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v-TRIAZOLINES. Part XXIII.[1] CYCLOADDITION REACTIONS OF 4-NITROPHENYLAZIDE TO ENAMINES OF 1,4,5,6,-TETRAPHENYL-7-OXO-BICYCLO [2.2.1] HEPT-5-EN-2-CARBOXALDEHYDE

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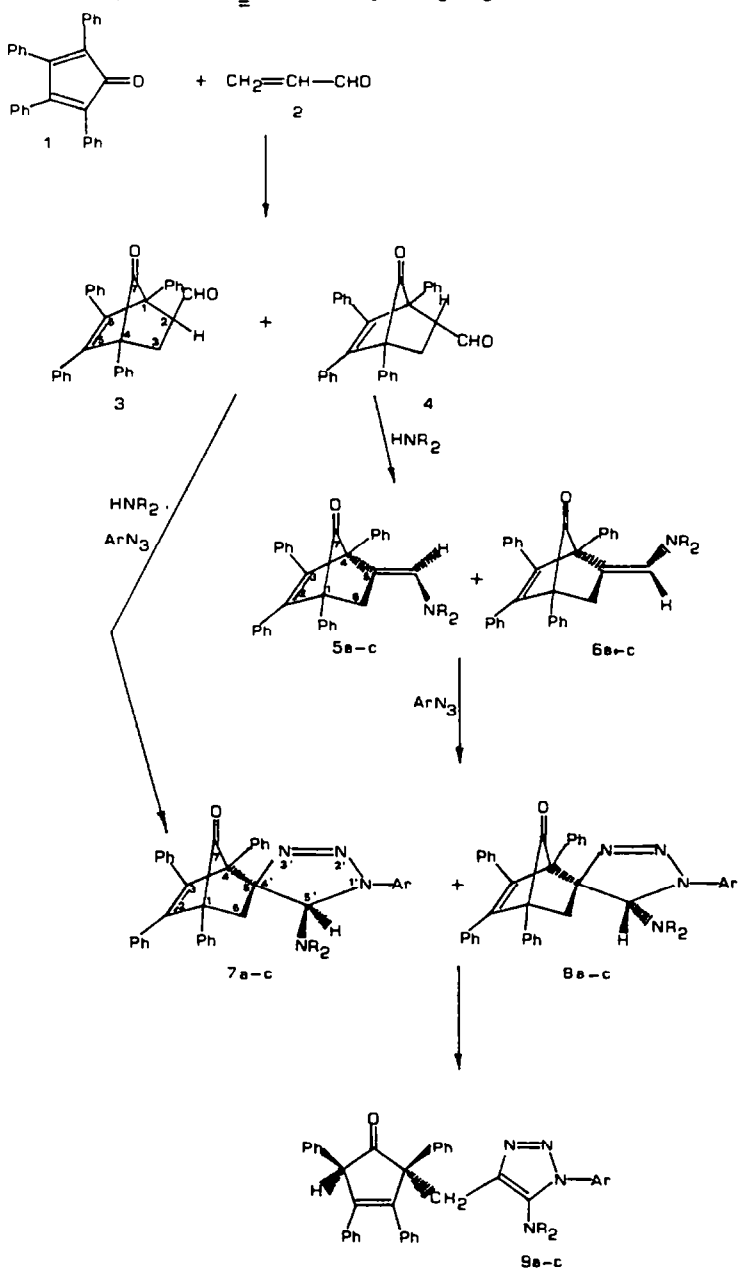
Abstract - Reaction of 4-nitrophenylazide with the enamines 5, 6 of 7-oxo-1, 4,5,6-tetraphenylbicyclo [2.2.1]hept-5-en-2-carboxaldehyde 3, 4 which may be isolated or prepared in situ from the aldehyde and the appropriate amine, resulted in the formation of a mixture of three products, namely two diastereoisomeric cycloadducts with the spiro [bicyclo-[2.2.1]hept-2-en-7-one [5.4']1',2',3'-triazole] structure 7 and 8 and rearrangement product of the former with the 5-amino-1-aryl-4-[cyclopent-3-en-1-one-2-yl]methyl-1,2,3-triazole structure (9).

