The Reaction of 1-[o-Bromomethylphenyl]alkylenemalonate, Cyanooacetate or Malononitrile with Azide Ion. Intramolecular 1,3-Dipolar Cycloaddition

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Evidence for intramolecular 1,3-dipolar cycloaddition is presented for the reaction of the title compounds with azide ion. The products are substituted isoindolino[2,1-c]A-triazolines (3) which vary greatly in thermal stability depending on the substituents in the 1- and 9b-positions. Thus, 1,1-dimethoxycarbonylisoindolino[2,1-c]A-triazoline (3a) is very stable, while the corresponding dicyano compound (3c) decomposes at -40°C to isoindolyldienemalonitrile (5c). Introduction of a methyl group in 9b-position of triazolines 3 leads to an increase in thermal stability and also to other decomposition products, viz. the hitherto unknown cyanomethoxybenzylic (6d) or dicyano-1-methyl-3H-isoindolenium methylide (6e). Mechanistic proposals are given for the formation of 5 and 6, involving a primary carbon-nitrogen bond cleavage of the A-triazolines 3.

Reactions of o-bromomethylbenzylidenemalonates with certain nucleophiles (methoxide or cyanide ion) yielded indans, while others gave the normal benzylic substitution products.1 Azide ion, however, reacts with the substrates in a more complex manner and evidence for intramolecular 1,3-dipolar cycloaddition constituting part of the reaction sequence is presented in this paper.

Substrates having both a 1,3-dipolar and a dipolarophilic function suitably spaced within the molecule may undergo intramolecular 1,3-dipolar cycloaddition to form annelated heterocyclic compounds.2 When the 1,3-dipole is an azide function, the isolated products may contain all three nitrogen atoms,3 or such compounds can be detected as intermediates by spectroscopic means.4

When o-bromomethylbenzylidenemalonate 1a was treated with sodium azide in aqueous methanol a compound with all three nitrogen atoms intact was obtained. The absence of azide and C=CN absorptions in the IR spectrum indicated that an intramolecular cycloaddition had taken place, and the compound was named 1,1-dimethoxycarbonylisoindolino[2,1-c]A-triazoline (3a). On the other hand, similar treatment of 1b and 1c yielded isoindolyldicyanooacetate (5b) and -malononitrile (5c), respectively.

Reaction of 1b with tetrabutylammonium azide at low temperature gave 3b after careful

Scheme 1. a: R = H, X = Y = CO₂Me. b: R = H, X = CO₂Me, Y = CN. c: R = H, X = Y = CN. d: R = Me, X = CO₂Me, Y = CN. e: R = Me, X = Y = CN.
work-up, whereas the same reaction of 1e at low temperature monitored by $^1$H NMR spectroscopy indicated the intermediacy of 3c. This technique also confirmed that the first step is a nucleophilic substitution of bromine by azide ion to give 2 (see Experimental).

In principle two structures (3 and 4) are possible for the primary cycloaddition product, both equally feasible as judged from molecular model considerations and both fitting the spectroscopic properties. However, based on the reported reactivity of the nitrogen atoms of the azido group, where N-1 is the more nucleophilic one and N-3 being most electrophilic, combined with the observed electrophilicity of the $sp^2$ benzylic carbon atom in 1, structure 3 is considered more reasonable.

The stability of the triazolines 3 varies considerably. While 3b and 3c decomposed spontaneously at (3b) or well below (3c) 20°C, 3a was thermally stable and could be recrystallized unchanged from triethylamine, in contrast to the addition product from phenyl azide and methyl acrylate which carries an acidic hydrogen. The thermal decomposition of 3b and 3c yielded quantitatively the isindolinylidene derivatives 5b and 5c with liberation of an equimolar amount of nitrogen.

