Diels-Alder Reactions of Pyrroles as an Entry to Substituted 3-Oxatropanes and Tetrasubstituted Pyrrolidines

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The Diels-Alder adduct of *N*-(*p*-toluenesulfonamido)pyrrole and dimethyl acetylenedicarboxylate, 2,3-dimethyl *N*-(*p*-toluenesulfonamido)-7-azabicyclo[2.2.1]-2,5-heptadiene-2,3-dicarboxylate (**1c**), was obtained in good yield and converted to remarkably stable 3-oxatropanes (**6** and **8**) in 25% yield.

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In the course of our attempts to prepare precursors of nitrogen analogs of *C*-nucleosides, we had occasion to study Diels-Alder (DA) reactions of pyrroles and the chemistry of the resulting adducts. As will be seen, some of these reactions lead to 3-oxatropanes of considerable stability, and suitable modifications of the sequence (1) could lead to an array of interesting oxatropane derivatives.

Pyrroles do not generally participate in Diels-Alder reactions with olefinic dienophiles. Our own attempts to condense methyl β-nitroacrylate with *N*-carbomethoxypyrrole met with failure: no reaction occurred upon heating in xylene, and reactions catalyzed by aluminum chloride (2) led to an intractable mixture. However, pyrroles do react with several acetylenes (2-4), the most useful being dimethyl acetylenedicarboxylate (DMAD).

The *N*-carbomethoxy adduct **1a** had been prepared *via* a thermal reaction (3) and by catalysis (2). Adducts **1b** and **1c** had been obtained in low yield by thermal reactions (3). We sought to apply the catalytic method as a general preparation of 7-azanorbornadiene-2,3-dicarboxylates. We obtained an optimum yield of 65% of pure **1b** by reacting *N*-acetylpyrrole and DMAD with a 5-fold excess of aluminum trichloride. A 10% yield of 2-substituted pyrrole **2b** was also isolated. The stereochemistry of this fumarate, a common side-product (2,3), was assigned by nmr spectroscopy (5). The highest yield of *N*-tosyl adduct **1c** was also obtained by using a five-fold excess of catalyst: 60% **1c** and 40% fumarate **2c** (m.p. 160°). A 3:1 aluminum trichloride:addends ratio yielded mainly **2c**, and a 7:1 ratio afforded equal amounts of products. Complete separation of **1c** and **2c** required preparative tlc.

Hydroxylation of the *N*-carbomethoxy and *N*-acetyl adducts **1a** and **1b** by catalytic osmylation (6) produced low yields (25%) of crude diols **3a** and **3b**. These were characterized as the diacetates **4a** and **4b** (m.p. 95-96°) and acetonides **5a**, **5b**. The hydroxylation of **1b** also afforded the retro-Diels-Alder product, 3,4-dicarbomethoxy-*N*-acetylpyrrole (m.p. 84°) in 20% yield. A reaction temperature of 5° lowered this to 15%. However, the *N*-tosyl adduct **1c** was cleanly and easily converted in a similar way to the crystalline products **4c** and **5c** in an overall yield of 50%. The *exo-cis* stereochemistry of the hydroxyl groups in all compounds was unambiguously assigned, based on nmr spectra, which were similar to those of analogous products (6,7).

Attempts to oxidize derivatives **4a-5b** to diketoesters, by means of ozone (8) or ruthenium dioxide-sodium periodate (ruthenium tetroxide) (9), afforded a mixture of products, whereas the *N*-tosyl norbornenes **4c**, **5c** were inert to electrophilic attack by ozone from -78° to 0°. Prolonged treatment of **4c** or **5c** with ozone at 10° effected partial degradation of the *N*-tosyl moiety.

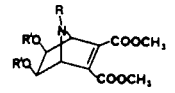
Oxidation of **5c** was accomplished cleanly by ruthenium tetroxide (9), producing the crystalline hemiketal **6** in over 50% yield. This 3-oxatropane was not dehydrated to diketoester **7** even by prolonged heating at 50° *in vacuo*. Furthermore, the simplicity of the nmr spectrum of **6** indicated that it probably existed with the hydroxyl groups in the thermodynamically favoured *syn-diaxial* conformation, as shown.

