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).

Acknowledgment. We are grateful to Dr. H. E. Gottlieb for his help with NMR and COSY experiments and to Dr. J. L. Wolk for AM1 calculations. Partial support of this research by a Grant from the US–Israel Binational Science Foundation is gratefully acknowledged.

Registry No. **1**, 132353-41-4; **2a**, 133602-44-5; **2b**, 132353-43-6; **2c**, 140662-71-1; **3**, 132353-44-7; **4**, 132353-47-0; **5**, 22875-63-4; **6**, 72253-28-2; **7**, 140662-76-6; **11**, 132353-46-9; **12**, 132353-45-8; **15**, 140662-75-5; **18**, 1499-53-2; **21**, 140662-72-2; **22**, 140662-73-3; $MeO_2CC{\equiv}CCO_2Me$, 762-42-5; ethyl diazoacetate, 623-73-4; thiophenol, 108-98-5; 5-bromovaleronitrile, 5414-21-1; dimethyl malonate, 108-59-8.

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

Pankaja K. Kadaba

Division of Medicinal Chemistry and Pharmaceutics, College of Pharmacy, A. B. Chandler Medical Center, University of Kentucky, Lexington, Kentucky 40536-0082

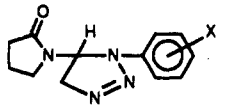
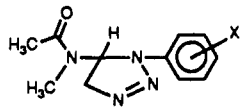
Received August 19, 1991 (Revised Manuscript Received February 18, 1992)

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-

0022-3263/92/1957-3075$03.00/0

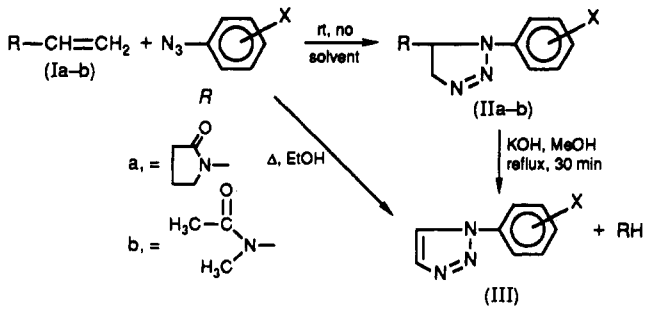
Table I. Synthesis of 1-Aryl-5-amido-1,2,3-triazolines

compd no.	X	reaction time	yield[a] (%)	mp (°C)	^{1}H NMR, δ, ppm[b] ring 4-CH_2 (multiplet of 8)	^{1}H NMR, δ, ppm[b] ring 5-CH (double doublet)
			 IIa			
1	4-NO_2	3 days	75	149–150	4.37–4.55	6.39–6.40; 6.42–6.43
2	3,4-Cl_2	30 days	70	133–133.5	4.26–4.44	6.28–6.30; 6.31–6.33
3	4-Cl	26 days	62	126–128	4.25–4.41	6.30–6.31; 6.33–6.34
		19 days	45			
4	4-CF_3	26 days	66	130–133	4.29–4.46	6.36–6.37; 6.39–6.40
5	3-CF_3	10 months	60	102–105	4.29–4.46	6.36–6.38; 6.40–6.41
6	4-CH_3	5 months	55	110.5–113	4.20–4.38	6.31–6.33; 6.34–6.36
7	4-OCH_3	5 months	62	122–125	4.20–4.37	6.30–6.31; 6.33–6.34
8	H	30 days	46	118.5–121	4.21–4.39	6.33–6.34; 6.35–6.37
			 IIb			
9	4-NO_2	7 days	83	141.5–143	4.40–4.56	6.92–6.94; 6.96–6.97
10	3,4-Cl_2	70 days	47	121–123	4.32–4.48	6.82–6.84; 6.85–6.87
11	4-Cl	70 days	91	134.5–137	4.28–4.45	6.84–6.86; 6.87–6.89
		19 days	22	138–140		
12	4-CF_3	70 days	66	122.5–125	4.33–4.50	6.90–6.91; 6.93–6.95
13	3-CF_3	10 months	51	68–70.5	4.33–4.50	6.90–6.92; 6.93–6.95
14	4-CH_3	10 months	61	122.5–126	4.22–4.40	6.83–6.85; 6.87–6.88
15	4-OCH_3	1 year[c]				
16	H	1 year	10	101.5–104.5	4.26–4.44	6.87–6.88; 6.90–6.91