The decomposition must involve a migration (onestep or multistep) of the hydrogen atom (as proton, hydrogen atom or hydride ion) from C-9b in 3 to the nitrogen atom in 5. Thus it would be of interest to see how the introduction of a methyl group at C-9b would influence the decomposition reaction. The alkylidene derivatives 1d and 1e were made from 1b and 1c respectively, by treatment with diazomethane giving the $^1$-pyrazolines which in situ decomposed to 1d and 1e. The triazoline 3d was surprisingly stable, could be recrystallized and kept for months at room temperature, while triazoline 3e decomposed under the same conditions. A qualitative estimate indicated the relative thermal stabilities: $3a > 3d > 3b > 3e > 3c$.

The decomposition of 3d and 3e followed entirely different routes. Thus 3e decomposed quantitatively at room temperature to the hitherto unknown 3H-isindolenium methyldide 6e, the structure of which was confirmed by X-ray crystallography. On heating above its melting point (120°C) 3d decomposed to an intractable mass (probably polymeric as judged from the $^1$H NMR spectrum) from which no single product could be obtained. Upon addition of catalytic amounts of trifluoroacetic acid 3d rapidly decomposed to 6d.

The thermolytic decomposition of $^1$-1,2,3-triazolines has been studied by several groups. 4-Methoxy carbonyl-1-phenyl-1,2,3-triazoline gave quantitative yields of the corresponding 1-phenyl-2-methoxy carbonyl-aziridine. In addition to aziridines enamines were also found as products in the decompositions of $^1$-1,2,3-triazolines having electro-negative substituents in 4-position. Aziridines and cyclic imines were observed as products of the thermal decomposition of bicyclic $^1$-1,2,3-triazolines having alkyl substituents in 4- and 5-positions. Although no conclusive evidence concerning the mechanism of decomposition is presented, it has been assumed that the first step is cleavage of one N-N bond. Based on kinetic measurements it is suggested that this bond breaking is homolytic.

The relative stabilities of the 3a, 3b and 3c and 3d and 3e, respectively, lead us to suggest that in this system the C$_1$-N$_4$ bond is the

Scheme 2.

weaker one. Cleavage of this bond gives us the zwiterture 7. The isolation of 4-substituted oxazolines from decomposition of 4-acetyl-substituted \(\alpha^4\)-1,2,3-triazoline also points to a corresponding zwiterture.\(^8\) The stability of 7 is a function of substituents X and Y. When both are methoxy carbonyl groups the equilibrium \(3 \equiv 7\) is shifted completely to the left. When X and/or Y are cyano groups, zwiterture 7 is expected to have lower free energy as the corresponding carbon acids dissociate easier by introduction of cyano groups. (Malononitrile, \(pK_A = 11.7\), malonic ester \(pK_A = 13.5\)).

The acid-catalyzed decomposition of 3d is understandable in that protonation of 7 leads to 10 which most certainly rapidly would lose nitrogen to give 11. That the azidines 9 are true intermediates, at least when R=Me, is reasonable. We have been able, by low temperature \(^1H\) NMR spectroscopic monitoring, to observe signals from an unknown intermediate in the acid-catalyzed decomposition of triazoline 3d. The signals appear in the vicinity of the methylene and methyl signals of 6d, and may possibly stem from aziridine 9d (or 12d).

The formation of the isodindolylidened derivatives 5 from the nonmethylated triazolines does not necessarily involve the intermediacy of azidines. They may simply be formed in a concerted manner directly from switerture 7 by a 1,2-shift of hydrogen. Another mechanistic possibility is that the imine 13 is formed in a concerted manner from 7 and tautomerized to 6.

**EXPERIMENTAL**

**General.** Spectroscopic data were recorded on a Varian A 60A NMR spectrometer, an HA 100-15D NMR spectrometer (operating at 98 MHz), a JEOL FX60-NMR-spectrometer, a Perkin-Elmer 457 IR spectrophotometer, a Cary 16 UV spectrophotometer and an AEI MS 902 mass spectrometer. Molecular weights were obtained using a Knauer Vapor Pressure Osmometer. Melting points are not corrected.

