A Facile Synthesis of Methyl (2Z,5E)-6-Aryl-4,4-Dicyano-5-Aza-2,5-hexadienoates [(1E,4Z)-2-Aza-1,4-Pentadienes]

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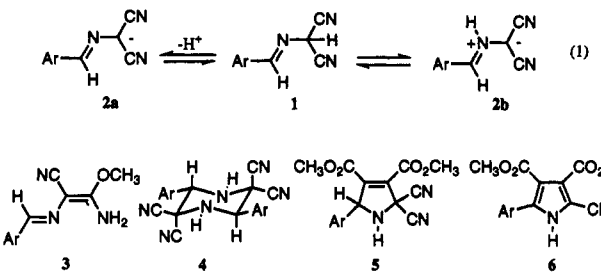
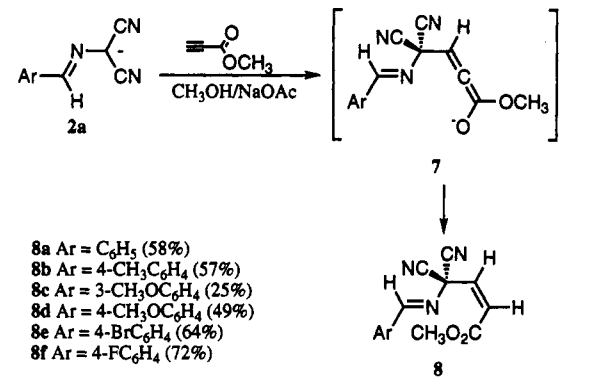
In the frontier molecular orbital treatment of [4 + 2] cycloadditions, the relative reactivity of a given 1,3-dipole toward a series of dipolarophiles is determined primarily by the stabilization afforded in the transition state by interaction of the HOMO and LUMO. Azomethine ylides react most readily with electron-deficient alkenes and alkynes owing to the small dipole HOMO-dipolarophile LUMO gap.[1-6] We observed[7-11] that either the 2-azaallyl anions **2a** or azomethine ylides **2b**[12-17] from the 2-azapropenes **1** led to highly functionalized 2-aza-1,3-butadienes **3** and piperazines **4**.[18-22] In the presence of dimethyl acetylenecarboxylate, the azomethine ylides **2** afforded 3-pyrrolines **5** which underwent dehydrocyanation to pyrroles **6**.[7,9,17]

Several experiments were performed in order to investigate the regioselectivity of the cycloaddition reaction.[7] An attempt to trap the anions **2a** or the ylides **2b** from **1** (Ar = C_6H_5)[12] with phenylethyne afforded a complex



mixture of products including (1*E*,3*E*)-4-amino-3-cyano-4-methoxy-1-phenyl-2-aza-1,3-butadiene and 2,2,5,5-tetracyano-*trans*-3,6-diphenylpiperazine.[7,8] The reaction of the anion **2a** (Ar = C_6H_5) with methyl propiolate gave methyl (2*Z*,5*E*)-4,4-dicyano-6-phenyl-5-aza-2,5-hexadienoate (**8a**) which may be viewed as an example of a rare highly functionalized 2-aza-1,4-pentadiene.[23,24] The formation of the (*E*,*Z*)-2-aza-1,4-pentadienes **8a–f** may involve Michael addition of anion **2a** to methyl propiolate (eq 2). Although 2-azaallyl anions and azomethine ylides



8a Ar = C_6H_5 (58%)
8b Ar = 4-$CH_3C_6H_4$ (57%)
8c Ar = 3-$CH_3OC_6H_4$ (25%)
8d Ar = 4-$CH_3OC_6H_4$ (49%)
8e Ar = 4-BrC_6H_4 (64%)
8f Ar = 4-FC_6H_4 (72%)

undergo cycloaddition reactions with methyl propiolate,[25-28] the proposed conjugate addition mechanism is reasonable since Michael reactions can take place under acidic experimental conditions[29] and because of the great susceptibility of triple bonds to nucleophilic attack.[30]

The ^{1}H NMR spectra of the (1*E*,4*Z*)-2-aza-1,4-pentadienes **8a–f** show an AB quartet pattern for the two vinylic protons in the 6.5–6.7 ppm region with J_{AB} values of 2–9 Hz which suggest that the substituents on the double bond are *cis* to each other. The ^{13}C NMR spectra of the two nitrile carbons appear as a singlet in the 112.3–112.7 ppm region and the quaternary carbon attached to the two cyano groups appear in the 52.5–53.6 ppm region. The structure of methyl (2*Z*,5*E*)-4,4-dicyano-6-(4-methylphenyl)-5-aza-2,5-hexadienoate (**8b**) was further confirmed by single crystal X-ray analysis.[31]