[a] Yields are for the purified products. [b] Elemental analysis (C, H, N) for all compounds were well within ±0.4% of the calculated values. [c] The dark material obtained from the reaction mixture could not be further purified.

hydro-1*H*-1,2,3-triazoles).[2-4] The literature abounds in cycloaddition reactions to the olefinic bond of enamines[4] including enamino esters, nitriles, and ketones.[5-7] However, there is no record of any studies on cycloadditions to the structurally related *N*-vinylamides or enamides. Thus, my continuing interest in the chemistry and pharmacology of 1,5-substituted 1,2,3-triazolines[4,8] prompted me to examine the dipolarophilic activity of the vinylic bond in enamides and how it compared with that of enamines. This paper describes for the first time the 1,3-cycloaddition reaction of aryl azides with two enamides, the *N*-vinyllactam *N*-vinyl-2-pyrrolidinone (NVP) (Ia) and the open-chain enamide *N*-methyl-*N*-vinylacetamide (NVA) (Ib), and a route for the synthesis of 1-aryl-5-amido-1,2,3-triazolines (IIa and IIb, Scheme I).

Scheme I



Results and Discussion

Reaction of equimolar amounts of the enamide and aryl azide at room temperature, over a period of time depending on the reactivity of both reagents, yielded the triazoline adducts (IIa and IIb) as stable, colorless, crystalline products. In refluxing ethanol, the reaction yielded the triazoles III as the major product. Azide addition to NVP (Ia) occurred relatively more readily compared to NVA (Ib). The results are presented in Table I.

The assignment of the 1,2,3-triazoline structures to the enamide–azide reaction products with the amido group in the 5-position (IIa and IIb) is based on several lines of experimental evidence and theoretical reasoning.

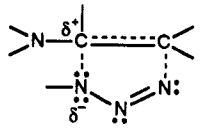
Enamides undergo acid-catalyzed hydrolysis to yield the amide and a carbonyl compound.[9,10] Studies on the kinetics and mechanism of acid-catalyzed hydrolysis of NVP[10] (Ia) indicate *N*-(1-hydroxyethyl)pyrrolidin-2-one as the main product at temperatures near 0 °C, while at higher temperatures, it decomposes to give acetaldehyde

(1) This paper was presented in part at the 2nd International Symposium on Povidone, University of Kentucky, Lexington, KY, 1987, and at the Eleventh International Congress of Heterocyclic Chemistry, Heidelberg, Germany, 1987.
(2) Huisgen, R.; Grashey, R.; Sauer, J. In *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley-Interscience: New York, 1964; p 835.
(3) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; p 1.
(4) Kadaba, P. K.; Stanovnik, B.; Tisler, M. *Adv. Heterocycl. Chem.* **1984**, *37*, 217.
(5) Bourgois, J.; Tonnard, F.; Texier, F. *Bull. Soc. Chim. Fr.* **1976**, 2025.
(6) Fusco, R.; Bianchetti, G.; Pocar, D.; Ugo, R. *Gazz. Chim. Ital.* **1962**, *92*, 1040.
(7) (a) Fusco, R.; Bianchetti, G.; Pocar, D.; Ugo, R. *Chem. Ber.* **1963**, *96*, 802. (b) Maiorana, S.; Pocar, D.; Croce, P. D. *Tetrahedron Lett.* **1966**, 6043.
(8) (a) Kadaba, P. K.; Edelstein, S. B. *J. Org. Chem.* **1990**, *55*, 5891. (b) Kadaba, P. K. *J. Med. Chem.* **1988**, *31*, 196. (c) Kadaba, P. K. *Drugs Future* **1990**, *15*, 1013.
(9) Csizmadia, V. M.; Koshy, K. M.; Lau, K. C. M.; McClelland, R. A.; Nowlan, V. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 974.
(10) Senogles, E.; Thomas, R. A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 825.