Previous work from this laboratory[1] dealt with the reactions of substituted cyclopentadienones with 1-aryl-5-amino-4-methylene-v-triazolines which afforded cycloaddition products containing the spiro-[bicyclo[2.2.1]hept-2-en-7-one-[5.4']-1',2',3'-triazole ring. The cycloaddition reaction showed a high specificity yielding only one isolable product. The cycloadducts spontaneously rearranged to the corresponding 5-amino-1-aryl-4-[cyclopent-3-en-1-one-2-yl]methyl-v-triazoles. This easy rearrangement pathway is probably correlated both to the relief of strain in the bridged molecule and to a favourable geometry of the bonds involved in the rearrangement.

To achieve a better understanding of these crowded and strained v-triazoline derivatives we have studied the cycloaddition of 4-nitrophenylazide to the enamine of 1,4,5,6-tetraphenyl-7-oxo-bicyclo[2.2.1]hept-5-en-2-carboxaldehyde. In principle this reaction should produce the same spiranic adducts which are formed through Diels-Alder addition of cyclopentadienones to methylene-v-triazolines, possibly with a different configuration at the asymmetric centers.

RESULTS

The hitherto unknown aldehydes 3 and 4 were readily produced by reacting tetraphenylcyclopentadienone 1 with excess acrolein 2 in boiling benzene solution. A mixture of both stereoisomers 3 and 4 was formed in an approximate exo-endo ratio of 95:5. The less abundant product (4) was obtained in small amount through the elaboration of the mother liquors of 3. The ^{1}H-NMR spectrum of 3 shows the aldehyde hydrogen as a doublet at δ 9.83 (J = 5.0 Hz) and H-2 as a multiplet centered at δ 3.95. In the spectrum of 4 the corresponding signals are found at δ 9.42 (J = 4.5 Hz)



and δ 3.30, respectively. The exo-structure was assigned to the more abundant isomer since it is known that in the Diels-Alder adducts derived from tetraphenylcyclopentadienone the exo configuration is generally associated with lower field resonances of the corresponding endo hydrogen atom[2].

Although interesting in itself, the stereochemical course of the cycloaddition of 1 to 2 is of little relevance in the preparation of the corresponding enamines: obviously, the configuration at the center bearing the aldehyde function is lost during the enamination reaction. A mixture of enamines 5a,c and 6a,c was obtained by reacting 3 and 4, separately or as a mixture, with the corresponding secondary amine under classical conditions.[3]

According to the ^{1}H-NMR spectra, in the enamine mixture the E-isomer (5a,c) strongly predominates. The assignment is further supported mainly by the ^{13}C chemical shifts of C-6, which in 5c is strongly shifted upfield with respect to 6c by a steric compression effect[4] (5c: C-6: δ 29.57; 6c: C-6: δ 35.52).Not surprisingly[5] enamines 5a,c and 6a,c were not separable and were reacted as an equilibrium mixture with 4-nitrophenylazide. The quick cycloaddition reaction resulted in a mixture of products 7, 8 and 9. The same compounds were obtained also by direct reaction of aldehydes 3+4 with 4-nitrophenylazide and the appropriate amine, thus avoiding the isolation of the intermediate enamines.[6] After work-up of the reaction mixture containing 7a, 8a and 9a only the triazole derivative 9a was obtained in a pure form, while 7a and 8a could not be separated completely from each other and only mixtures of varying composition could be obtained. Instead, column chromatography of mixtures 7b, 8b, 9b and 7c, 8c, 9c resulted in a complete separation of all components. Compounds 8a, 8b and 9a, 9b were identified by comparison with authentic samples, since they were already known from the Diels-Alder addition of tetraphenylcyclopentadienone to the corresponding 5-amino-4-methylene-v-triazolines.[1] By analogy 8c and 9c could be identified also. The structure and stereochemistry of compounds 7a-c was obtained from an x-rays structural analysis of 7b.[7] Mass spectra of 7b and 7c are very similar to that of 8c which has been decribed in a previous paper.[1] Moreover no significant differences were found between the mass spectra of diastereoisomeric compounds 7b and 8b. ^{1}H- and ^{13}C-NMR data were in accord with these structures: the close similarit of the NMR spectral parameters between 7a-c and the corresponding compounds 8a-c strongly suggests that structure 8 is epimer of 7 at the C-5' chiral center. (e.g. 7b C-5': δ 73.53; C-6: δ 32.78; H-5': δ 5.51; CH_2-6: δ 3.03, 3.38 (J = 12.5 Hz); 8b C-5': δ 74.20; C-6: δ 32.47, H-5' δ 4.89, CH_2-6: δ 2.99, 3.50 (J = 12.5 Hz)). An alternative diastereoisomer with an inverted configuration at C-4' (and possibly at C-5' as well) would be expected to exhibit very different chemical shifts for the CH-5' group since in such a structure the C-5' center would be positioned in the shielding cone of the norbornen-7-one keto group.