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(12) The addition of aminopropanedinitrile to aromatic aldehydes in the presence of sodium acetate in methanol affords amino alcohols which undergo dehydration to the imines **1**.[7] Loss of the acidic proton in **1** leads to the 2-azaallyl anion **2a** while a 1,2-prototropic shift in **1** affords the azomethine ylide **2b**. Although the 2-azaallyl anion **2a** is the likely reactive intermediate, the imine **1**, **2a**, and azomethine ylide **2b** may be in equilibrium in the reaction mixture.
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(17) The 2-azaallyl anions resemble 1,3-dipoles in their molecular orbital schemes and undergo 1,3-cycloaddition reactions.[5]
(18) Normally, dimerization of acyclic 1,3-dipoles is rare,[19-22] although the 3-oxido-1-arylpyridiniums are exceptional in this regard.[2]
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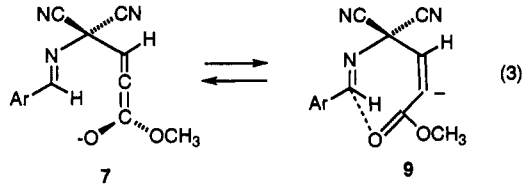
The diastereoselective formation of the *Z* double bond in **8** is of interest.[32-46] The *cis*-stereochemistry lies in dipole-directed coiling of the anionic intermediate **7** (eq 3) that places the partially negative oxygen close to the



partially positive benzylidene carbon atom.[32,34] Protonation of the anion **9** leads to the *cis*-stereochemistry in the product **8**.

Experimental Section

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ 07940. HRMS were obtained at 70eV. CIMS (2-methylpropane) and EIMS were obtained at an ionization potential of 70 or 100 eV. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 at 300 and 125 MHz, respectively. IR spectra were obtained as KBr disks.

Analytical TLC was performed on Analtech Uniplate 10 × 20 cm (250 μm thick) silica gel GF prescored glass plates, which were developed with 1:1, 2:1, or 10:1 hexanes/ethyl acetate. The plates were visualized by UV or I_2. Flash column chromatography was performed on 230–400 mesh silica gel.

Aminopropanedinitrile (aminomalononitrile) was generated from aminopropanedinitrile 4-methylbenzenesulfonate (tosylate).[7,8]

General Procedure for the Preparation of Methyl (2*Z*,5*E*)-6-Aryl-4,4-dicyano-5-aza-2,5-hexadienoates (8). To a solution of aminopropanedinitrile 4-methylbenzenesulfonate (1.17 g, 4.6 mmol), absolute methanol (20 mL), and anhydrous NaOAc (0.5 g, 6.05 mmol) were added, dropwise, with stirring at rt, phenylmethanal (0.50 g, 4.6 mmol) and methyl propiolate (0.58 g, 6.9 mmol). The reaction mixture was stirred at rt for 12–16 h, diluted with 100 mL of (1:1) ethyl acetate/ether solution, and washed with H_2O (3 × 100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated *in vacuo*. The residue was chromatographed (1:3 ethyl acetate/hexanes) to afford **methyl (2*Z*,5*E*)-4,4-dicyano-6-phenyl-5-aza-2,5-hexadienoate** (**8a**, 58%): mp 103–104 °C; IR (cm^{-1}) 3059 (=C—H), 2958 (C—H), 1719 (C=O), 1638 (C=N), 1580 (C=C); ^{1}H NMR δ 3.88 (s, 3 H), 6.65 (q, 2 H, *J* = 9.4 Hz), 7.63–8.08 (m, 5 H), 8.91 (s, 1 H); ^{13}C NMR δ 56.3, 60.5, 115.8, 130.9, 133.1, 133.6, 137.3, 142.0, 168.2, 171.4; HRCIMS *m* + *1/z* 254.0929 (calcd for $C_{14}H_{11}N_3O_2$ 254.0929). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.32; H, 4.32; N, 16.61.

Methyl (2*Z*,5*E*)-4,4-Dicyano-6-(4-methylphenyl)-5-aza-2,5-hexadienoate (8b): 57%; mp 88–89 °C; IR (cm^{-1}) 2958 (C—H), 1718 (C=O), 1624 (C=N), 1605 (C=C); ^{1}H NMR δ 2.42 (s, 3 H), 3.84 (s, 3 H), 6.50–6.51 (m, 2 H, *J* = 2.41 Hz), 7.37–7.40 (m, 2 H), 7.88–7.91 (m, 2 H) 8.80 (s, 1 H); ^{13}C NMR δ 21.6, 52.6, 57.8, 112.6, 127.6, 130.5, 132.1, 139.5, 144.9, 165.0, 167.5; HREIMS *m/z* 267.1010 (calcd for $C_{15}H_{13}N_3O_2$ 267.1008). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73. Found: C, 67.21; H, 4.84; N, 15.81.