and 2-pyrrolidinone. The rate-determining step of the hydrolysis reaction has been established as proton transfer to the terminal vinylic carbon of NVP, and the reaction conforms to a general acid catalysis mechanism. An identical mechanism has been shown to govern the acid-catalyzed hydrolysis of *N*-vinylacetamides.[9] Furthermore, the mechanism of acid hydrolysis of enamides is similar to that of enamines[11] and enol ethers;[12] in both of the latter reactions, the general acid-catalyzed protonation on the terminal olefinic carbon is the rate-limiting step.

The mechanistic similarities in the acid hydrolysis of enamides and enamines/enol ethers clearly indicate that the electron flow in all three compound groups is along the direction of the vinylic bond; thus, unlike in amides, the flow of electrons from the nitrogen toward the carbonyl group in enamides is insignificant. This is in agreement with the respective hydrogen–tritium (H/T) and hydrogen–deuterium (H/D) exchange rates observed for NVP (Ia) and 2-pyrrolidinone.[13] While the synthesis of [3-^{3}-H]-NVP from NVP was accomplished by an H/T exchange reaction in 6 days, no such H/D exchange was observed in 2-pyrrolidinone, even after 33 days.[13]

The vinyl bonds in enamines and enol ethers exhibit a high degree of dipolarophilic activity in 1,3-dipolar cycloaddition reactions;[3,4,14] azide addition is controlled by electronic rather than steric factors,[3-5,14,15] and as a rule, the amino or ether group always appears in the 5-position of the 1,2,3-triazoline adduct. Electrophilic attack by the terminal azido nitrogen on the terminal nucleophilic vinyl carbon is the rate-limiting step[14] similar to the protonation of this carbon in acid hydrolysis[11] and is compatible with a transition state IV, in which the positive charge on C-5



IV

is stabilized by the electron-releasing substituent group.[3,4,16,17] The chemical similarities in the mechanisms of acid hydrolysis of enamines/enol ethers and enamides clearly indicate that the nitrogen electrons in enamides resonate with the vinylic double bond and not with the carbonyl of the amide function; thus, logically enamides would be expected to react similar to enamines in 1,3-cycloaddition reactions with azides to yield 1-aryl-5-amido-1,2,3-triazolines.

Elemental analyses of the products from enamide–azide reaction at room temperature were consistent with the expected empirical composition for the triazoline adducts. The products underwent characteristic decomposition with nitrogen evolution at their melting points.[18] Further evidence for the triazoline structures ensued from the facile conversion of the 1-aryl-5-amidotriazolines to the corresponding 1-aryltriazoles (III, Scheme I), when refluxed with methanolic potassium hydroxide. This reaction apparently involves the loss of an amide molecule (pyrrolidinone from IIa and *N*-methylacetamide from IIb), very similar to the base-induced elimination of an amine molecule from 5-aminotriazolines to yield the respective triazoles.[15] The incipient aromaticity of the 1*H*-1,2,3-triazole ring system stabilizes the transition state of the elimination step and facilitates the removal of stable fragments of amide and amine. These observations were consistent with the NMR spectra of the enamide–azide reaction products before and after base treatment. The triazoline adducts reveal, in addition to the chemical shifts arising from the 5-amido groups, two sets of multiplets with eight and four peaks, respectively, in the ranges of δ 4.2–4.6 and δ 6.3–6.4 (for IIa) or δ 6.8–7.0 (for IIb) (Table I). This is an ABX pattern characteristic of 1,5-substituted 1,2,3-triazoline structures bearing a 4-methylene group adjacent to the asymmetric 5-CH bearing the amide group; an ABC spectrum results when the 5-substituent is a heteroaryl group.[4,19] The 1-aryl triazoles, on the other hand, exhibit two doublets in the δ 7.9–8.2 region characteristic of the aromatic CH protons in the 4 and 5 positions of the triazole ring system.[20]

