1,3-Dipolar Cycloaddition Reactions of Cyclooctyne with Azomethine Ylides

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Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Cyclooctyne smoothly underwent 1,3-dipolar cycloaddition with aziridines and pyridinium ylides to afford the corresponding pyrroles and indolizines in moderate to good yields.

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Cyclooctyne is the smallest cyclic alkyne that is stable at room temperature and has been prepared by a number of methods which either start from cyclooctene or from cyclooctanone [1-5]. Usually, 1,3-dipolar cycloaddition reactions (HOMO-LUMO controlled) of dipoles with acetylene and non-activated alkynes either proceed only sluggishly or fails [6]. In spite of high strain and high reactivity of cyclooctyne as well as synthetic potential of its cycloadditions, only few examples of 1,3-dipolar cycloaddition reactions have been reported [7,8]. We describe below 1,3-dipolar cycloadditions of cyclooctyne (**1**) onto azomethine ylides generated from aziridines **2** and stable azomethine ylides such as pyridinium dicyanomethylides and pyridinium bis(methoxycarbonyl)methylides **4**.

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First, we chose certain aziridines as precursors of azomethine ylides since we have investigated their 1,3-dipolar cycloadditions with three and four membered cycloalkenes [9] as well as their ^{13}C nmr spectra [10]. Reaction of (*Z*)-1-benzyl-2,3-diphenylaziridine [11] (**2a**, 1.30 mmoles) with **1** (1.62 mmoles) in refluxing toluene for 96 hours gave, after usual work up, 33% yield of the pyrrole **3**. No primary 1:1 adduct could not be isolated. In contrast, (*E*)-1-benzyl-2,3-diphenylaziridine reacted more smoothly with **1** under the similar conditions, to afford 61% yield of the same pyrrole [12]. A less reactive aziridine than **2a** [11], (*Z*)-1,2,3-triphenylaziridine (**2b**) and 1-cyclohexyl-2-benzoyl-3-phenylazirine (**2c**) (mixture of (*E*) and (*Z*) isomers) underwent a similar cycloaddition, producing the corressponding pyrroles, albeit in low yields. The results are summarized in Table 1.

Next, reactions of **1** with pyridinium dicyanomethylides and pyridinium bis(methoxycarbonyl)methylides **4** were

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2a: $R^1 = PhCH_2$, $R^2 = R^3 = Ph$
2b: $R^1 = R^2 = R^3 = Ph$
2c: $R^1 = C_6H_{11}$, $R^2 = PhCO$, $R^3 = Ph$

Table 1

Pyrroles **3** by Reaction of Aziridines **2** with Cyclooctyne (**1**) [a]

R^1	R^2	R^3	2 (mmoles)	1 (mmoles)	Time (h)	Yield (%)	mp (°C)
Ph	Ph	Ph	2.21	2.75	64	11	159
CH_2Ph	Ph	Ph	1.30	1.62	96	33	134-135
C_6H_{11}	COPh	Ph	2.00	3.22	7	18	111

[a] Isolated yields. Reaction conditions were not optimized.

Table 2

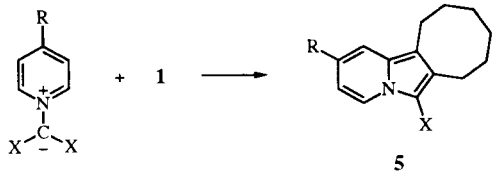
Pyrroles **5** by Reaction of Pyridinium Ylides **4** with **1** [a]

R	X	3 (mmoles)	1 (mmoles)	Time (h)	Yield (%)	mp (°C)
H	CN	1.64	1.64	1.5	62	126-127
Me	CN	1.42	1.71	5	41	100-101
COMe	CN	1.64	2.31	1	64	165-167
H	CO_2Me	2.14	3.00	9	62	82-83
Me	CO_2Me	0.96	1.20	1	41	82-83
COMe	CO_2Me	0.61	0.78	2	66	173