Both 7a-c and 8a-c rearranged spontaneously to compounds 9a-c when kept in solution for a sufficient time. The rearrangement rate was enhanced by heating. Compounds 8a-c were found to rearrange at a higher rate (half-life of about two days) than their stereoisomers 7a-c (half-life of about a week) at room temperature.

DISCUSSION

4-Nitrophenylazide adds rapidly to the enamine double bond of compounds 5 and 6. This cycloaddition shows the high regiospecificity which is typical of enamine - azide reactions.[8] The potentially competitive addition to the alkene double bond was not appreciably observed. This fact agrees with the known superior reactivity of azides with enamines when compared with unactivated double bonds.[9] In the present case the steric crowding on the C-2-C-3 bond should also play a significant role, since in the enamines derived from unsubstituted 5-norbornene-2-carboxaldehyde

5c, 6c (1.18 g, 28% yield), m.p. 166–169°, dec. This product was quite unstable and no satisfactory elemental analysis could be obtained. IR: cm^{-1}, 1775 (CO); 1650 (C=C); ^{1}H-NMR, 5c+6c: δ, 2.74 (s, 6H, $N(CH_3)_2$); 3.00 – 3.75 (m, 2H, CH_2-6); 6.05 (broad s, 1H, -CH=); 6.20 – 7.80 (m, 20H, arom). ^{13}C-NMR: δ, 5c, 29.57 (C-6); 43.56 ($N(CH_3)_2$); 109.34 (C-5); 200.54 (C-7); 6c: 35.52 (C-6); 49.84 ($N(CH_3)_2$).

Reaction of 5a, 6a with 4-nitrophenylazide. The enamines 5a, 6a (2.0 g, 3.8 mmol) were dissolved in anhyd C_6H_6 (40 ml) and 4-nitrophenylazide (0.6 g, 3.8 mmol) in C_6H_6 (5 ml) was added. The reaction mixture was stirred for 48 hr and then the solvent evaporated. The residue was chromatographed on a silica gel column (CH_2Cl_2: AcOEt, 95:5) yielding three main fractions (i-iii). Since fractions (i) and (ii) contained different amounts of 7a and 8a, they were added and evaporated; the residue was purified by dissolving in CH_2Cl_2 and adding diisopropyl ether, affording 7a+8a, m.p. 156–162°[1] (1.15 g, 45% yield). (Found: C, 68.2; H, 4.9; N, 8.95. $C_{42}H_{35}N_5O_4$. CH_2Cl_2 requires: C, 68.05. H, 4.9; N, 9.25%). IR: cm^{-1}, 1780 (CO). Fraction (iii) was evaporated and the residue was dissolved in few ml of CH_2Cl_2 and precipitated with n-pentane affording pure 9a (0.51 g, 20% yield), m.p. 210–211°.

Reaction of 3 with morpholine and 4-nitrophenylazide. The aldehyde 3 (1.0 g, 2.27 mmol) was dissolved in C_6H_6 (10 ml). 4-Nitrophenylazide (0.36 g, 2.27 mmol) and morpholine (0.23 g, 2.27 mmol) were then added in that sequence and the reaction mixture was stirred at room temperature for 24 hr. The solvent was evaporated and the residue worked up by chromatography as described above affording similar results.

