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

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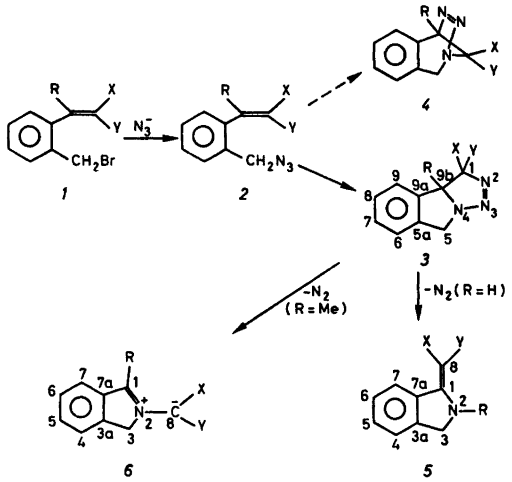
Evidence for intramolecular 1,3-dipolar cycloaddition is presented for the reaction of the title compounds with azide ion. The products are substituted isoindolino[2,1-*c*]Δ^2-triazolines (*3*) which vary greatly in thermal stability depending on the substituents in the 1- and 9b-positions. Thus, 1,1-dimethoxycarbonylisoindolino[2,1-*c*]Δ^2-triazoline (*3a*) is very stable, while the corresponding dicyano compound (*3c*) decomposes at −40 °C to isoindolylidenemalonitrile (*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 cyanomethoxycarbonyl- (*6d*) or dicyano-1-methyl-3*H*-isoindolenium methylide (*6e*). Mechanistic proposals are given for the formation of *5* and *6*, involving a primary carbon-nitrogen bond cleavage of the Δ^1-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=C absorptions in the IR spectrum indicated that an intramolecular cycloaddition had taken place, and the compound was named 1,1-dimethoxycarbonylisoindolino[2,1-*c*]Δ^2-triazoline (*3a*). On the other hand, similar treatment of *1b* and *1c* yielded isoindolylidenecyanoacetate (*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=CO_2Me. *b:* R=H, X=CO_2Me, Y=CN. *c:* R=H, X=Y=CN. *d:* R=Me, X=CO_2Me, Y=CN. *e:* R=Me, X=Y=CN.

work-up, whereas the same reaction of *1c* 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 [5] combined with the observed electrophilicity of the sp^2 benzylic carbon atom in *1*, [1,6] structure *3* is considered more reasonable.

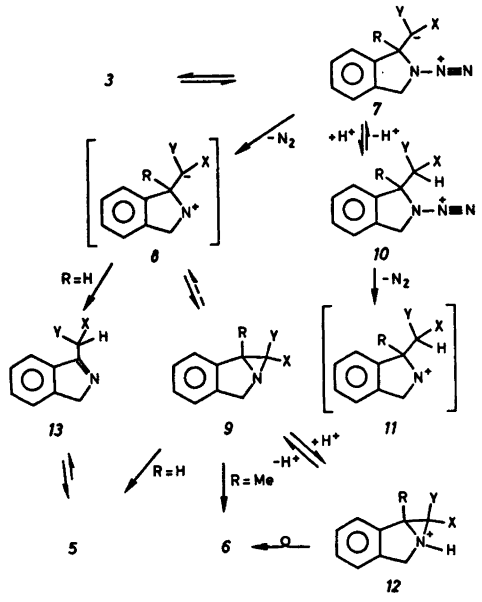
The stability of the triazolines *3* varies considerably. While *3b* and *3c* decomposed spontaneously at (*3b*) or well below (*3c*) 20 °C, *3a* was thermally stable and could be recrystallized unchanged from triethylamine, in contrast to the addition product from phenyl azide and methyl acrylate which carries an acidic hydrogen.[7] The thermal decomposition of *3b* and *3c* yielded quantitatively the isoindolinylidene 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 Δ^1-pyrazolines which *in situ* decomposed to *1d* and *1e*.[8] 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: $3a > 3d > 3b \geqslant 3e > 3c$.

The decomposition of *3d* and *3e* followed entirely different routes. Thus *3e* decomposed quantitatively at room temperature to the hitherto unknown 3*H*-isoindolenium methylide *6e*, the structure of which was confirmed by X-ray crystallography.[9] 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 trifluoracetic acid *3d* rapidly decomposed to *6d*.