[a] Isolated yields. The reaction conditions were not optimized.

investigated because we have explored facile synthesis of indolizines by their 1,3-dipolar cycloadditions with alkynes and related equivalents [13], and have studied regioselectivity in the 1,3-dipolar cycloaddition reaction of unsymmetric pyridinium dicyanomethylides with dimethyl acetylenedicarboxylate and methyl propiolate [14]. For example, reactions of pyridinium dicyanomethylide (**4a**, 1.64 mmoles) with **1** (1.64 mmoles) in refluxing toluene for 1.5 hours gave, after spontaneous dehydrogenation, 62% yield of the indolizine **5a**. Pyridinium bis(methoxycarbonyl)methylides **4d-f** also underwent smooth cycloaddition with **1** to afford the corresponding indolizines in moderate to good yields. The results are summarized in Table 2. The fact that higher yields were obtained when electron withdrawing substituents were present in 4-position of pyridinium ylides suggests that the reactions were controlled by dipole-(LUMO)-cyclooctyne(HOMO). This is in agreement with the molecular orbital calculations performed by Extend Hückel, PM3, AM1 and MNDO methods (CAChe).

Further studies are underway employing other dipoles as well as dienes including regioselective aspects.



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4a: R = H, X = CN
4b: R = Me, X = CN
4c: R = COMe, X = CN
4d: R = H, X = CO_2Me
4e: R = Me, X = CO_2Me
4f: R = COMe, X = CO_2Me

Typical Examples of Spectroscopic and Analytical Data.

10-Benzyl-9,11-diphenyl-10-azabicyclo[6.3.0]undeca-8,11-diene (**3a**).

This compound was obtained as a white solid, mp 134-135° (ethanol/hexane); ^1H nmr (deuteriochloroform): 1.60 (s, 8H), 2.40-2.66 (m, 4H), 4.90 (s, 2H), 7.20 (m, 10H); ^{13}C nmr (deuteriochloroform): 23.3 (t), 26.2 (t), 32.4 (t), 48.7 (t), 122.5 (d)' 125.8 (d), 126.3 (s), 126.8 (d), 127.9 (d), 128.0 (d), 130.6 (d), 131.8 (s), 133.4 (s), 140.0 (s); ir (potassium bromide): 2920, 1600, 1450, 1350, 750, 700 cm^{-1}; ms: m/z (relative intensity) 391 (100, M^+), 300 (86), 91 (79).

Anal. Calcd. for $C_{28}H_{27}N$: C, 88.96; H, 7.46; N, 3.58. Found: C, 89.01; H, 7.32; N, 3.50.

8-Cyano-7-azatricyclo[7.6.0.$0^{2,7}$]pentadeca-1,3,5,8-tetraene (**5a**).

This compound was obtained as a white solid, mp 126-127° (ethanol/hexane); ^1H nmr (deuteriochloroform): 1.40-2.00 (m, 8H), 2.68-3.10 (m, 4H), 6.66-7.15 (m, 2H), 7.50 (d, J = 6.0 Hz, 1H), 8.25 (d, J = 3.0 Hz, 1H); ^{13}C nmr (deuteriochloroform): 22.0 (t), 24.1 (t), 25.6 (t), 25.8 (t), 30.2 (t), 30.8 (t), 93.1 (s), 111.9 (d), 114.1 (s), 114.4 (s), 116.9 (d), 120.7 (d), 125.3 (d), 133.7 (s), 138.0 (s); ir (potassium bromide): 2940, 2850, 2200, 1460, 1445, 1400, 1315, 1240, 1140, 750, 725 cm^{-1}; ms: m/z (relative intensity) 224 (100, M^+), 196 (46), 181 (82), 169 (52), 168 (77), 156 (36).

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.41; H, 7.29; N, 12.51.

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[12] This is in accord with the results by MM2 calculations (CAChe), the primary adduct from (*E*)-isomer being more stable than that from (*Z*)-isomer.

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