Reaction of 3 with pyrrolidine and 4-nitrophenylazide. The aldehyde 3 (2.0 g, 5.54 mmol) was dissolved in C_6H_6 (11 ml) and 4-nitrophenylazide (0.72 g, 5.54 mmol) in C_6H_6 (5 ml) was added. Pyrrolidine (0.36 ml, 2.54 mmol) was added dropwise and the reaction mixture was stirred at room temp for 24 hr. A precipitate of 8b formed slowly and was filtered, m.p. 156° (1.11 g, 30.5% yield). The mother liquors were dried (Na_2SO_4) and evaporated. The residue was recrystallized twice by dissolving in C_6H_6 and adding n-pentane affording impure 7b which was dissolved in $CHCl_3$ and precipitated by adding diisopropyl ether, m.p. 164–166°, dec., (0.54 g, 15% yield). (Found: C, 76.9; H, 5.5; N, 10.35. $C_{42}H_{35}N_5O_3$ requires: C, 76.7; H, 5.35; N, 10.65%). IR: cm^{-1}, 1775 (CO). ^{1}H-NMR: δ 3.03, 3.38 (dd, J = -12.5 Hz, 2H, CH_2-6); 5.51 (s, 1H, H-5'). ^{13}C-NMR: δ, 25.10 (C-β-pyrrolidino); 32.78 (C-6); 73.53 (C-5'); 91.56 (C-4'); 196.78 (C-7); MS: m/z 657 (M^+·, 0,2); 384 (27); 356 (23); 276 (10); 178 (100); 176 (17); 152 (14); 129 (6); 96 (6); 76 (10). In the mother liquors of the crystallization of 7b, compound 9b was identified by TLC comparing with an authentical sample but it was not isolated.

Reaction of 3 with dimethylamine and 4-nitrophenylazide. The aldehyde 3 (1.0 g, 2.27 mmol) was dissolved in C_6H_6 (10 ml) and a benzene solution (5 ml) of 4-nitrophenylazide (0.36 g, 2.27 mmol) was added. The mixture was cooled at -2° and $HN(CH_3)_2$ (0.15 ml, 2.3 mmol) was added. The solution was stirred at 0° for 3 hr and at room temp for 30 hr. During this time a precipitate of 7c separated. It was then filtered and recrystallized by dissolving in C_6H_6 and adding n-pentane, m.p. 167–169°, dec. (0.215 g, 15% yield). (Found: C, 76.3; H, 5.2; N, 10.9. $C_{40}H_{33}N_5O_3$ requires: C, 76.05; H, 5.25; N, 11.1%). IR: cm^{-1}, 1775 (CO). ^{1}H-NMR: δ, 1.94, 2.74 (s, 6H, $N(CH_3)_2$); 3.22, 3.34 (dd, J = -12.5 Hz, 2H, CH_2-6); 5.14 (s, 1H, H-5'). MS: m/z 631 (M^+·, 0.2); 384 (70); 356 (52); 278 (19); 276 (19); 247 (11); 178 (100); 176 (38); 152 (24); 129 (48); 82 (65); 78 (66). The filtrate was evaporated and chromatographed on a silica gel column (AcOEt: PhH 1:99) yielding fractions (i) and (ii). Fraction (i) was evaporated and the solid residue was washed several times with diisopropyl ether affording pure 8c, m.p. 143–148°, dec. (0.29 g, 20% yield). (Found: C, 75.95; H, 5.25; N, 10.8. $C_{40}H_{33}N_5O_3$ requires: C, 76.05; H, 5.25; N, 11.1%). IR: cm^{-1}, 1775 (CO). ^{1}H-NMR: δ, 1.93, 2.47 (s, 6H, $N(CH_3)_2$); 3.03, 3.65 (dd, J = -12.5 Hz, 2H, CH_2-6); 4.57 (s, 1H, H-5'). Fraction (ii) was evaporated and the residue was crystallized by dissolving in CH_2Cl_2 and adding n- pentane, affording pure 9c, m.p. 203–207°, dec. (0.26 g, 18% yield). Found: C, 72.1; H, 5.4; N, 10.0. $C_{40}H_{33}N_5O_3$. 0.5 CH_2Cl_2 requires: C, 72.15; H, 5.10; N, 10.4%). IR: cm^{-1} 1750 (CO). ^{1}H-NMR: δ, 2.18 (s, 6H, $N(CH_3)_2$); 3.15, 4.02 (dd, J = -15.0 Hz, 2H, CH_2); 5.50 (s, 1H, H-4). MS: m/z 631 (M^+·, 15), 400 (7); 384 (14); 356 (9); 246 (7); 218 (10); 178 (40); 172 (30); 171 (23); 70 (100).