Aromatization can occur spontaneously or may be aided by heat, dilute base, or even by dilute acid in the case of stable triazolines that are not susceptible to acid degradation. Apparently, the triazoles III resulting from the enamide–azide reactions in refluxing ethanol are formed by loss of the amide molecule from the initially formed triazoline adducts IIa and IIb by a mechanism analogous to the heat-induced decomposition of *N*-(1-hydroxyethyl)pyrrolidin-2-one to acetaldehyde and 2-pyrrolidinone.[9,10] In fact, the triazole from the reaction of NVP and *p*-nitrophenyl azide, in refluxing ethanol, is identical to the one formed from 1-(*p*-nitrophenyl)-5-*N*-morpholino-1,2,3-triazoline by loss of morpholine under the influence of a base.[21] Also, both triazolines 3 and 11, when refluxed with 2 N methanolic KOH, yielded identical triazoles. The great facility with which 5-amidotriazolines aromatize under the influence of heat appears to be consistent with the greater electron-withdrawing power of the amido substituent[9] compared to that of the amino group;[22] in the presence of a base, aromatization is further enhanced by proton abstraction from the 4-position of the triazoline ring.

The lower reactivity of enamides compared to that of enamines provides further evidence for the similarities in azide addition to enamides and enamines. In terms of the FMO treatment of 1,3-cycloadditions,[3,4] the dominant $HOMO_{olefin}$–$LUMO_{azide}$ interactions in azide–enamine/enol ether additions cause the electron-donor groups to always appear at the C-5 position of the triazoline adducts.[3,5,14] As the energy level of the $HOMO_{olefin}$ is increased and that of the $LUMO_{azide}$ is decreased by the presence of electron-donating or -withdrawing substituents,[3,4] respectively, the σ values (σ_p^+) for the acetamido group (−0.65)[9] and the amino group (−1.3)[22] clearly reflect the diminished HOMO-energy and hence the dipolarophilic activity of the olefinic bond in enamides relative to enamines. Similarly, the electron-withdrawing groups in enamino esters, nitriles, and ketones are also known to reduce the dipolarophilic activity of these enamines,[23] although, in azide additions, they act as enamines and not as acrylic derivatives, the

(11) (a) Jordan, F. *J. Am. Chem. Soc.* **1974**, *96*, 825. (b) Sollenberger, P. Y.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4261.
(12) Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B* **1967**, 53.
(13) (a) McClanahan, J. *Synthesis and In vivo Disposition of N-Vinyl-2-pyrrolidinone*; Ph.D. Dissertation, University of Kentucky, 1984. (b) McClanahan, J.; Chaney, J.; Blecher, L.; Digenis, G. A. *Proc. Int. Symp. Povidone* **1983**, 250. (c) Hawi, A. A.; Wells, D.; Digenis, G. A. *Proc. Int. Symp. Povidone* **1987**, 310.
(14) Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.* **1967**, *100*, 2494.
(15) Munk, M. E.; Kim, Y. K. *J. Am. Chem. Soc.* **1964**, *86*, 2213.
(16) Scheiner, P. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; p 327.
(17) Sheradsky, T. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1971; p 331.
(18) Kadaba, P. K. *Tetrahedron* **1966**, *22*, 2453.
(19) Kadaba, P. K. *J. Heterocycl. Chem.* **1975**, *12*, 143.
(20) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33.
(21) Ferutti, P.; Pocar, D.; Bianchetti, G. *Gazz. Chim. Ital.* **1967**, *97*, 109.
(22) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(23) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.

reaction being controlled by a $LUMO_{azide}$–$HOMO_{olefin}$ interaction.[4] In the case of both NVP and NVA this is evident from the effect of substituents on the aryl azide; electron-withdrawing groups on the phenyl ring facilitate reaction (compounds 1–4, 9, and 11) while electron-releasing groups have a retarding effect (compounds 6, 7, 14, and 15) (Table I).

