+ – HNO_2, 40); IR (KBr pellet) ν_{max} 1738 (CO_2Et), 1559, 1361 (NO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 53.55; H, 7.19. Found: C, 53.25; H, 7.07.

1-(Carbethoxymethyl)-2-oxopiperidine (5). Hydroxide Procedure. To a solution of **1** (0.05 g, 0.2 mmol) in acetone (3 mL) was added Na_2CO_3 (5% aqueous solution, 1 mL). The solution was heated under reflux for 18 h, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ and neutralized with 5% aqueous HCl. The aqueous solution was extracted with $CHCl_3$ (3 × 3 mL). After drying and solvent evaporation the residue (which contained the product and acetone self-condensation products) was chromatographed (EtOAc–hexane (1:1) and EtOAc) to yield **5** as a colorless oil (0.011 g, 30%): ^{1}H NMR δ 4.14 (OEt, q, 2 H), 4.06 (NCH_2E, s, 2 H), 3.30 (CH_2N, m, 2 H), 2.39 (CH_2, m, 2 H), 1.83 (CH_2CH_2, m, 4 H), 1.25 (OEt, t, 3 H), ^{13}C NMR δ 170.42 (N(CO)), 169.13 (CO_2Et), 61.10 (OEt), 49.20 (NCH_2E), 48.64 (CH_2N), 32.10 (CH_2(CO)), 23.19, 21.38 (CH_2), 14.16 (OEt); MS (CI) m/z 186 (MH^+, 100), 140 (MH^+ – EtOH, 85). Anal. Calcd for $C_9H_{15}NO_3$ C, 58.36; H, 8.16. Found: C, 58.31; H, 8.40.

Ethoxide Procedure. A solution of **1** (0.053 g, 0.21 mmol), Et_3N (0.03 mL, 0.21 mmol), and a catalytic amount of NaI (0.004 g) in EtOH (3 mL) was heated under reflux for 46 h. Product **5** was obtained (0.019 g, 49%) after chromatography (EtOAc–hexane (1:1) and then EtOAc).

2-Oxopiperidine-1-acetic Acid (6). A solution of **1** (0.12 g, 0.48 mmol) and NaI (0.073 g, 0.48 mmol) in dry acetone (2 mL) was heated under reflux for 24 h. After filtration and evaporation a white solid (0.073 g, 98%) was obtained. Crystallization from $CHCl_3$–ether gave **6** as white feathers (mp 184 °C): ^{1}H NMR (CD_3OD) δ 4.08 (NCH_2CO_2H, s, 2 H), 3.40 (CH_2N, br t, J = 5 Hz, 2 H), 2.37 (CH_2(CO), br t, J = 6 Hz, 2 H), 1.87 (CH_2CH_2, m, 4 H); ^{13}C NMR (CD_3OD) δ 173.20 (CO_2H), 172.35 (N(CO)), 50.42 (NCH_2CO_2H), 49.88 (CH_2N), 32.82 (CH_2(CO)), 24.00, 22.15 (CH_2); MS (CI) m/z 158 (MH^+, 100), 140 ($MH^+ - H_2O$, 38), 112 ($MH^+ - HCO_2H$, 68).

1,2-Dicarbomethoxy-3-carbethoxy-5,6,7,8-tetrahydroindolizine (11). A solution of **1** (0.073 g, 0.29 mmol), NaCN (0.014 g, 0.29 mmol), DMAD (0.036 mL, 0.29 mmol), and NaI (0.008 g) in dry acetone (3 mL) was heated under reflux for 10 h. The product was obtained after evaporation of the solvent and chromatography of the residue (EtOAc–hexane (1:2)) as a light yellowish solid (0.072 g, 80%): Crystallization from ether–petroleum ether yielded white cubic crystals, mp 109 °C: ^{1}H NMR δ 4.32 (CH_2N, t, J = 6 Hz, 2 H), 4.25 (CO_2Et, q, 2 H), 3.89, 3.77 (CO_2Me, s, 3 H), 3.08 (CH_2-pyrrole, t, J = 6 Hz, 2 H), 1.95 (CH_2, m, 2 H), 1.83 (CH_2, m, 2 H), 1.30 (CO_2Et, t, 3 H); ^{13}C NMR δ 166.96, 163.66, 159.67 (CO_2Et, CO_2Me), 141.43, 125.69, 118.79, 109.49 (pyrrole carbons), 60.56 (CO_2Et), 52.40, 51.26 (CO_2Me), 46.19 (CH_2N), 24.16 (CH_2-pyrrole), 22.73, 18.96 (CH_2), 13.99 (CO_2Et); MS (CI) m/z 310 (MH^+, 100), 278 (MH^+ – MeOH, 19). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19. Found: C, 58.54; H, 6.47.

