

DIELS - ALDER REACTIONS OF HETREO-DIENES WITH MALEIC

ANHYDRIDE AND p-Benzoquinone

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Abstract

An efficient, and stereoselective route of (4+2) cycloaddition of cyclic dienophiles (mainly maleic anhydride (4), and p-benzoquinone (5) with Hetero-substituted dienes have been investigated. Only one stereoisomer (after workup) was obtained in all cases. While these hetero-dienes reacted smoothly with maleic anhydride and p-benzoquinone, replacement of oxygen in furfural by sulfur or nitrogen resulted in a dramatic decrease in the reactivity of the dienes.

Key Words: Diels-Alder reaction, Furan, Pyrrole, Thiophene, Maleic anhydride, p-Benzoquinone

Introduction

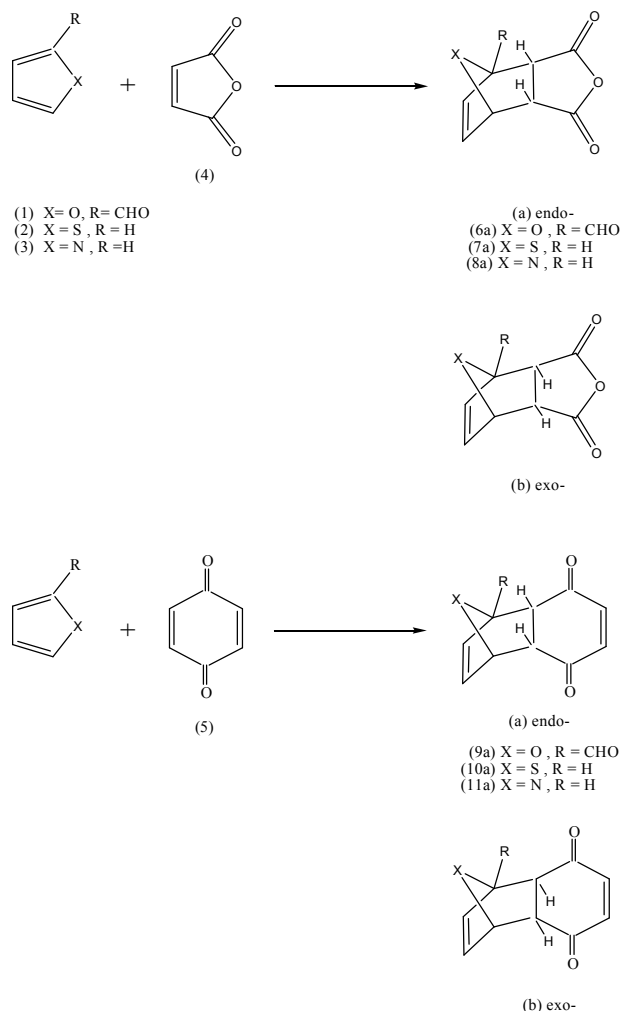
The Diels-Alder reaction is a convenient, predictable route for the cycloaddition of an electron deficient dienophiles to an electron-rich diene⁽¹⁾. This reaction often occurs rapidly under mild conditions and has been employed innumerable times for the synthesis of complex materials. In general, however, the Diels-Alder reaction has been a valuable tool for the construction of polycyclic ring systems⁽²⁾.

Heterocyclic rings a valuable tool for the construction of containing nitrogen, oxygen, and sulfur atoms is a common structural feature in natural products. The central problem in the total synthesis of natural products containing nitrogen, oxygen, and sulfur atoms has been concerned with the preparation and modification of some derivatives of furan, pyrrole, and thiophene. The Diels-Alder reaction of hetero diene⁽³⁾ 3 and dienophiles⁽⁴⁾ offers an important solution to his problems. The value of this reaction is that in one step two ring bonds are formed with potential control of stereochemistry at the new tetrahedral centers.

The versatility of furan as the diene in this process has been demonstrated by elaboration of its cycloadducts into aromatic systems⁽⁵⁾, and oxabicyclo[2.2.1.] heptane systems⁽⁶⁾. In this work we report the cyclo-addition of furfural, pyrrole, and thiophene as dienes with maleic anhydride and p-benzoquinone as dienophiles in an attempt to utilize these cycloadducts for the synthesis of natural products containing highly substituted furan, pyrrole and thiophene system.