Selective hydrolysis of diester **6** with sodium hydroxide in THF-water afforded the crystalline acid-ester **8** in

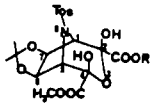
(1)

(a) R = COOMe (b) R = COCH$_3$ (c) R = Tosyl

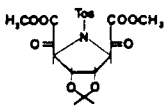
(2)



(3) R' = H
(4) R' = COCH$_3$
(5) R'R' = C(CH$_3$)$_2$



(6) R = CH$_3$
(8) R = H



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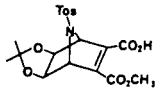
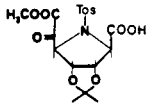
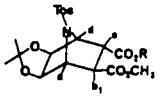


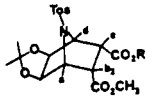
(9)



(10)



(11a) R = H, m.p. 109-113
(12a) R = CH$_3$



(11b) R = H, m.p. 57-61
(12b) R = CH$_3$

60% yield. A similar hydrolysis of unsaturated diester **5c** to acid-ester **9** was accomplished in 70% yield, but all attempted oxidations of **9** to **8** with ruthenium tetroxide gave intractable products. Interestingly, the nmr spectrum of **9** in acetone-d_6 displayed an unusual 'acid' proton absorption at δ 6.4 ppm (9.1 in deuteriochloroform), indicating that it may form a stable orthoester-type adduct (a 5-membered ring) by interaction between its acid and ester groups in a very polar solvent.

Oxidative decarboxylation of **8** to ketoester-acid **10**, an important azacyclic precursor of *C*-nucleosides, could not be carried out cleanly with either lead tetraacetate (10) or sodium periodate (11). Reactions of **8** with benzoic anhydride-pyridine (12) failed to produce a ketoester-aldehyde, thus confirming that **8** is not in equilibrium with a reactive open form (a ketoacid-ketoester) (12). It appears that both 3-oxatropanes **6** and **8** are conformationally very stable.

In another attempt to obtain **10**, we tried to initially reduce the acid function of **9**: but reaction with borane-tetrahydrofuran (13) led exclusively to reduction of the electron-deficient olefinic linkage, producing acids **11a** (30%) and **11b** (65%) upon work-up with water-methanol. Their stereochemistry was assigned, based on their nmr spectra, and those of their methyl esters **12a**, **12b**, in deuteriochloroform, acetone-d_6 and pyridine-d_5. The *cis*-isomer **11b** appeared to exist in a closed form similar to **9** in acetone-d_6.

Further work is required to evaluate the synthetic potential of the described sequence as a source of 3-oxatropanes and multisubstituted pyrrolidines, but because of the ease of epoxidation (14) or reduction (15) of the isolated double bond in systems similar to **5c**, a variety of oxatropanes and stereospecifically substituted pyrrolidines should be obtainable by this route with only slight modifications (1).

EXPERIMENTAL

Melting points were determined on a Gallenkamp block in open capillary tubes and are uncorrected. Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 eV using a direct insertion probe. Infrared (ir) spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 spectrophotometer. Ultraviolet (uv) spectra were obtained on a Unicam SP-800. Proton magnetic resonance (nmr) spectra were recorded on a Varian T-60 instrument using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in the δ scale in parts per million (ppm). Analytical thin layer chromatography (tlc) was performed on silica gel-coated plates (Eastman Kodak) and on a preparative scale on silica gel (Merck uv 254, 366) coated glass plates. Woelm silica gel (activity II-III) was used for column chromatography.

Dimethyl *N*-Acetyl-7-azabicyclo[2.2.1]-2,5-heptadiene-2,3-dicarboxylate (**1b**) and Dimethyl 1-Acetyl-2-pyrrolylfumarate (**2b**).

N-Acetyl pyrrole (2.20 g., 20 mmoles) dissolved in 30 ml. of dry methylene chloride was added to a solution of 2.85 g. (20 mmoles) of DMAD and 13.4 g. (0.1 mole) of aluminum chloride in 170 ml. of methylene chloride. The mixture was stirred at 40° for 90 minutes, then cooled. Ice chips were added slowly, then the organic phase was washed with 100 ml. water. Drying (sodium sulfate) and evaporation left a dark oil which was chromatographed on silica gel. Elution with methylene chloride-benzene (1:1) afforded pyrrole **2b** in 10% yield; nmr (deuteriochloroform): δ 2.48 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 6.27 (s, 1H), 6.32 (s, 1H), 6.93 (s, 1H), 7.28 ppm (t, 1H, J = 2.5 Hz); ir (film): 3160, 1735, 1650, 1640 cm^{-1}; ms: m/e 251 (M^+), 220 ($M^+ - CH_3O$), 209, 192.

