MONO- AND DI-SUBSTITUTED 3-AZA-α-TROPOLONES[1]

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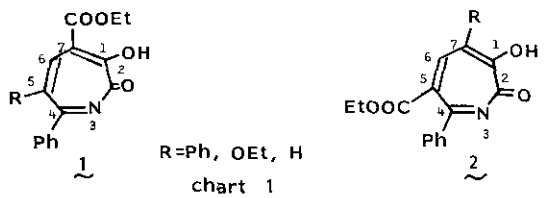
Abstract ——— New mono- and di-substituted 3-aza-α-tropolones 6 were synthesized by deethoxycarbonylation and subsequent DDQ oxidation of dihydroazatropolones 4. In methanol, 6 undergoes a skeletal rearrangement to give methyl pyridine-2-carboxylates 7, suggesting that the reaction is characteristic of the azatropolone nucleus.

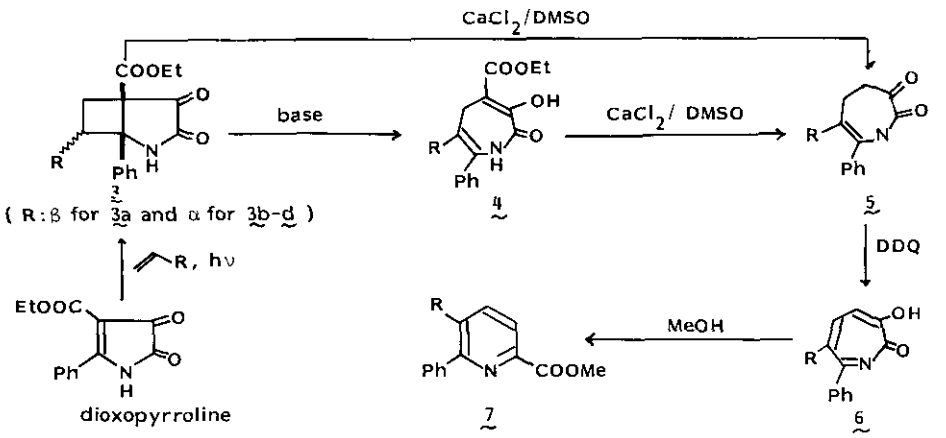
Previously we reported the synthesis of a new heteroaromatic, 3-aza-α-tropolones 1 and 2, both of which carried an ethoxycarbonyl group on the nucleus and readily underwent skeletal rearrangement to afford pyridine-2-carboxylates in protic solvents.[2] In connection with the chemical reactivity of azatropolones, we are interested in removing that group from the molecule, since the rearrangement of α-tropolone to benzoic acid is known to be facilitated by the presence of an electron attractive substituent.[3] In this paper we present the syntheses of 4-phenyl- and 5-ethoxy-4-phenyl-3-aza-α-tropolones.[4]



1 R=Ph, OEt, H 2

chart 1

Removal of the ethoxycarbonyl group was achieved at the stage of dihydroazatropolones 4 which were prepared by base-catalysed ring expansion of the photoadducts 3 of olefins to dioxopyrroline.[5] Dihydroazatropolones 4a-d, when heated with $CaCl_2$ in DMSO,[6] gave the expected deethoxycarbonylated products 5a-d[7] in satisfactory yields, respectively. Similar deethoxycabonylation of 3a directly afforded 5a in 31 % yield.



a: R=Ph, b: R=OEt, C: R=OAc, d: R=H

chart 2

All the products had the diketo structure 5 as proved from their spectral data. For example, 5a showed two carbonyl groups at 1725 and 1665 cm^{-1} (which corresponded to ^{13}C-NMR peaks at 200.4 and 167.5 ppm) in its IR spectrum and four protons as multiplets at δ 3.0 in its ^{1}H-NMR spectrum. Dehydrogenation of 5 to 3-aza-α-tropolones 6 was achieved by DDQ oxidation, but the reaction rate and the stability of the products were markedly influenced by the nature of substituents on the azatropolone nucleus. Oxidation of 5b rapidly proceeded to give 6b in 50 % yield on reaction in CH_2Cl_2 at 50°C. Conversion of 5d into 6d was achieved by reaction in benzene at 110°C, though the yield was low (10 %). Although we could not isolate 6a and 6c from the reaction mixture in CH_2Cl_2 or benzene, the rearranged products 7a and 7c were produced when the reaction was carried out in methanol, thus suggesting the intermediary formation of the 3-aza-α-tropolones 6a and 6c, respectively. The possibility that the formation of 7a from 5a was due to the initial ring contraction of 5a and the subsequent dehydrogenation of the resulting dihydropyridine may be eliminated, since 5a was stable in methanol on heating at 100°C for 24 h.