2-Methyl-3-carbethoxy-5,6,7,8-tetrahydroindolizine (12). A solution of **1** (0.1 g, 0.4 mmol) and pyrrolidine (0.033 mL, 0.4 mmol) in the presence of a catalytic amount of NaI in dry acetone (4 mL) was heated under reflux for 20 h. The product was obtained after evaporation of the solvent and chromatography of the residue (EtOAc–hexane (1:4)) as a colorless oil (0.055 g, 66%): ^{1}H NMR δ 5.74 (H-3, s, 1 H), 4.29 (CH_2N, t, J = 6 Hz, 2 H), 4.27 (CO_2Et, q, 2 H), 2.75 (CH_2-pyrrole, t, J = 6 Hz, 2 H), 2.31 (CH_3, s, 3 H), 1.93 (CH_2 m, 2 H), 1.78 (CH_2, m, 2 H), 1.35 (CO_2Et, t, 3 H); ^{13}C NMR δ 162.07 (CO_2Et), 135.71, 129.86, 118.03 (pyrrole carbons), 108.83 (CH), 59.11 (CO_2Et), 45.83 (CH_2N), 23.91, 23.70, 20.15 (CH_2), 14.57, 14.29 (CO_2Et, Me); MS (CI) m/z 208 (MH^+, 100), 162 (MH^+ – EtOH, 27). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.85; H 8.12.

2-(4′-Pyrrolidinobutyl)-5-ethoxyoxazole (21) and 1-(Carbethoxymethyl)-2-(1-pyrrolidinium)piperidine Bromide (22). A solution of **1** (0.056 g, 0.22 mmol), pyrrolidine (0.21 mL, 0.23 mmol), and a catalytic amount of NaI (0.005 g) in acetonitrile was heated under reflux for 1.5 h. The solvent was evaporated. The crude residue contained two products (**21** and **22**) in a ratio of 1.5:1. **21** ^{1}H NMR δ 5.87 (H-4, s, 1 H), 4.01 (OEt, q, 2 H), 3.00 (CH_2NCH_2, br t, J = 6 Hz, 4 H), 2.88 (CH_2N, br t, J = 6 Hz, 2 H), 2.62 (CH_2-oxazole, t, J = 6 Hz, 2 H), 1.97 (CH_2CH_2, m, 4 H), 1.85 (CH_2CH_2, m, 4 H), 1.25 (OEt, t, 3 H); ^{13}C NMR δ 159.38 (C-5), 154.38 (C-2), 98.95 (C-4), 68.02 (OEt), 53.73 (CH_2NCH_2), 55.4 (CH_2N), 27.43 (CH_2-oxazole), 23.31 (CH_2NCH_2), 25.65, 24.27 (CH_2CH_2), 14.43 (OEt); MS (EI) m/z 238 (M^+, 86); HRMS calcd for $C_9H_{13}NO_2$ (M – pyrrolidine) 167.0943, found 167.0958.

22: ^{1}H NMR δ 4.54 (NCH_2E, s, 2 H), 4.20 (OEt, q, 2 H), 3.68 (CH_2NCH_2, br t, J = 6 Hz, 2 H), 3.52 (CH_2N, br t, J = 6 Hz, 2 H), 2.88 (CH_2, br t, J = 6 Hz, 2 H), 1.97 (CH_2CH_2, m, 4 H), 1.85 (CH_2CH_2, m, 4 H), 1.35 (OEt, t, 3 H); ^{13}C NMR δ 168.32 (CO_2Et), 167.38 (NC=N), 62.37 (CO_2Et), 56.09 (NCH_2E), 53.64 (CH_2N), 52.71 (CH_2NCH_2), 31.40 (CH_2), 24.02 (CH_2CH_2), 21.41, 18.75 (CH_2CH_2), 14.04 (CO_2Et); MS (EI) m/z 239 (M^+ – Br, 64), 151 ($M^+ - CH_3$(CO)OEt, 33); HRMS calcd for $C_9H_{16}N_2$ (M – CH_2CO_2Et) 152.1310, found 152.1290.

Reaction of *N*-Ethyl-2-phenyl-5-ethoxyoxazolium Tetrafluoroborate (15) with NaCN. A solution of **15** (0.121 g, 0.39 mmol) and NaCN (0.019 g, 0.39 mmol) in acetone (2.5 mL) was heated under reflux for 24 h. The solid was removed by filtration, and the filtrate was evaporated and chromatographed to give ethyl *N*-benzoylglycinate (**18**) as a colorless oil (0.05 g, 62%): ^{1}H NMR δ 7.80 (Ph-*o*, 2 H), ~7.45 (Ph-*m* + *p*, 3 H), 6.87 (NH, br s, 1 H), 4.23 (CO_2Et, q, 2 H), 4.20 (CH_2, d, J = 6 Hz), 1.28 (CO_2Et, t, 3 H); MS (CI) m/z 208 (MH^+, 100), 162 (MH^+ – EtOH, 15).

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Triazolines. 25. 1,3-Cycloaddition of Aryl Azides to Enamides and the Synthesis of 1-Aryl-5-amido-1,2,3-triazolines[1]

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This paper describes for the first time the 1,3-dipolar cycloaddition of aryl azides to the vinylic bond of enamides, represented by the *N*-vinyllactam *N*-vinyl-2-pyrrolidinone (NVP) (Ia) and the open-chain enamide, *N*-methyl-*N*-vinylacetamide (NVA) (Ib). Mechanistically, enamides react like enamines in azide cycloaddition reactions to yield 1-aryl-5-amido-1,2,3-triazolines (II).

The olefinic bonds are typical dipolarophiles that undergo 1,3-dipolar cycloadditions with octet-stabilized 1,3-dipoles such as organic azides to yield five-membered nitrogen heterocycles, the Δ^2-1,2,3-triazolines (4,5-di-

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