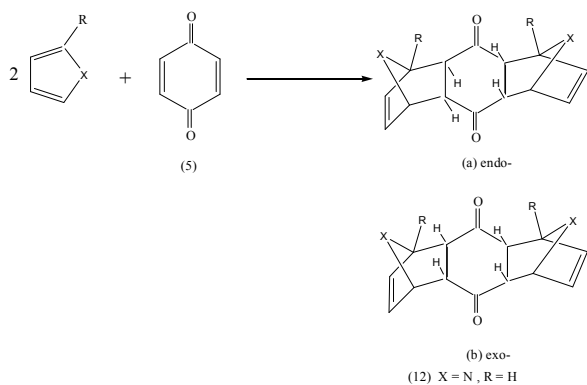
Results and Discussion

The cycloaddition of furfural (1), thiophene (2), pyrrole (3), maleic anhydride (4) and p-benzoquinone (5) have been examined and led exclusively to cycloaddition at the dienophile α,β -double bond site and formation of Diels-Alder adducts as shown in (scheme 1).



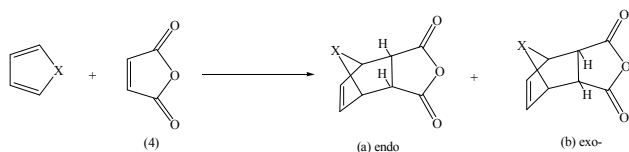
(Scheme 1)

The reaction of p-benzoquinone with excess diene yields a bis-adducts as shown in Scheme II.



(Scheme II)

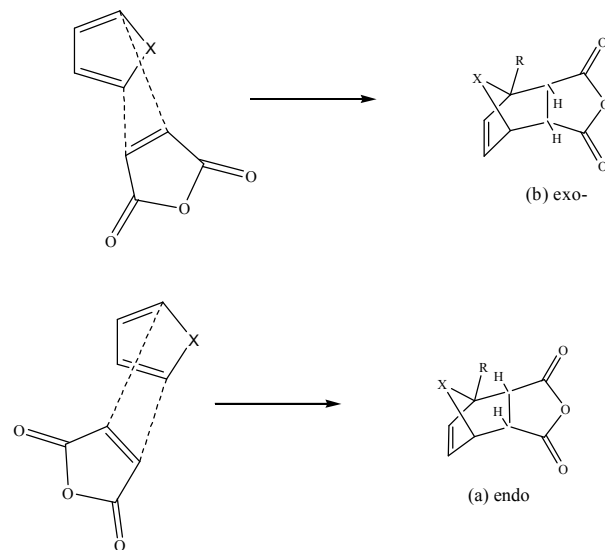
Furfural and maleic anhydride yielded cycloadduct (6a), (16.46%), however, diastereoisomeric excess with good endo selectivity (20.86%) was obtained by using an excess of Lewis acid such as AlCl_3 . Pyrrole and thiophene with maleic anhydride yield cycloadducts at low yield (11.23%), and (16.64%) respectively, but with p-benzoquinone gave a much better yield (41.89%), and (36.13%) respectively. The reaction of excess Pyrrole (2 moles) with p-benzoquinone gave (45.60%) of bisadduct. Pyrrole and thiophene are generally less reactive than furfural and they required longer reaction time. Furfural, pyrrole, and thiophene gave diastereoisomeric excess with good endo selectivity in the presence of excess Lewis acid such as AlCl_3 ^(9,10) Table I show the product ratios for the Diels-Alder reaction of heterodiene with dienophiles.