Elution with methylene chloride gave 3.3 g. (65%) of oily **1b**; nmr (deuteriochloroform): δ 1.95 (s, 3H), 3.84 (s, 6H), 5.55 (m, 1H), 5.72 (m, 1H), 7.10 ppm (m, 2H); uv (95% ethanol): λ max 210 nm, (ε 13,000), shoulder 290 nm (ε, 1,200); ir (film): 1735 (esters), 1690 (amide), 1648 cm^{-1} (C=C); ms: m/e 251 (M^+), 225 (M^+ - acetylene).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.53; H, 5.27.

Dimethyl *exo-cis*-5,6-Dihydroxy-*O*-isopropylidene-*N*-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (**5a**).

To a solution of 2.20 g. (8.14 mmoles) of adduct **1a** in 40 ml. ethyl ether and 20 ml. acetone was added 3.0 ml. of osmium tetroxide solution (1.0 g. osmium tetroxide in 200 ml. of purified *t*-butyl alcohol) (6) and 2.0 ml. of 30% hydrogen peroxide. After stirring vigorously for 48 hours at room temperature, tlc showed the complete disappearance of starting material. The reaction was quenched by addition of 20 ml. of 10% sodium bisulfite, and this aqueous phase was back-extracted with 2 x 25 ml. of ethyl acetate. The combined organic layers were dried (sodium sulfate) and evaporated, leaving a yellow oil. Chromatography on silica gel, eluting with ethyl ether-methylene chloride (1:1), afforded crude diol **3a** as the most polar component of the mixture.

The crude diol was reacted with 20 ml. of dry acetone and 10 ml. of 2,2-dimethoxypropane, catalyzed by 10 mg. of *p*-toluenesulfonic acid monohydrate. Once the diol was completely reacted, the solvents were evaporated and the residue was chromatographed on silica gel, eluting with methylene chloride. The clear, colorless oily product was recovered in 25% overall yield; nmr (deuteriochloroform): δ 1.33 (s, 3H), 1.43 (s, 3H), 3.70 (s, 3H), 3.83 (s, 6H), 4.54 (s, 2H), 5.00 p.p.m. (s, 2H); ir (film): 1745 (urethane), 1730 and 1720 (esters), 1640 (C=C), 1390 and 1380 cm^{-1} (*gem*-dimethyl); ms: m/e 326 (M^+-CH_3), 310 (M^+-CH_3O).

Anal. Calcd. for $C_{15}H_{19}NO_8$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.47; H, 5.38; N, 4.18.

Dimethyl *exo-cis*-5,6-Dihydroxy-*O*-isopropylidene-*N*-(*p*-toluenesulfonamido)-7-azabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (**5c**).

Treatment of adduct **1c** with osmium tetroxide-hydrogen peroxide afforded diol **3c** in over 50% yield upon extraction. Without further purification, ketalization was carried out, producing the crystalline acetonide **5c** in 50% overall yield, m.p. (methylene chloride-ether) 182.5°; nmr (deuteriochloroform): δ 1.28 (s, 3H), 1.47 (s, 3H), 2.39 (s, 3H), 3.72 (s, 6H), 4.42 (s, 2H), 4.80 (s, 2H), 7.25 (X_2, 2H), 7.67 p.p.m. (A_2, 2H); ir (potassium bromide): 1735 and 1725 (C=O's), 1645 (C=C of unsaturated diester), 1603 (aromatic C=C), 1390 and 1380 cm^{-1} (*gem*-dimethyl); uv (95% ethanol): λ max 227 nm (ε, 17,000); ms: m/e 422 (M^+-CH_3), 378 (M^+-CH_3COO), 337 (3,4-dicarbomethoxy-*N*-(*p*-tosyl)pyrrole), 306.

Anal. Calcd. for $C_{20}H_{23}NO_8S$: C, 54.92; H, 5.30; N, 3.20; S, 7.32. Found: C, 54.64; H, 5.03; N, 3.10; S, 7.51.

2,4-Dihydroxy-2,4-dicarbomethoxy-*exo-cis*-6,7-dihydroxy-*O*-isopropylidene-*N*-(*p*-toluenesulfonamido)-3-oxa-8-azabicyclo-[3.2.1^{1,5}]octane (**6**).