The thermolytic decomposition of Δ^2-1,2,3-triazolines has been studied by several groups.[10–12] 4-Methoxycarbonyl-5-phenyl-Δ^2-1,2,3-triazoline gave quantitative yields of the corresponding 1-phenyl-2-methoxycarbonylaziridine.[10] In addition to aziridines enamines were also found as products in the decompositions of Δ^2-1,2,3-triazoline having electronegative substituents in 4-position.[11] Aziridines and cyclic imines were observed as products of the thermal decomposition of bicyclic Δ^2-1,2,3-triazolines having alkyl substituents in 4- and 5-positions.[3] 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 [10] it is suggested that this bond breaking is homolytic.[12]

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_2 bond is the



Scheme 2.

weaker one. Cleavage of this bond gives us the zwitterion *7*. The isolation of 4-substituted oxazolines from decomposition of 4-acetyl-substituted Δ^2-1,2,3-triazoline also points to a corresponding zwitterion.[13] The stability of *7* is a function of substituents X and Y. When both are methoxycarbonyl groups the equilibrium 3 ⇌ 7 is shifted completely to the left. When X and/or Y are cyano groups, zwitterion *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 loose nitrogen to give *11*. That the aziridines *9* are true intermediates, at least when R = Me, is reasonable. We have been able, by low temperature ^{1}H 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 isoindolinylidene derivatives *5* from the nonmethylated triazolines does not necessarily involve the intermediacy of aziridines. They may simply be formed in a concerted manner directly from switterion *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 then tautomerized to *5*.

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] Alkylidene derivatives *1d* and *1e* were made by mixing ether solutions of *1b* and *1c* 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 °C. Found: C 53.6; H 4.3; N 5.1 Calc. for $C_{13}H_{12}BrNO_2$: C 53.1; H 4.1; N 4.8. ^{1}H NMR (98 MHz, $CDCl_3$): δ 2.75 (3H,s), 3.89 (3H,s), 4.46 (2H,s), 6.9 – 7.6 (4H,m). *1e:* M.p. 75 – 77 °C. Anal. $C_{12}H_9BrN_2$: C, H. ^{1}H NMR (98 MHz, $CDCl_3$): 2.65 (3 H, s), 4.42 (2 H, s), 6.9 – 7.3 (1 H, m), 7.3 – 7.6 (3 H, m).

(3a). *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 °C (MeOH). Anal. $C_{18}H_{13}N_3O_4$: C, H, N. Mol. wt., calc. 275, found 274. MS: 247 ($M^+ - N_2$). IR (KBr): 1735 (s) cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.70 (3 H, s), 3.92 (3 H, s), 4.68 (1 H, d, J 15.5 Hz), 5.34 (1H, d, J 15.5 Hz), 5.71 (1 H, s) 7.0 – 7.4 (4 H, m). ^{13}C NMR (15 MHz, $CDCl_3$): δ 53.0 and 54.0 ($2 \times CH_3O$), 55.0 (C5), 68.2 (C9b) 95.0 (C1), 123.2 – 127.9 – 129.3 (C6 – C9), 136.0 and 137.6 (C5a + C9a), 165.0 and 165.3 (C = O).

(5b). *1b* (10.2 g, 0.035 mol) was dissolved in 350 ml of methanol kept at 40 – 50 °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 cooling for 24 h the precipitate was collected, 4.0 g (52 %), m.p. 236 °C (MeOH). Anal. $C_{12}H_{10}N_2O_2$: C, H, N. MS: [IP 70 eV; *m/e* (% rel.int.)] 214 (100, M), 199 (20, M – CH_3), 183 (30, M – OCH_3), 181 (28, M – CH_3 – H_2O); *m** 199 – 181, obs. 164.7, calc. 164.6. ^{1}NMR (60 MHz, CF_3COOH): δ 3.92 (3 H, s), 4.77 (2 H, s) 7.5 – 7.8 (3 H, broad), 8.2 – 8.6 (1 H, broad). ^{13}C NMR (15 MHz, DMSO-d_6): δ 50.5 (OCH_3), 51.8 (C3), 63.1 (C8), 118.1 (C≡N), 122.8 – 124.0 – 127.4 – 131.3 (C4 – C7) 132.2 – 143.3 (C3a + C7a), 163.9 – 167.4 (C = O and Cl). IR (KBr): 3330 (s), 2210 (s), 1670 (s), 1605 (s) cm^{-1}.