Diene	Dienophile	Condition	Endo/exo ratio	%
Furfural	Maleic	RT. Catalyzed	77:23	16.46
			80:20	20.86
Furfural	p-Benzoquinone	R T. Catalyzed	74:26	31.25
			75:25	42.08
Thiophene	Maleic	RT. Catalyzed	78:22	16.64
			74:26	19.02
Thiophene	p-Benzoquinone	RT. Catalyzed	79:21	28.52
			79:21	36.13
Pyrrole	Maleic	RT. Catalyzed	73:27	28.52
			76:24	36.13
Pyrrole	p-Benzoquinone	RT. Catalyzed	71:29	36.13
			73:27	41.89
Excess	p-Benzoquinone	RT. Catalyzed	75:25	43.18
			70:30	45.60

The reaction of heterodiene with dienophile such as maleic anhydride or p-benzoquinone can in principle occur in two distinct ways to give two stereoisomeric adduct endo- (a) and exo- (b) (scheme III) These paths are described as the (a) and (b) Alder's rule. The reaction of dienophile and diene is expected to produce under conditions of kinetic control the isomer, which is derived

from maximum overlap between the two systems.^(7, 1), it might be expected that path (a) and (b) in scheme III are operative and that (6a) and (6b) would be the products for the first run.



(Scheme III)

The main point of interest is the influence of the anhydride ring on the addition of pyrrole and thiophene. If overlap of the thiophene system with the maleic anhydride moiety contributes substantially to lowering the energy of the transition state of this reaction, results might be expected which differ from the observed in addition of cyclopentadiene to norbornadiene⁽⁹⁾. A summary of the products ratio (table I) of a facial isomers were determined by careful ¹H NMR of the crude reaction mixtures by the analysis of the coupling constants of the bridgehead protons. GC analysis was also used through retention times of the isomers and integration's. In all cases the NMR and GC of the crude reaction mixture indicated exo-isomer which disappear during workup and purification and no evidence of products other than the unreacted starting materials and the facial stereoisomers of the adducts. The absolute stereostructures of (6a-12a) should be tentatively assigned on the basis of the proposed mechanism we reported previously. All these compounds were fully characterized on the basis of their ¹Hnmr and ¹³CNMR spectra (Vide Experimental Section). Adduct (6a), (7a), and (8a) were separated by chromatography and characterized spectroscopically, these structures were further confirmed through their hydrolysis to the corresponding diacid compounds (14a), (15a), and (16a) respectively scheme (IV). The adducts (14a), (15a) and (16a) have identical IR, ¹H NMR and ¹³C NMR spectra of the diacid adducts obtained from cycloaddition of heterodiene and fumaric acid as dienophile.

Experimental

Melting points were determined on a Griffin melting point apparatus MFB-590-010T. Thin layer chromatography (TLC) and preparative thin layer chromatography (PLC) were carried out on glass supported silica gel plates and also on Riedel-de Haen AG cards SI (silica gel with fluorescentindication 254 nm on glass plates). Gas liquid chromatography (glc) was performed on a Pye Unicam series 304 gas chromatograph. Infrared (ir) spectra were recorded as KBr disks for solids and thin films on sodium chloride plates for liquid, with JASCO 100 infrared spectrometer, and Shimadzu 435 pin 204-03000 infrared spectrometer. NMR spectra were obtained by using a Both ¹H and ¹³C NMR spectra were determined in CDCl_3 (unless otherwise stated). Tetramethylsilane

(TMS) was used as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm). Positive shifts are downfield from TMS. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet.

All air-sensitive reactions were carried out in pre-flame dried glass apparatus under dry oxygen free atmosphere. All solvents and starting material were purified by distillation prior to use.

7-Oxabicyclo[2.2.1]hepta-5-ene-1-carboxyaldehyde-2,3-dicarboxylic Anhydride (6a)