**Materials.** The o-bromomethylbenzylidene compounds 1a, 1b and 1c were synthesized as described previously.\(^1\) Alkyldiene derivatives 1d and 1e were made by mixing ether solutions of 1d and 1e with 5\% excess of diazomethane in ether. After the nitrogen evolution had ceased the ether was evaporated leaving oils which partly crystallized. Recrystallization from methanol gave pure 1d and 1e. 1d: M.p 93–95\(^\circ\)C. Found: C 53.6; H 4.3; N 5.1. Calc. for \(C_8H_7BrNO_2\): C 53.1; H 4.1; N 4.9.\(^2\) \(^1H\) NMR (98 MHz, CDCl\(_3\)): \(\delta\) 2.75 (3H, s), 3.81 (2H, q), 4.86 (2H, s), 6.9–7.6 (6H, m).\(^2\)

Anal. \(C_{13}H_{19}BrNO_2\): C, H. \(^1H\) NMR (98 MHz, CDCl\(_3\)): 2.65 (3H, s), 4.42 (2H, s), 6.9–7.3 (1H, m), 7.3–7.6 (3H, m).

(3d). 1a (15.7 g 0.05 mol) was dissolved in 250 mL of methanol and sodium azide (3.25 g, 0.05 mol) dissolved in 100 mL of water was added dropwise (room temperature) while nitrogen was bubbled through the solution. After 2 h the greyish precipitate was collected, 10.8 g (78\%), m.p. 95–96\(^\circ\)C (MeOH). Anal. \(C_7H_{13}N_3O_2\): C, H, N. Mol. wt., calc. 275, found 274. MS: 247 (M+–N\(_2\)). IR (KBr):\(1735\) (s) cm\(^{-1}\), \(^1H\) NMR (60 MHz, CDCl\(_3\)): \(\delta\) 3.70 (3H, s), 3.92 (3H, s), 4.68 (1H, d, \(J 15.5\) Hz), 5.34 (1H, d, \(J 15.5\) Hz), 5.71 (1H, s) 7.0–7.4 (4H, m).\(^3\) \(^13C\) NMR (15 MHz, CDCl\(_3\)): \(\delta\) 53.0 and 54.0 (2x CH\(_2\)O), 55.0 (C5), 68.2 (C9b) 125.0 (C1), 123.2–127.9–129.3 (C6–C9), 130.0 and 137.8 (C5a+C9a), 163.0 and 166.3 (C=C=O).

(5b). 1b (10.2 g, 0.035 mol) was dissolved in 350 mL of methanol kept at 40–50\(^\circ\)C. An aqueous solution (0.8 M) of sodium azide (2.4 g, 0.035 mol) was added dropwise while nitrogen was bubbled through the solution. After holding for 24 h the precipitate was collected, 4.0 g (52\%), m.p. 236\(^\circ\)C (MeOH). Anal. \(C_7H_{13}N_3O_2\): C, H, N. MS: [M]+ 70 ev; \(m/\varepsilon\) (rel. int.) 214 (100, M), 199 (20, M–CH\(_3\)), 183 (30, M–OCH\(_3\)), 181 (28, M–CH\(_2\)-H\(_2\)); \(m/\varepsilon\) 199–181, obs. 164.7, calc. 164.6. \(^1H\) NMR (60 MHz, \(CF_3COOH\)): \(\delta\) 3.92 (3H, s), 4.77 (2H, s) 7.5–7.8 (3H, broad), 8.2–8.6 (1H, broad).\(^3\) \(^13C\) NMR (15 MHz, DMSO-d\(_6\)): \(\delta\) 50.5 (OCH\(_3\)), 51.8 (C3), 63.1 (C8), 118.1 (C=CN), 122.8–124.0–127.4–131.3 (C4–C7) 132.3–143.3 (C9a+C9b), 163.9–167.4 (C=O and C). IR (KBr): 3390 (s), 2210 (s), 1870 (s), 1605 (s) cm\(^{-1}\).