Sodium periodate (4.1 g., 19.0 mmoles) and ruthenium dioxide hydrate (40 mg.) (9) were dissolved in a potassium dihydrogen phosphate-sodium hydroxide buffer solution (75 ml., *p*H 6), and to this was added dropwise a solution of 2.07 g. (4.75 mmoles) of unsaturated diester **5c** in 75 ml. of acetone. After two hours another 500 mg. of periodate was added, and after 4 hours, a final 400 mg. was added. After a total of 4.5 hours, 10 ml. of 2-propanol was added, and the mixture was filtered through a bed of Kieselguhr. The solid was washed well with chloroform, and the combined filtrates were evaporated to remove the organic solvents. The remaining aqueous solution was extracted with 3 x 100 ml. chloroform. Drying (sodium sulfate) and evaporation left a solid which was recrystallized from methylene chloride-carbon tetrachloride, m.p. 213-215°; yield 1.2 g. (55%); nmr (deuteriochloroform): δ 1.03 (s, 3H), 1.18 (s, 3H), 2.39 (s, 3H), 3.74 (s, 6H), 4.24 (s, 2H), 4.50 (s, 2H, exchanged with deuterium oxide), 4.72 (s, 2H), 7.23 (X_2, 2H), 7.78 p.p.m. (A_2, 2H); ir (potassium bromide): 3400 and 3320 (O-H), 1763, 1754, 1738, 1607 (aromatic C=C), 1389 cm^{-1} (*gem*-dimethyl); uv (95% ethanol): λ max 233 nm (ε, 16,000); ms: m/e 472 ($M^+ - CH_3$), 457 ($M^+ - CH_2{=}O$), 454 ($M^+ - CH_3 - H_2O$), 414.

Anal. Calcd. for $C_{20}H_{25}NO_{11}S$: C, 49.28; H, 5.17; N, 2.87; S, 6.58. Found: C, 49.79, 49.66; H, 5.20, 5.10; N, 2.97; S, 6.61.

2,4-Dihydroxy-4-carbomethoxy-*exo-cis*-6,7-dihydroxy-*O*-isopropylidene-*N*-(*p*-toluenesulfonamido)-3-oxa-8-azabicyclo[3.2.1^{1,5}]-octane-2-carboxylic Acid (**8**).

The diester **6** (685 mg., 1.40 mmoles) was dissolved in 10 ml. of tetrahydrofuran, and to this was added slowly 15.0 ml. of 0.1*N* sodium hydroxide. The reaction was followed by tlc until the total disappearance of starting material (22 hours). The tetrahydrofuran was evaporated off under reduced pressure, and the resulting aqueous suspension was extracted with 10 ml. of ethyl acetate to remove impurities. It was then cooled in ice, acidified to *p*H 3.5 with 3% hydrochloric acid, and extracted with 15 ml. of ethyl acetate. The *p*H of the solution rose; re-acidification and extraction was repeated three more times, and the combined organic extracts were dried (sodium sulfate) and evaporated to dryness. The oily residue solidified when triturated with methylene chloride, and recrystallization from ethyl acetate-carbon tetrachloride afforded 400 mg. (60%) of light white powder, m.p. 186-189°; nmr (deuteriopyridine): δ 1.30 (s, 3H), 1.65 (s, 3H), 2.28 (s, 3H), 3.60 (s, 3H), 4.67 (q, 2H), 5.35 (q, 2H), 7.15 (X_2, 2H), 8.06 p.p.m. (A_2, 2H), 3 protons under solvent absorption; ir (potassium bromide): 3420 and 3340 (O-H), 1765 (ester), 1750 (acid), 1395 and 1385 cm^{-1} (*gem*-dimethyl); ms: m/e 442 ($M^+ - CH_3O$), 439, 425, 410, 295.

Anal. Calcd. for $C_{19}H_{23}NO_{11}S$: C, 48.20; H, 4.90; N, 2.96. Found: C, 48.49; H, 5.03; N, 3.25.

3-Carbomethoxy-*exo-cis*-5,6-dihydroxy-*O*-isopropylidene-*N*-(*p*-toluenesulfonamido)-7-azabicyclo[2.2.1]hept-2-ene-2-carboxylic Acid (**9**).

The unsaturated diester **5c** was selectively hydrolyzed in a manner similar to the hydrolysis of **6**. The residue obtained from the evaporation of the organic extracts was crystallized from chloroform-carbon tetrachloride, giving a 70% yield of acid **9**, m.p. 192-193°; nmr (deuterioacetone): δ 1.34 (s, 3H), 1.54 (s, 3H), 2.49 (s, 3H), 3.94 (s, 3H), 4.63 (q, 2H), 4.92 (m, 2H), 6.34 (b.m., 1H, varies with concentration), 7.54 (X_2 2H), 7.80 p.p.m. (A_2, 2H); ir (potassium bromide): 2800-2700 (acid), 1745 (ester C=O), 1695 (acid C=O), 1633 (C=C of unsaturated diester), 1607 (aromatic C=C), 1392 and 1383 cm^{-1} (*gem*-dimethyl); uv (acetonitrile): λ max 230 nm, shoulder 255; ms: m/e 408 ($M^+ - CH_3$), 306, 292.