To a mixture of maleic anhydride (9.806 g, 0.1mole) in dry pure 1,4-dioxane (20 mL) was added freshly distilled furfural (9.60 g, 0.1 mole) and dry pure 1,4-dioxane (20mL). The reaction mixture was stirred at room temperature for ten days (10 days). 1,4-dioxane was then removed from the reaction solution by evaporation under reduced pressure; the residual white solid was collected by vacuum filtration to give 1.98 g of crude product. The crude product was purified as previously described to yield 1.58 g (16.04%), mp 148-151° and 2.00 g (20.86%) on using AlCl_3 as a catalyzed agent, upon recrystallization from ethyl acetate / hexane (1:1 volume / volume) as crystallization mixed solvent; IR $_{\text{vmax}}$ (KBr) 2950-2599; 1770; 1650; 1590; 1222; 1090; 920; 905; 820; 805 and 730 cm^{-1} . ^1H nmr (250 MHz) (DMSO) δ_{H} 9.89(s, 1 H); 6.90 (m, 1 H); 6.85(m, 1 H); 5.22 (brs, 1 H); 3.60-3.50(m, 1 H) and 3.42-3.36(d, 1H,J=3.0Hz), ^{13}C nmr (DMSO) δ_{C} 206.80, 179.60, 139.41, 137.34, 86.67, 78.35, 76.62, 7344 and 69.20. Anal. Calcd For $\text{C}_9\text{H}_5\text{O}_5$; C; 55.68 and H; 3.12% Found C; 55.49 and H; 3.23%.

7-Thiobicyclo[2.2.1]-5-hepten-2,3-dicarboxylic anhydride (7a)

To a mixture of maleic anhydride (9.8g, 0.1 mole) in dry pure 1,4-dioxane (25mL) was added freshly distilled thiophene (8.414g, 0.1 mole) and dry pure 1,4-dioxane (20 ml). The reaction mixture was stirred at room temperature for 72 hr; 1,4-dioxane was then removed from the reaction solution by evaporation under reduced pressure to give 2.8g of crude product melting at 139-142. The crude product was dissolved in a minimum amount of ether and placed on a 4.5x80 cm column of neutral alumina packed with petroleum ether (bp 60-90°C). The product was eluted with 1:18 ether-petroleum ether. The major product (7a) eluted was collected by vacuum filtration to give 1.40g (16.60%) and 1.06(19.02%) on using AlCl_3 as a catalyzed agent of a white solid, mp 137-138°, upon recrystallization from ethylacetate. IR $_{\text{vmax}}$ (KBr) 3060-2955, 2950, 1765, 1650; 1450, 1250, 1230, 1070, 950, 900, 840, 800, 750 and 730 cm^{-1} . ^1H nmr (250 MHz) (DMSO) δ_{H} 6.52 (m, 2H); 3.26(m, 2H), 3.20 (m, 2H) ^{13}C nmr (DMSO) δ_{C} 189.80,132.12,130.25,81.72,75.92,72.91,70.56 and 68.86. Anal. Calcd for $\text{C}_8\text{H}_7\text{NO}_3$; C; 58.16, H; 4.28, and N; 8.49%. Found C; 57.82, H; 4.68, and N; 8.15%.

7-Azabicyclo[2.2.1]-5-hepten-2,3-dicarboxylic anhydride (8a)

To a mixture of maleic anhydride (9.8g, 0.1 mole) in dry pure 1,4-dioxane (25 ml) was added freshly distilled pyrrole (9.57 g 0.143 mole) and dry 1,4-dioxane (20 ml). The reaction mixture was stirred at room temperature for 168 hr. monitoring and workup proceeded as previously described, the residual solid was collected by vacuum filtration to give 2.88 g of crude product. The crude product was purified to yield 1.10 g (11.23%) and 1.29 g (13.16%) on using AlCl_3 of a brown solid, mp 285-287° recrystallization from ethylacetate; IR $_{\text{vmax}}$ (KBr) 3360, 3050, 2920, 1745, 1650,

1455, 1260, 1235, 1065,922, 908, 800, 745 and 730 cm^{-1} , ^1H nmr (250 MHz) (DMSO) δ_{H} 6.36(m, 1H), 6.32 (m, 1H), 3.32 (m, 1 H), 3.22 (m, 1 H), 2.95 (m, 1 H) and 2.80-2.65(brd, 1 H). ^{13}C nmr (DMSO) δ_{C} 186.90, 131.85,130.12,81.55,75.60,72.20,69.89 and 68.75. Anal calcd for $\text{C}_8\text{H}_7\text{NO}_3$; C; 58.16, H; 4.28 and N; 8.49%. Found C; 57.82, H; 4.68, and N; 8.15%.