Reaction of 5c, 6c with 4-nitrophenylazide. Enamines 5c, 6c (1.0 g, 2.1 mmol) were dissolved in C_6H_6 (15 ml) and reacted with 4-nitrophenylazide (0.34 g, 2.1 mmol) in C_6H_6 (2.5 ml). The reaction was run at room temperature for 24 hr and afforded results which were essentially the same as obtained above.

Rearrangement of spiranic cycloadducts 7 and/or 8 to 9. a) The mixture of 7a and 8a obtained as described above (0.3 g, 0.45 mmol) was dissolved in $CHCl_3$ (10 ml). The reaction mixture was left standing at room temp for nine days; the progress of the reaction was followed by TLC. Compound 8a was nearly completely rearranged after 3 days. At the end of the reaction the solution was evaporated and the residue recrystallized from CH_2Cl_2/n-pentane affording 9a, m.p. 209–210° (0.18 g, 60% yield).

some evidence of the reactivity of the alkene double bond has been found.[10] Both cycloadducts 7 and 8 are clearly produced by approach of the azide to the exo side of the norbornene system. This is in agreement with previous findings [10,11] which are also in favour of the general rule that cycloaddition reactions on substrates containing the methylenenorbornane or methylenenorbornene structure invariably occur as exo additions. Another feature which must be noticed is that products 7 and 8 are found in similar amounts starting from an enamine mixture in which E-isomer is the main component. This may be explained both by considering that the reaction does not afford quantitative yields and by assuming a rather rapid E-Z-equilibrium in the enamine mixture. An equilibrium between 7 and 8 through epimerization at C-5', which is known for some simpler 5-amino-v-triazolines [12] has been excluded in this case since 7 and 8 were demonstrated not to epimerize in solution. Instead, both products rearranged spontaneously to the same triazole derivative 9, although with different rates. A base-catalyzed elimination mechanism which involves the carbonyl bridge and would account for this transformation has been already suggested.[1] It was postulated there that the driving forces of the transformation are the relief of the appreciable ring strain which characterizes structures 7 and 8[7] and the energy gain associated with the aromatization of the triazole ring. Since these factors must be nearly equivalent in both stereoisomers, the higher rearrangement rate shown by 7 should be associated with the trans relationship between the C(5')-H and the C(1)-C(2) bond in compounds 8.

EXPERIMENTAL

M.ps are not corrected. They were obtained with a Tottoli instrument. IR spectra were recorded with a 197 - Perkin Elmer spectrophotometer (Nujol mull). ^{1}H-NMR spectra were obtained on Varian 360A and XL-200 spectrometers at 60MHz, respectively, with Me_4Si as internal standard, in $CDCl_3$; ^{13}C-NMR spectra were recorded at 50.3 MHz on a Varian XL-200 instrument. Chemical shifts are given in ppm from TMS. Mass spectra were recorded on a Varian MAT-311-A spectrometer by using the direct inlet technique (probe temp. 130-160°, ion source temperature 250°, electron energy 70 eV). Ready-to-use silica gel plates were employed for TLC.