1-Cyano-1-methoxycarbonylisodindolino[2,3-c]-\(\alpha^4\)-triazoline (3b). 1b (5.6 g, 0.02 mol) was dissolved in 35 mL methylene chloride and cooled to –10\(^\circ\)C. While stirring the solution tetrabutylammonium azide (6.0 g, 0.021 mol) dissolved in 35 mL methylene chloride was added dropwise. After 30 min \(^1H\) NMR showed the absence of peaks from the starting material and 100 mL iced water was added, stirring was continued for 15 min at 0\(^\circ\)C. The phases were separated and the lower organic phase was twice washed with iced water. After drying (MgSO\(_4\)) the solvent was evaporated at 0\(^\circ\)C. The residue (6 g) was dissolved in chloroform and pentane added. After cooling (–35\(^\circ\)C) the triazoline precipitated as off-white crystals. Leaving these crystals at room temperature for a prolonged time (15–20 min.) resulted in decomposition (see below). \(^1H\) NMR (98 MHz, CDCl\(_3\)): \(\delta\) 3.98 (3H, s), 4.75 (1H, d, \(J 16.0\) Hz), 5.08 (1H, s), 5.35 (1H, d, \(J 15.5\) Hz), 7.2–7.6

(4 H, m), <sup>13</sup>C NMR (15 MHz, CHCl<sub>3</sub>, -35 °C): δ 55.2 (C5), 55.4 (OCH<sub>3</sub>), 68.8 (C9b), 84.1 (C1), 111.9 (C=NN), 123.1 - 124.6 - 128.4 - 130.0 (C6 - C9), 134.2 and 136.6 (C5a + C9a), 163.0 (C=O).

Decomposition of triazoleine (3b). 3b (484 mg, 2 mmol) was dissolved in chloroform kept at 50 °C. Rapid nitrogen evolution occurred. Found 47.4 ml N<sub>2</sub>, calc. 49.2 ml (T = 300 K). Evaporation of the solvent gave a quantitative yield of 3b.

(5c). 1c (4.9 g, 0.02 mol) was dissolved in 100 ml methanol kept at 40 - 50 °C. An aqueous solution (1 M) of sodium azide (1.3 g, 0.02 mol) was added dropwise (under nitrogen). After cooling for 24 h a precipitate was collected, 1.5 g, m.p. > 250 °C (MeOH). Anal. C<sub>3</sub>H<sub>11</sub>N<sub>4</sub>; C, H, MS [IP 70 eV; m/e (% rel.int.)] 181 (100, M<sup>+</sup>), 180 (82, M-1). <sup>13</sup>C NMR (15 MHz, DMSO-d<sub>6</sub>): 51.9 (C3), 115.5 - 116.0 (C=NN), 122.9 - 123.5 - 123.6 - 131.7 (C4 - C7), 131.2 - 143.8 (C3a; C7a), 165.9 (C1). IR (KBr): 3270 (s), 2218 (s), 2210 (s), 1623 (s), 1610 (s), 1580 (s) cm<sup>-1</sup>. Reaction between bromide 1c and tetrabutylammonium azide. Equimolar quantities of 1c and tetrabutylammonium azide in deuterochloroform were mixed at -60 °C and the reaction was monitored by <sup>1</sup>H NMR (HA 100 - 16D). At -60 °C a peak gradually appeared in the olefinic region at 8.32 ppm (1c: 8.43) and another at 4.51 ppm (1c: 4.61). This corresponds to substitution of the bromide ion by the azido group (1c → 2a). At -40 °C the only change was an increase of the intensity of the peaks at 8.32 and 4.51 ppm. At -15 °C these peaks decreased in intensity while peaks at 4.69, 4.86, 5.33, 5.49 (AB-pattern of geminal methylene protons at C5 in 3c) and 5.61 ppm (methyl proton at C9b in 3c) increased. At even higher temperature gas was evolved and 3c started to precipitate.