In conclusion, this work has successfully demonstrated the dipolarophilic activity of the vinylic bond in enamides by the 1,3-dipolar cycloaddition of aryl azides to NVP and the related NVA, and the synthesis of a number of 1-aryl-5-amido-1,2,3-triazolines bearing 2-oxo-1-pyrrolidinyl or *N*-methyl-*N*-acetamido groups.

Experimental Section

Melting points are uncorrected. NMR spectra were run on a 300-MHz spectrometer in $CDCl_3$ solutions with TMS as internal standard. C, H, and N elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

1,3-Dipolar Cycloaddition of Aryl Azides to the Enamides *N*-Vinyl-2-pyrrolidinone and *N*-Methyl-*N*-vinylacetamide: Synthesis of 1-Aryl-5-(2-oxo-1-pyrrolidinyl)- (IIc) and 1-Aryl-5-(*N*-methyl-*N*-acetamido)-1,2,3-triazolines (IId). A mixture of the enamide (0.06 mol) and aryl azide (0.06 mol) was placed in a loosely capped dark brown bottle and allowed to stand, protected from light, with periodic shaking. The reaction course was followed by the appearance of the product as a crystalline mass from the oily reaction mixture and worked up when all or most of the oil had solidified. The chunky crystalline mass was triturated with small portions of ethanol, suction filtered, and washed several times with ether or an ether–petroleum ether mixture, as the case may be, until all of the unreacted residual enamide was removed, as indicated by the absence of the characteristic unpleasant odor of the enamide reagent.

Crystallization was effected from acetone or acetone–petroleum ether mixture. As the amidotriazolines are sensitive to heat and yield the 1-aryltriazoles by loss of an amide molecule, the crystallization had to be conducted with minimum heating. Hot acetone was added to the products until solution was achieved and then filtered. The filtrate was either treated with petroleum ether and cooled or concentrated under reduced pressure and then cooled; if crystals failed to appear, petroleum ether was added. The results are presented in Table I.

Reaction of Aryl Azides with Enamides in Refluxing Ethanol: Synthesis of 1-Aryl-1,2,3-triazoles. A mixture of enamide (0.02 mol) and aryl azide (0.02 mol) in ethanol (7 mL) was refluxed on a steam bath. At the end of the reaction, the mixture was poured into crushed ice and cooled. The solid products were filtered, washed with petroleum ether–ether mixture to remove the unreacted oily enamide, and crystallized from acetone–petroleum ether mixture or from methanol.

NVP and 4-$(NO_2)PhN_3$, after 24 h of reflux, gave 1-(4-nitrophenyl)-1,2,3-triazole, mp 202–204 °C (lit.[21] mp 203–204 °C), yield, 66%. When 25 mL of EtOH was used, the yield of triazole was reduced to 34%: ^1H NMR δ 7.93 (s, br, 4-CH), 8.14 (s, br, 5-CH).

NVP and 4-(Cl)PhN_3, after 38.5 h of reflux, gave 1-(4-chlorophenyl)-1,2,3-triazole, mp 114–115.5 °C (lit.[24] mp 115 °C), yield 50%: ^1H NMR δ 7.86 (s, br, 4-CH), 8.00 (s, br, 5-CH).

NVA and 4-(Cl)PhN_3 similarly yielded 53% of the triazole.

