A Synthesis of some Novel 4,5-Dihydroazepines by the Reaction of Oxazolium 5-Oxides with 1,2-Dicyanocyclobutene (1)

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Heating primary or secondary α-amino acids in acetic anhydride in the presence of 1,2-dicyanocyclobutene leads to 4,5-dihydroazepines *via* the intermediacy of mesoionic oxazolium 5-oxides.

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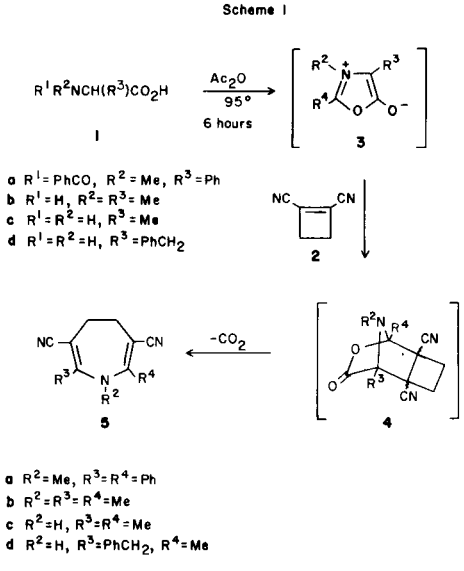
Mesoionic compounds are versatile intermediates in heterocyclic synthesis (2). Over the past decade, oxazolium 5-oxides, otherwise known as Munchnones, have been exploited extensively in pyrrole synthesis (2-4). 1,3-Dipolar cycloaddition of the masked azomethine ylide of the Munchnone system to various acetylenic dipolarophiles followed by a 1,3-dipolar cycloreversion of carbon dioxide from the initially-formed adduct provides pyrrole derivatives (4a). Hershenson (5) and Albonico, *et al.* (6), among others (7) have applied this concept successfully to the synthesis of the indolizidine and pyrrolizidine skeletons *via* the use of Munchnones derived from cyclic α-amino acids such as proline and piperidinecarboxylic acid. Rebek and Gehret have explored this pathway in an approach to mitosenes (8).

Several groups have studied the 1,3-dipolar cycloaddition of mesoionic oxazoles and thiazoles to cyclopropenes and cyclopropenones (9). This process leads to the formation of pyridine derivatives. 1,4-Thiazine 1,1-dioxides arise from the dipolar addition of 2,3-diphenylthiirene 1,1-dioxide to mesoionic oxazoles (10). 2,4-Diphenyl-3-methyloxazolium 5-oxide reacts with cyclobutenes to afford monocyclic 4,5-dihydroazepines (11).

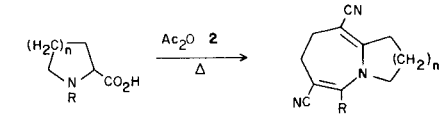
Scheme I



We have found 1,2-dicyanocyclobutene (**2**) (12) to be an effective dipolarophile in its reactions with a variety of Munchnones to provide both monocyclic and fused bicyclic 4,5-dihydroazepines **5** and **7**, respectively, in good yield. As depicted in Scheme I below, this transformation probably involves initial formation of the mesoionic oxazoles of type **3** from the α-amino acids **1**, followed by 1,3-dipolar cycloaddition of **2** to **3**. Elimination of carbon dioxide with cleavage of the cyclobutane ring of **4** leads to the observed 4,5-dihyroazepines **5**. Support for this mechanism comes from the case of **1a** in which the mesoionic oxazole **3a** was isolated (4a) and converted to **5a** by warming with **2** in toluene.

In a similar manner, the fused bicyclic dihydroazepines **7** are formed in good yields when the cyclic α-amino acids **6** are heated in acetic anhydride in the presence of **2** (Scheme II).

Scheme II



6

a n=1, R=CHO
b n=1, R=H
c n=1, R=PhCO
d n=2, R=CHO
e n=2, R=H
f n=3, R=H (13)

7

a n=1, R=H
b n=1, R=Me
c n=1, R=Ph
d n=2, R=H
e n=2, R=Me
f n=3, R=Me

Thus the procedure outlined above constitutes a viable method for the construction of the 1-azabicyclo[5.n.0]-alkane system (14). We are currently investigating the reactions of mesoionic systems with cyclobutenes and heterocyclobutenes in order to extend the scope of this transformation to include other types of 7-membered ring heterocycles.