1-Cyano-1-methoxycarbonylisoindolino[2,1-c]-Δ^2-triazoline (3b). *1b* (5.6 g, 0.02 mol) was dissolved in 35 ml methylene chloride and cooled to – 10 °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 ^{1}H NMR showed the absence of peaks from the starting material and 100 ml icewater was added, stirring was continued for 15 min at 0 °C. The phases were separated and the lower organic phase was twice washed with icewater. After drying ($MgSO_4$) the solvent was evaporated at 0 °C. The residue (6 g) was dissolved in chloroform and pentane added. After cooling (– 35 °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). ^{1}H NMR (98 MHz, $CDCl_3$ – 40 °C: δ 3.98 (3 H, s), 4.75 (1 H, d, J 16.0 Hz), 5.08 (1 H, s), 5.35 (1 H, d, J 15.5 Hz), 7.2 – 7.6

(4 H, m). ^{13}C NMR (15 MHz, $CHCl_3$, −35 °C): δ 55.2 (C5), 55.4 (OCH_3), 68.8 (C9b), 84.1 (C1), 111.9 (C≡N), 123.1−124.6−128.4−130.0 (C6−C9), 134.2 and 136.6 (C5a+C9a), 163.0 (C=O).

Decomposition of triazoline (3b). *3b* (484 mg, 2 mmol) was dissolved in chloroform kept at 50 °C. Rapid nitrogen evolution occurred. Found 47.4 ml N_2, calc. 49.2 ml (T=300 K). Evaporation of the solvent gave a quantitative yield of *5b*.

(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. $C_{11}H_7N_3$): C, H. MS [IP 70 eV; *m/e* (% rel.int)] 181 (100, M), 180 (82, M-1). ^{13}C NMR (15 MHz, DMSO-d_6): 51.9 (C3), 115.5−116.0 (C≡N), 122.9−123.5−127.6−131.7 (C4−C7), 131.2−143.6 (C3a; C7a), 165.9 (C1). IR (KBr): 3270 (s), 2218 (s), 2210 (s), 1623 (s), 1610 (s), 1580 (s) cm^{-1}.

Reaction between bromide 1c *and tetrabutylammonium azide.* Equimolar quantities of *1c* and tetrabutylammonium azide in deuteriochloroform were mixed at −60 °C and the reaction was monitored by ^{1}H NMR (HA 100−15D). 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 ($1c \xrightarrow{N_3^-} 2c$). 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 5.51 ppm (methin proton at C9b in *3c*) increased. At even higher temperature gas was evolved and *5c* started to precipitate.

1-Cyano-1-methoxycarbonyl-9b-methylisoindolino[2,1-c]Δ²-triazoline (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 ^{1}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 (dec.-MeOH). Anal. $C_{13}H_{12}N_4O_2$: C, H, N. MS: 228 ($M^+ - N_2$). ^{1}H NMR (60 MHz, $CDCl_3$): 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 (m, 4 H). ^{13}C NMR (15 MHz, $CDCl_3$): δ 24.7 (CH_3-C), 53.7 (C5), 53.9 (CH_3O), 76.6 (C9b), 86.2 (C1), 112.4 (C≡N), 122.3−123.5−28.4−129.8 (C6−C9), 135.9−139.8 (C5a+C9a), 162.6 (C=O).

1,1-Dicyano-9b-methylisoindolino[2,1-c]Δ²-triazoline (3e). Following the same procedure as for preparation of triazoline *3b*, *3e* was obtained. Left at room temperature for some time (~30 min) the triazoline decomposed (see below). ^{1}H NMR (98 MHz, $CDCl_3$, −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). ^{13}C NMR (15 MHz, $CDCl_3$, −40 °C): δ 23.0 (CH_3-C), 53.8 (C5), 74.3 (C9b), 81.5 (C1), 109.0−109.2 (2×C≡N), 123.1−123.8−128.6−130.4 (C6−C9), 134.7−137.9 (C5a-C9a).

3H-Isoindolenium methylide (6d). Upon addition of catalytic amounts of trifluoroacetic acid to a deuteriochloroform solution of *3d* in the NMR tube *6d* was formed. ^{1}H NMR (98 MHz, $CDCl_3$): 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). ^{13}C NMR (15 MHz, $CDCl_3$) δ 15.7 (CH_3-C), 56.3 (CH_3O), 58.8 (C3), 109.0 (C8), 118.7 (C≡N), 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 methylide (6e). *3e* decomposed in the NMR-tube when the probe temperature was raised to 30 °C. Anal. $C_{12}H_8N_2$: C, H. ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.78 (3 H, t, J=2 Hz), 5.26 (2 H, q, J=2 Hz), 7.52 (4 H, s). ^{13}C NMR (15 MHz, $CDCl_3$): δ 16.6 (CH_3-C), 63.9 (C3), 99.0 (C8), 119.0 (2×C≡N), 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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