NVP and PhN_3 gave after 90 h of reflux 1-phenyl-1,2,3-triazole, mp 53–55.5 °C (lit.[25] mp 56 °C), yield 17%: ^1H NMR δ 7.83 (d, 4-CH), 8.04 (d, 5-CH); $J_{4H,5H} = J_{5H,4H} = 1.2$ Hz. A 20 h reflux gave no triazole.

Reaction of 1-Aryl-5-amidotriazolines with KOH. To a solution of 0.5 g of triazoline 11 in methanol (10 mL) was added a solution of KOH (2 N, 10 mL), and the mixture was refluxed with magnetic stirring for 30 min. The reaction mixture was diluted with ice-cold water and cooled to afford 1-(4-chlorophenyl)-1,2,3-triazole as a pure, crystalline material, mp 114–115.5 °C, yield 84%.

Similar treatment of triazoline 3 yielded the identical triazole, mp 114–115 °C, yield 70%.

Acknowledgment. The author thanks undergraduate laboratory assistants, Michelle Morgan, and Andrea Moore for their skillful assistance and the University of Kentucky Medical Center Research Advisory Committee for partial support.

Registry No. 1, 139871-49-1; 2, 139895-24-2; 3, 121318-96-5; 4, 139871-50-4; 5, 139871-51-5; 6, 139871-52-6; 7, 139871-53-7; 8, 121318-95-4; 9, 139871-54-8; 10, 139871-55-9; 11, 139871-56-0; 12, 139871-57-1; 13, 139871-59-3; 15, 139871-60-6; 16, 139871-61-7; 4-$NO_2C_6H_4N_3$, 1516-60-5; 3,4-$Cl_2C_6H_3N_3$, 66172-16-5; 4-$ClC_6H_4N_3$, 3296-05-7; 4-$CF_3C_6H_4N_3$, 5586-13-0; 3-$CF_3C_6H_4N_3$, 22001-17-8; 4-$CH_3C_6H_4N_3$, 2101-86-2; 4-$CH_3OC_6H_4N_3$, 2101-87-3; PhN_3, 622-37-7; 1-vinyl-2-pyrrolidinone, 88-12-0; *N*-vinylacetamide, 5202-78-8; 1-(4-nitrophenyl)-1,2,3-triazole, 1204-91-7; 1-(4-chlorophenyl)-1,2,3-triazole, 20320-16-5; 1-phenyl-1,2,3-triazole, 1453-81-2.

(24) El Khadem, H.; Mansour, H. A. R.; Meshreki, M. H. *J. Chem. Soc. C* **1968**, 1329.
(25) Begtrup, M. *Acta Chem. Scand.* **1973**, *27*, 3101.

Synthesis of 1-Deoxycastanospermine and Stereoisomers

Yves St-Denis and Tak-Hang Chan*

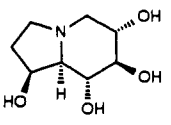
Department of Chemistry, McGill University, Montréal, Québec, Canada H3A 2K6

Received October 29, 1991

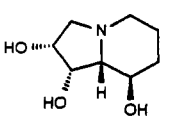
Four different isomers of 1-deoxycastanospermine (6,7,8-trihydroxyindolizidine) were synthesized. Their basic skeleton was constructed from a proline derivative and the anion of allyl phenyl sulfide, followed by an allylic sulfide rearrangement and a subsequent nucleophilic cyclization. The aminotriols were obtained in good yields with a concise overall sequence.

Introduction

Castanospermine 1[1] and swainsonine 2[2] have attracted much attention over the past decade. These two polyhydroxylated indolizidine alkaloids have displayed a wide variety of biological properties.[3] In a recent review,[3]



Castanospermine 1



Swainsonine 2

castanospermine has been reported to function as a plant

(1) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.
(2) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Hegarty, M. P.; Bell, E.A. *Phytochemistry* **1988**, *27*, 1403.

0022-3263/92/1957-3078$03.00/0