Anal. Calcd. for $C_{19}H_{21}NO_8S$: C, 53.90; H, 5.00; N, 3.31; S, 7.56. Found: C, 53.64; H, 5.06; N, 3.51; S, 7.47.

3-Carbomethoxy-*exo-cis*-5,6-dihydroxy-*O*-isopropylidene-*N*-(*p*-toluenesulfonamido)-7-azabicyclo[2.2.1]heptane-2-*endo*-3-*exo*-2-carboxylic Acid (**11a**) and the -2-*endo*-3-*endo*-2-carboxylic Acid (**11b**).

Reduction of unsaturated acid ester **9** was carried out with one equivalent (3 hydrides) of borane-tetrahydrofuran (13) for one hour at 25°. Quenching with water, evaporation to dryness, and co-evaporation with methanol left a semi-solid residue which was recrystallized from chloroform-carbon tetrachloride. The *trans* isomer **11a**, m.p. 109-113°, was thus obtained in 35% yield: addition of excess carbon tetrachloride precipitated a 65% yield of *cis* isomer **11b**, m.p. 57-61°; nmr of **11a** (deuteriopyridine): δ 1.25 (s, 3H), 1.40 (s, 3H), 2.30 (s, 3H), 3.53 (d, 1H, J ≅ 6 Hz), 3.84 (s, 3H), 4.43 (t, 1H, J ≅ 6 Hz), 4.84 (q, 2H), 5.06 (m, 2H), 7.47 (X_2, 2H), 8.30 p.p.m. (A_2, 2H), acid proton under solvent absorption; ir (potassium bromide): 2800-2700 (broad, acid), 1755 (ester C=O), 1720 and 1705 (acid C=O), 1610 cm^{-1}; ms: m/e 410 ($M^+ - CH_3$), 394 ($M^+ - CH_3O$), 270, 252; nmr of **11b** (deuterioacetone): δ 1.18 (s, 6H), 2.43 (s, 3H), 3.47 (m, 2H), 3.63 (s, 3H), 4.29 (m, 2H), 4.70 (q, 2H), 6.9 (b.m., 1H), 7.32 (X_2, 2H), 7.80 p.p.m. (A_2, 2H); ir and ms similar to the *trans*-isomer.

Anal. Calcd. for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29; S, 7.54. Found: C, 53.38; H, 5.31; N, 3.16; S, 7.61.

REFERENCES AND NOTES

(1) G. Just and K. Grozinger, *Tetrahedron Letters*, 4165 (1974).

(2) R. C. Bansal, A. W. McCulloch and A. G. McInness, *Can. J. Chem.*, **47**, 2391 (1969).

(3) R. Kitzing, R. Fuchs, M. Joyeux and H. Prinzbach, *Helv. Chim. Acta*, **51**, 888 (1968).

(4) G. W. Gribble, N. R. Easton, Jr., and J. T. Eaton, *Tetrahedron Letters*, 1075 (1970); A. P. Marchand and R. W. Allen, *J. Org. Chem.*, **40**, 2551 (1975).

(5) By comparing nmr spectra with those of dimethyl fumarate, dimethyl maleate, and similar compounds (*c.f.*, ref. 2).

(6) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

(7) G. Just and G. Reader, *Tetrahedron Letters*, 1521 (1973).

(8) J. J. Pappas, W. P. Keaveney, E. Gancher and M. Berger, *ibid.*, 4273 (1966).

(9) D. M. Piatak, H. B. Bhat and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969); Ruthenium dioxide (industrial grade, 58%) was purchased from Engelhard Industries, Newark, N. J.

(10) E. Baer, *J. Am. Chem. Soc.*, **62**, 1597 (1940); *ibid.*, **64**, 1416 (1942); R. Criegee and E. Buchner, *Chem. Ber.*, **73**, 563 (1940).

(11) Y. Yanuka, R. Katz and S. Sarel, *Tetrahedron Letters*, 1725 (1968).

(12) T. Cohen and I. H. Song, *J. Am. Chem. Soc.*, **87**, 3780 (1965).

(13) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

(14) G. Just and M.-I. Lim, "C-Nucleosides and Related Compounds XIII," *Can. J. Chem.*, in press.

(15) G. Stork, E. E. Van Tamelan, L. J. Friedman and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953).