EXPERIMENTAL

Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 283 Spectrophotometer, nmr with a Perkin-Elmer

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R32 (90 MHz) spectrometer, and mass spectra with either a Hitachi RMU 6E (electron impact) or a Finnigan GC/MS Model 3200 (chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by our Analytical/Physical Chemistry Department.

1-Methyl-2,7-diphenylazepine-3,6-dicarbonitrile (**5a**).

A mixture of 2,4-diphenyl-3-methyloxazolium 5-oxide (**3a**, 10 mmoles, 2.51 g.) (4a) and 1,2-dicyanocyclobutene (**2**, 12 mmoles, 1.25 g.) in toluene (20 ml.) was heated to 50° in a water bath for 30 minutes. The mixture was concentrated under reduced pressure and the residue recrystallized from ethanol to give **5a** (85%, 2.65 g.).

General Procedure for the Preparation of **5a,d** and **7a-f**.

A mixture of the amino acid **1** or **6** (10 mmoles) and 1,2-dicyanocyclobutene (**2**, 12 mmoles) in acetic anhydride (10 ml.) was heated (95%, 6 hours for **5a-d**; reaction temperatures and times for **7a-f**, given below). The volatile materials were removed under reduced pressure and the residue was dissolved in methylene chloride, washed with 10% sodium bicarbonate solution, then with water and dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was passed through a column of silica gel (chloroform eluent) and the material thus obtained was recrystallized (solvents given below) to afford analytically pure products.

1-Methyl-2,7-diphenylazepine-3,6-dicarbonitrile (**5a**).

This compound was recrystallized from ethanol, 78% yield, m.p. 243-245°; ir (potassium bromide): 770, 1335, 1345, 1575, 1585, 1625, 2205, 2215, 2940, 3065 cm^{-1}; nmr (DMSO-d_6): δ 2.36 (s, 3H), 2.81 (s, 4H), 7.48 (s, 10H); me: (electron impact) m/e 311 (M^+), 283, 118.

Anal. Calcd. for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.03; H, 5.49; N, 13.42.

1,2,7-Trimethylazepine-3,6-dicarbonitrile (**5b**).

This compound was recrystallized from aqueous ethanol, 93% yield, m.p. 93-94°; ir (potassium bromide): 1000, 1050, 1110, 1130, 1160, 1180, 1220, 1260, 1330, 1395, 1480, 1580, 1640, 2200, 2850 cm^{-1}; nmr (deuteriochloroform): δ 2.21 (s, 6H), 2.52 (s, 4H), 3.00 (s, 3H); ms: (electron impact) m/e 187 (M^+), 159, 56, 43.

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.57; H, 7.00; N, 22.44. Found: C, 71.01; H, 6.98; N, 22.34.

2,7-Dimethylazepine-3,6-dicarbonitrile (**5c**).

This compound was recrystallized from aqueous ethanol, 76% yield, m.p. 185-186° ir (potassium bromide): 1040, 1220, 1300, 1390, 1420, 1540, 1620, 1680, 2200, 2970, 3100, 3180, 3300, 3350 cm^{-1}; nmr (deuteriochloroform): δ 2.00 (s, 6H), 2.37 (s, 4H), 6.87 (br s, 1H, NH); ms: (electron impact) 173 (M^+), 70, 43.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.73; H, 6.46; N, 24.10.

2-Benzyl-7-methylazepine-3,6-dicarbonitrile (**5d**).

This compound was recrystallized from aqueous ethanol, 84% yield, m.p. 115-116°; ir (potassium bromide): 695, 1300, 1400, 1440, 1500, 1540, 1635, 1680, 2200, 2950, 3100, 3190, 3300, 3350, cm^{-1}; nmr (deuteriochloroform): δ 2.02 (s, 3H), 2.50 (s, 4H), 3.73 (s, 2H), 6.83 (br s, 1H, NH), 7.27 (s, 5H); ms: (chemical ionization) m/e 250 ($M^+ + 1$), 249 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.23; H, 5.76; N, 16.73.

2,3,7,8-Tetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-6,9-dicarbonitrile (**7a**).