The azatropolone 6b rearranged into methyl pyridine-2-carboxylate 7b on treatment with methanol under reflux. This rearrangement was greatly accelerated on addition of sodium acetate. A similar rearrangement was also suggested for 6d from its UV spectral change after 48 h in methanol, although all attempts of isolation of 7d were failed.

The present investigation suggests that the ring contraction reaction of azatropolones by protic solvents is characteristic of azatropolone nucleus, although ease of the reaction is influenced by the nature of substituents.

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus and are uncorrected. IR spectra were taken in Nujol mulls with a Hitachi 260-10 spectrometer and are given in cm^{-1}. UV spectra were recorded in dioxane with a Hitachi 200-10 spectrophotometer. ^{1}H-NMR (60 MHz and 100 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a Hitachi Perkin-Elmer spectrometer and a JEOL FX-100 spectrometer, respectively. High resolution mass spectra were taken by JEOL JMS-D 300 spectrometer. For column chromatography, Wakogel C-200 (silica gel) was used.

Preparation of 5 by deethoxycarbonylation of 4

A mixture of 4 (200 mg) and calcium chloride (4 eq.) in DMSO (5 ml) was heated at 140-150°C for 15-60 min. The mixture was diluted with CH_2Cl_2, washed with 5% HCl and water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed in benzene-CH_2Cl_2 (1:1) to give the 4,5-dihydro-1H-azepine-2,3-diones 5.

5a: 101 mg (64 %). Pale yellow needles from CH_2Cl_2-Et_2O, mp 204-208°C. IR: 1725, 1665. UV λ_{max} nm (ε): 232 (13,100), 286 (8,800). ^{1}H-NMR (60 MHz) δ :3.0 (4H, m, C_4-H, C_5-H), 7.5 (10 H, m, Ar-H). MS m/z: M^+ Calcd for $C_{18}H_{15}NO_2$; 277.1102. Found: 277.1117.

5b: 100 mg (65 %). Colorless prisms from Et_2O-hexane, mp 121-126°C. IR: 1730, 1665. UV λ_{max} nm (ε): 225 (9,500), 262 (9,400). ^{1}H-NMR (60 MHz) δ : 1.18 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.97 (4H, m, C_4-H, C_5-H), 3.73 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 7.2 (5H, m, Ar-H). MS m/z: M^+ Calcd for $C_{14}H_{15}NO_3$; 245.1050. Found: 245.1028.

5c: 98 mg (63 %). Colorless prisms from CH_2Cl_2-Et_2O, mp 101-103°C. IR: 1760, 1720, 1675. UV λ_{max} nm (ε): 228 (8,600), 253 (9,300). ^{1}H-NMR (60 MHz) δ: 2.00 (3H, s, OAc), 2.85-3.27 (4H, m, C_4-H, C_5-H), 7.28 (5H, m, Ar-H). MS m/z: M^+ Calcd for $C_{14}H_{13}NO_4$; 259.0845. Found: 259.0890.

5d: 92 mg (63 %). Colorless prisms form Et_2O-hexane, mp 162-164°C. IR: 1725, 1665, 1640. UV λ_{max} nm (ε): 252 (9,200). ^{1}H-NMR (60 MHz) δ : 2.63-3.2 (4H, m, C_4-H, C_5-H), 6.11 (1H, t, J=8 Hz, olefinic-H), 7.4 (5H, m, Ar-H). MS m/z: M^+ Calcd for $C_{12}H_{11}NO_2$; 201.0790. Found: 201.0805.

Preparation of 5a from 3a

A mixture of 3a (200 mg) and calcium chloride (500 mg) in DMSO (5 ml) was heated at 150°C for 20 min. Work-up of the mixture as described above gave 5a (50 mg, 31 %) and 4a (5 mg, 2.5 %).