Exo- and endo-7-oxo-1,4,5,6-tetraphenylbicyclo[2.2.1]hept-5-en-2-carboxaldehyde 3 and 4. Tetraphenylcyclopentadienone (5.0 g, 13 mmol) was dissolved in anhyd C_6H_6 (150 ml). Acrolein (3.0 g, 54 mmol) was added and the reaction mixture was kept at reflux for 5 hr. The solvent was evaporated under reduced pressure and the residue crystallized from diisopropyl ether yielding pure 3 (5.38 g, 94% yield), m.p. 176-177° (Found C, 87.2; H, 5.55. $C_{32}H_{24}O_2$ requires: C, 87.25; H, 5.5). IR: cm^{-1}, 1785 (CO ketone); 1725 (CO aldehyde). ^{1}H-NMR: δ, 2.2 - 2.9 (m, 2H, CH_2); 3.95 (m, 1H, CH); 6.35 - 7.74 (m, 20H, arom.); 10.10 (d, J = 5Hz, 1H, CHO). The mother liquors of the crystallization of 3 were chromatographed on a silica gel column (AcOEt: PhH, 1:99) yielding impure 4 (115 mg, 2% yield), IR: cm^{-1} 1780 (CO ketone); 1725 (CO aldehyde). ^{1}H-NMR, δ, 2.4 - 3.0 (m, 2H, CH_2); 3.30 (m, 1H, CH); 6.30 - 7.60 (m, 20H, arom); 9.42 (d, J = 4.5 Hz, 1H, CHO).

E- and Z-5-Morpholinomethylene-1,2,3,4-tetraphenyl-bicyclo[2.2.1]hept-2-en-7-one 5a, 6a. The aldehyde 3 (4.0 g, 9.1 mmol) was dissolved in C_6H_6 (40 ml) and morpholine (0.87 g, 10 mmol) was added and the solution was refluxed for 20 hr, with continuous separation of the reaction water. The mixture was evaporated and the residue taken up with diisopropyl ether yielding 5a, 6a, m.p. 180-181° (diisopropyl ether)(3.3 g, 72% yield). (Found: C, 85.0; H, 5.95; N, 2.7. $C_{36}H_{31}NO_2$ requires: C, 84.85; H, 6.15; N, 2.75). IR: cm^{-1} 1785 (CO); 1675 (C=C). ^{1}H-NMR (5a+6a): δ, 2.8 - 3.2 (m, 4H, NCH_2); 3.2 - 3.4 (m, 2H, CH_2-6); 3.5 - 3.8 (m, 4H, OCH_2); 5.8 - 6.0 (m, 1H, =CH-); 6.5 - 7.5 (m, 20H, arom). ^{13}C-NMR: 6a, δ, 35.87 (C-6); 51.51 (C-N-morpholino); 66.76 (C-O-morpholino); 114.61 (C-5); 202.05 (C-7).

E- and Z-Dimethylaminomethylene-1,2,3,4-tetraphenyl-bicyclo[2.2.1]hept-2-en-7-one, 5c, 6c. Aldehyde 3 (4.0 g, 9.1 mmol) was dissolved in anhyd C_6H_6 (120 ml). The solution was cooled to 0° and K_2CO_3 (1.25 g, 9.1 mmol) and dimethylamine (0.6 ml, 9.1 mmol) were added. The reaction mixture was stirred at 0° for 6 hr and then at room temp. for 18 hr. The suspension was filtered and evaporated. The residue was dissolved in C_6H_6 and precipitated by adding n-pentane, yielding

b) The adduct 7b (0.5 g, 0.76 mmol) was dissolved in $CHCl_3$ (40 ml) and the solution was kept at room temp for a week. After evaporation the residue was purified by column chromatography yielding pure 9b, m.p. 207-210°[1] (0.235 g, 47% yield).
c) The adduct 7c (0.2 g, 0.31 mmol) was dissolved in $CHCl_3$ (6 ml) and kept at room temp for ten days and evaporated. The residue was crystallized from CH_2Cl_2/n-pentane yielding 9c (0.11 g, 55% yield), m.p. 204°.
d) The adduct 8c (0.1 g, 0.15 mmol) was rearranged by dissolving in $CHCl_3$ (5 ml) and keeping at room temp for 4 days. The solution was evaporated and the residue crystallized as above yielding 9c, m.p. 203-206° (350 mg, 35% yield).

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