Methyl (2*Z*,5*E*)-4,4-Dicyano-6-(3-methoxyphenyl)-5-aza-2,5-hexadienoate (8c): yield 25%; mp 76–77 °C; IR (cm^{-1}) 3065 (=C—H), 2997 (C—H), 2840 (C—H), 1721 (C=O), 1648 (C=N), 1588 (C=C); ^{1}H NMR δ 3.84 (s, 3 H), 3.85 (s, 3 H), 6.47 (q, 2 H, *J* = 6.22 Hz), 7.15–7.56 (m, 4 H), 8.78 (s, 1 H); ^{13}C NMR δ 52.5, 55.7, 57.6, 112.3, 114.1, 120.2, 123.2, 127.5, 130.8, 135.6, 138.0, 160.7, 164.8, 167.42; HREIMS *m/z* 283.0957 (calcd for $C_{15}H_{13}N_3O_3$, 283.0957). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 63.60; H, 4.59; N, 14.84. Found: C, 63.59; H, 4.62; N, 14.81.

Methyl (2*Z*,5*E*)-4,4-Dicyano-6-(4-methoxyphenyl)-5-aza-2,5-hexadienoate (8d); yield 49%; mp 119–120 °C; IR (cm^{-1}) 3072 (=C—H), 2985 (C—H), 2951 (C—H), 2823 (C—H), 1716 (C=O), 1635 (C=N), 1600 (C=C); ^{1}H NMR δ 3.84 (s, 3 H), 3.90 (s, 3 H), 6.45–6.49 (q, 2 H, *J* = 7.52 Hz) 7.08–7.11 (m, 2 H), 7.95–7.98 (m, 2 H), 8.74 (s, 1 H); ^{13}C NMR δ 52.5, 56.0, 57.7, 112.7, 115.1, 115.3, 127.3, 127.5, 132.5, 139.7, 164.7, 165.0, 166.8; HRCIMS *m* + *1/z* 284.1024 (calcd for $C_{14}H_{13}N_3O_3$ + 1, 284.1043). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 63.60; H, 4.59; N, 14.84. Found: C, 63.88; H, 4.57; N, 14.87.

Methyl (2*Z*,5*E*)-(4-Bromophenyl)-4,4-dicyano-5-aza-2,5-hexadienoate (8e): yield 64%; mp 115–116 °C; IR (cm^{-1}) 3255 (=C—H), 3070 (=C—H), 2959 (C—H), 2221 (C=N), 1719 (C=O), 1646 (C=N), 1588 (C=C); ^{1}H NMR δ 3.84 (s, 3 H), 6.51 (q, 2 H, *J* = 3.10 Hz), 7.65–7.98 (m, 4 H), 8.85 (s, 1 H); ^{13}C NMR δ 52.6, 112.3, 127.7, 128.2, 132.0, 132.1, 133.1, 133.8, 139.1, 165.0, 166.8; HREIMS *m/z* 330.9827 (calcd for $C_{14}H_{10}N_3O_2Br$, 330.9956). Anal. Calcd for $C_{14}H_{10}N_3O_2Br$: C, 50.76; H, 3.02; N, 12.69. Found: C, 50.65; H, 3.08; N, 12.49.

Methyl (2*Z*,5*E*)-6-4,4-Dicyano-(4-fluorophenyl)-5-aza-2,5-hexadienoate (8f): yield 72%; mp 102–103 °C; IR (cm^{-1}) 3008 (=C—H), 2956 (C—H), 1725 (C=O), 1642 (C=N), 1595 (C=C); ^{1}H NMR δ 3.84 (s, 3 H), 6.51–6.55 (m, 2 H, *J* = 7.96 Hz), 7.31–7.38 (m, 2 H), 8.08–8.14 (m, 2 H), 8.85 (s, 1 H); ^{13}C NMR δ 52.6, 112.5, 116.9, 117.1, 127.7, 131.3, 133.0, 133.2, 139.2, 165.0, 166.5; HREIMS *m/z* 271.0780 (calcd for $C_{14}H_{10}N_3O_2F$, 271.0757). Anal. Calcd for $C_{14}H_{10}N_3O_2F$: C, 61.99; H, 3.69; N, 15.50. Found: C, 62.00; H, 3.66; N, 15.40.

(1*E*,3*E*)-4-Amino-3-cyano-4-methoxy-1-phenyl-2-aza-1,3-butadiene and 2,2,5,5-Tetracyano-*trans*-3,6-diphenylpiperazine. The general procedure described above was used with phenylethyne in place of methyl propiolate to afford (1*E*,3*E*)-4-amino-3-cyano-4-methoxy-1-phenyl-2-aza-1,3-butadiene (7%), mp 134–135 °C [lit.[8] mp 134–135 °C], and 2,2,5,5-tetracyano-*trans*-3,6-diphenylpiperazine (23%), mp 238–240 °C [lit.[7] mp 238–240 °C].

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