5-Ethoxy-4-phenyl-3-aza-α-tropolone 6b

A mixture of 5b (100 mg) and DDQ (100 mg) in dry CH_2Cl_2 (5 ml) was heated at 50°C for 1-2 min. After evaporation of the solvent, the residue in benzene-CH_2Cl_2 was rapidly passed through a column to give 6b as a yellow gum (52 mg, 50 %). IR (CH_2Cl_2): 1680, 1660. UV λ_{max} nm (ε): 262 (5,600), 300 (5,800), 388 (7,000). ^{1}H-NMR (100 MHz) δ: 1.00 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.57 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 6.60 (1H, d, J=13 Hz, C_7-H), 7.13 (1H, d, J=13 Hz, C_6-H), 7.4 (5H, m, Ar-H). MS m/z: M^+ Calcd for $C_{13}H_{13}NO_3$; 243.0896. Found: 243.0912.

4-Phenyl-3-aza-α-tropolone 6d

A mixture of 5d (50 mg) and DDQ (50 mg) in dry benzene (5 ml) was heated at 110°C for 1 h. The reaction mixture was passed through a column. Elution with benzene-

CH_2Cl_2 (1:1) gave the 2-aza-α-tropolone 6d (5 mg, 10 %) as pale yellow prisms from Et_2O-hexane, mp 133-138 °C. IR: 1690, 1650, 1615. UV λ_{max} nm (ε): 235 (10,700), 308 (4,800), 369 (9,600). ^{1}H-NMR (100 MHz) δ: 6.20 (1H, d, J=9 Hz, C_5-H), 6.67 (1H, d, J=12 Hz, C_7-H), 7.12 (1H, d.d, J=9, 12 Hz, C_6-H), 7.5 (5H, m, Ar-H). MS m/z: M^+ Calcd for $C_{12}H_9NO_2$; 199.0631. Found: 199.0610.

Methyl 5-ethoxy-6-phenylpyridine-2-carboxylate 7b

6b (20 mg) in MeOH (10 ml) containing AcONa (5 mg) was heated for 6 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated to dryness. Chromatography of the residue in benzene gave 7b (13 mg, 60 %) as colorless gum. IR (CH_2Cl_2): 1720. UV λ_{max}^{EtOH} nm (ε): 228 (16,200), 260 (10,000), 298 (8,500). ^{1}H-NMR (60 MHz) δ: 1.43 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.97 (3H, s, $COO\underline{CH_3}$), 4.15 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 7.23 (1H, d, J=9 Hz, C_4-H), 7.5 (3H, m, Ar-H), 7.9 (2H, m, Ar-H), 8.00 (1H, J=9 Hz, C_3-H). MS m/z: M^+ Calcd for $C_{15}H_{15}NO_4$; 257.1053. Found: 257.1036.

DDQ oxidation of dihydroazatropolone 5a and 5c in MeOH

A mixture of 5a or 5c (100 mg) and DDQ (1.5 eq.) in dry MeOH (5 ml) was heated for 30 min. The mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed in benzene to give the pyridine-2-carboxylate 7a (31 mg, 30 %) or 7c (25 mg, 24%) as colorless gum.

7a IR (CH_2Cl_2): 1720. UV λ_{max}^{EtOH} nm (ε): 242sh (14,000), 280sh (8,900). ^{1}H-NMR δ (60 MHz) : 4.00 (3H, s, $COO\underline{CH_3}$), 7.2 (10H, m, Ar-H), 7.73 (1H, d, J-8 Hz, C_3-H), 8.07 (1H, d, J=8 Hz, C_4-H). Ms m/z: M^+ Calcd for $C_{15}H_{15}NO_2$; 289.1101. Found: 289.1084.

7c IR (CH_2Cl_2): 1770, 1720. UV λ_{max}^{EtOH} nm (ε): 230 (11,500), 252 (12,000), 282 (7,200). ^{1}H-NMR (60 MHz)δ : 2.20 (3H, s, OAc), 4.00 (3H, s, $COO\underline{CH_3}$), 7.6 (5H, m, Ar-H), 7.63 (1H, d, J=8 Hz, C_3-H), 8.15 (1H, d, J=8 Hz, C_4-H). MS m/z: M^+ Calcd for $C_{15}H_{13}NO_4$; 271.0843. Found: 271.0837.

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