This compound was recrystallized from aqueous ethanol, 52% yield, m.p. 138-139°, (reaction time-temperature: 12 hours 95°); ir (potassium bromide): 1310, 1400, 1425, 1600, 1650, 2190, 2970 cm^{-1}; nmr (deuteriochloroform): δ 2.01 (m, 2H), 2.55 (s, 4H), 2.92 (t, J = 8 Hz, 2H), 3.79 (t, J = 7.5 Hz, 2H), 6.74 (s, 1H); ms: (electron impact) m/e 185 (M^+), 157, 133.

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.68. Found: C, 71.33; H, 5.88; N, 22.63.

2,3,7,8-Tetrahydro-5-methyl-1*H*-pyrrolo[1,2-*a*]azepine-6,9-dicarbonitrile (**7b**).

This compound was recrystallized from ethanol, 85% yield, m.p. 117-118°, (reaction time-temperature: 6 hours 90°); ir (potassium bromide): 1195, 1225, 1305, 1355, 1385, 1585, 1625, 2150, 2180, 2940 cm^{-1}; nmr (deuteriochloroform): δ 1.98 (m, 2H), 2.26 (s, 3H), 2.53 (s, 4H), 2.92 (t, J = 8.0 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H); ms: (electron impact) 199 (M^+), 184, 171, 147.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.08. Found: C, 72.26; H, 6.92; N, 21.08.

2,3,7,8-Tetrahydro-5-phenyl-1*H*-pyrrolo[1,2-*a*]azepine-6,9-dicarbonitrile (**7c**).

This compound was recrystallized from aqueous ethanol or toluene-hexane, 65% yield, m.p. 136-137°, (reaction time-temperature: 12 hours 95°); ir (potassium bromide): 695, 745, 1155, 1185, 1225, 1310, 1385, 1585, 1620, 2185, 2900, 3050 cm^{-1}; nmr (deuteriochloroform): δ 1.79 (m, 2H), 2.60 (br s, 4H), 2.91 (t, J = 8.0 Hz, 2H), 3.25 (t, J = 8.0 Hz, 2H), 7.38 (br s, 5H); ms: (electron impact) 261 (M^+), 233, 209, 104.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.01; H, 5.70; N, 16.09.

1,2,3,4,8,9-Hexahydropyrido[1,2-*a*]azepine-7,10-dicarbonitrile (**7d**).

This compound was recrystallized from ethanol, 50% yield, m.p. 124-126°, (reaction time-temperature: 2 hours 75°); ir (potassium bromide): 1165, 1205, 1330, 1405, 1445, 1465, 1590, 1645, 2195, 2875, 2965 cm^{-1}; nmr (deuteriochloroform): δ 1.80 (m, 4H), 2.53 (s) and 2.65 (m, overlapping signals, 6H), 3.48 (distorted t, 2H), 6.59 (s, 1H); ms: (electron impact) m/e 199 (M^+), 171, 147, 82.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.30; H, 6.55; N, 21.18.

1,2,3,4,8,9-Hexahydro-6-methylpyrido[1,2-*a*]azepine-7,10-dicarbonitrile (**7e**).

This compound was recrystallized from aqueous ethanol, 85% yield, m.p. 95-96° (reaction time-temperature 2 hours 85°); ir (potassium bromide): 1310, 1330, 1405, 1455, 1580, 1630, 2200, 2260, 2900-3000 cm^{-1}; nmr (deuteriochloroform): δ 1.82 (m, 4H), 2.23 (s, 3H), 2.55 (s, 4H), 2.76 (m, 2H), 3.42 (distorted t, 2H); ms: (chemical ionization) m/e 214 ($M^+ + 1$).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.30; H, 6.96; N, 19.82.

2,3,4,5,9,10-Hexahydro-7-methyl-1*H*-azepino[1,2-*a*]azepine-8,11-dicarbonitrile (**7f**).

This compound was recrystallized from ethanol, 73% yield, m.p. 124-126°, (reaction time-temperature: 4 hours, 85°); ir (potassium bromide): 975, 1190, 1215, 1230, 1250, 1265, 1315, 1325, 1415, 1445, 1570, 1640, 2180, 2860, 2920 cm^{-1}; nmr (deuteriochloroform): δ 1.70 (br, s, 6H), 2.25 (s, 3H), 2.55 (s, 4H), 2.70 (m, 2H), 3.50 (distorted t, 2H); ms: (chemical ionization) m/e 228 ($M^+ + 1$).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.48. Found: C, 73.83; H, 7.60; N, 18.79.

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