1-Hydroxy-carbonyl-9b-methylisodolin[2,1-c]d<sub>3</sub>-triazone (3d). 1d (5.88 g, 0.02 mol) was dissolved in 35 ml methylene chloride. Tetrabutylammonium azide (6.0 g, 0.021 mol) dissolved in 35 ml methylene chloride was added slowly to the above solution (while stirring). After 30 min all starting material had reacted (checked by <sup>1</sup>H NMR) and tetrabutylammonium bromide was removed by repetitive extraction with water. Evaporation of the organic solvent gave 3d, 4.0 g (78 %), m.p. 120 °C (decd.-MeOH). Anal. C<sub>3</sub>H<sub>11</sub>N<sub>4</sub>O; C, H, N, MS: 228 (M<sup>+</sup> - NO<sub>2</sub>), <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>): δ 1.92 (3 H, s), 3.72 (3 H; s), 4.66 (1 H, d, J = 16 Hz), 5.28 (1 H, d, J = 16 Hz), 6.9 - 7.5 (4 H). <sup>13</sup>C NMR (15 MHz, CDCl<sub>3</sub>): δ 24.7 (CH<sub>3</sub>-C), 53.7 (C5), 53.9 (CH<sub>3</sub>O), 76.6 (C9b), 86.2 (C1), 112.4 (C=NN), 122.3 - 123.5 - 126.8 - 139.6 - 139.8 (C5a + C5b), 162.6 (C=O).

1,1-Dieyano-9b-methylisodolin[2,1-c]d<sub>3</sub>-triazone (3e). Following the same procedure as for preparation of triazolineine 3b, 3e was obtained. Left at room temperature for some time (~30 min) the triazoline decomposed (see below). <sup>1</sup>H NMR (98 MHz, CDCl<sub>3</sub>, -40 °C): δ 1.93 (3 H, s), 4.71 (1 H, d, J = 16 Hz), 5.37 (1 H, d, J = 16 Hz), 7.2 - 7.8 (4 H, m). <sup>13</sup>C NMR (15 MHz, CDCl<sub>3</sub>, -40 °C): δ 22.8 (CH<sub>3</sub>-C), 53.8 (C5), 74.3 (C9b), 81.5 (C1), 109.0 - 109.2 (2 x C=NN), 123.1 - 123.8 - 128.6 - 130.4 (C6 - C9), 134.7 - 137.9 (C5a + C9a).

3H-Isoindolenium methyldiene (6d). Upon addition of catalytic amounts of trifluoroacetic acid to a deuterochloroform solution of 3d in the NMR tube 6d was formed. <sup>1</sup>H NMR (98 MHz, CDCl<sub>3</sub>): δ 3.00 (t, 3 H, J = 2 Hz), 3.90 (s, 3 H), 5.20 (q, 2 H, J = 2 Hz), 7.5 - 8.2 (m, 4 H). <sup>13</sup>C NMR (15 MHz, CDCl<sub>3</sub>): δ 15.7 (CH<sub>3</sub>-C), 56.3 (CH<sub>3</sub>OH), 58.8 (C3), 109.0 (C8), 118.7 (C=NN), 125.5 - 128.1 - 132.2 - 139.0 (C4-C7), 134.9 - 147.8 (C3a - C7a), 166.8 (C=O), 186.5 (C1).

3H-Isoindolenium methyldiene (6c). 3e decomposed in the NMR-tube when the probe temperature was raised to 30 °C. Anal. C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O; C, H. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>): δ 2.78 (3 H, t, J = 2 Hz), 5.26 (2 H, q, J = 2 Hz), 7.52 (4 H, s). <sup>13</sup>C NMR (15 MHz, CDCl<sub>3</sub>): δ 16.6 (CH<sub>3</sub>-C), 63.9 (C3), 99.0 (C8), 119.0 (2 x C=NN), 121.1 - 122.1 - 129.6 - 131.3 (C4-C7), 136.7 - 137.6 (C3a + C7a), 175.0 (C1). IR (KBr): 2135 (s), 2170 (s).

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