9- Thiotricyclo [6.2.1.0^{4a},sa]-2,6-undecen-5,Sdion (10a)

To a mixture of pure 1,4-benzoquinone (2.70 g, 0.025 mole) in dry pure 1,4-dioxane (10 ml) was added freshly distilled thiophene (2.104 g, 0.025 mole). The reaction mixture was stirred at room temperature for 120 hours. Monitoring and workup proceeded as described above; yielded a mixture of Diels-Alder adduct and excess of p- benzoquinone which was removed by crystallization from carbon tetrachloride, the residual solid was collected by vacuum filtration to give 0.85 g of crude product. The crude product was purified by chromatography as previously described to yield 0.6 g (28.52%) and 0.76 g(36.13%) on using AlCl_3 as catalyzed of bright black solid, mp 147-149° upon recrystallization from carbon tetrachloride and 0.9 g (42.75%) of bright yellow solid (excess p-benzoquinone), mp 108-109°, IR $_{\text{vmax}}$ (KBr) 3400, 3050,2950,2800, 1715, 1640, 1450, 1300, 1250, 1150, 1000, 980,800, 750 and 730 cm^{-1} . ^1H nmr (250 MHz) (CDCl_3) δ_{H} 6.70 (m, 2H), 6.65 (m, 2H), 3.90(dd, 1 H,J=2.0Hz), 3.88 (dd,1 H,J=2.0Hz), 3.35-3.20 (dd, 2H,J=2.0Hz); ^{13}C nmr (CDCl_3) δ_{C} 201.60, 145.80, 142.60, 75.90, 74.95,48.20 and 46.80. Anal calcd for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}$; C,2.48; H,4.20; and S, 16.60. Found; C, 63.01; H, 4.42; and S, 16.25

9-Azatricyclo [6.2.1. 0^{4a,8a}] -2,6-undecen-5,8-dione (11a)

To a mixture of pure p-benzoquinone (2.70g, 0.025 mol) in dry solvent (1,4-dioxane, 15 ml) was added freshly distilled pyrrole (1.68 g, 0.025 mol) in (15 ml) 1,4-dioxane. The reaction mixture was stirred at room temperature for six days. Monitoring and workup proceeded as previously described above, to give 0.606 g (36.12%) and 0.70 g (41.89%) on using AlCl_3 as a catalyzed agent of pale yellow solid, mp 275-278°. IR $_{\text{vmax}}$ (KBr); 3600-3450, 3340, 3000, 2950, 2800, 705, 1640, 400, 1350, 1250, 1000,950,900,780 and 730 cm^{-1} . ^1H nmr (250 MHz) (DMSO) δ_{H} 6.75 (m, 2H), 6.70 (m, 2H), 3.79 (dd, 1H,J=2.0Hz) and 3.60-3.45 (dd, 2H,J=2.0Hz). ^{13}C NMR (DMSO) δ_{C} 200.60, 146.80,144.90, 142.70, 73.20, 52.30, 49.90 and 48.85. Anal calcd for $\text{C}_{10}\text{H}_9\text{NO}_2$; C, 68.56; H, 5.18 and N, 8.00%. Found; C, 68.92; H, 5.22; and N, 7.89%.

9-0xatricyclo [6.2.1. 0^{4a,8a}]-2,6-undecen-5,8-dione -1-carboxyaldehyde (9a)

To a mixture of a pure p-benzoquinone (2.7 g 0.025 mol) in (15 ml) 1,4-dioxane was added distilled furfural (2.40 g, 0.25 mol) and (15 ml) 1,4-dioxane. The reaction mixture was stirred at room temperature for seven days (7 days). Monitoring and workup proceeded as previously described. To give 0.95 g of crude product (9). The crude product was purified by chromatography to yield 0.75 g (31.25%) and 1.01g(42.08%) on using AlCl_3 as a catalyzed of white solid, mp 156-158°, upon recrystallization from ethylacetate/hexane (1:1 v/v): IR $_{\text{vmax}}$ (KBr) 3350, 3070, 2990,1715,1640,1450, 1250,1235,1050,930,905,745 and 730 cm^{-1} . ^1H nmr (250 MHz) (acetone- d_6) δ_{H} 9.25 (s, 1 H),6.95 (m, 1 H), 6.62 (m, 1H), 5.98 (s, 2H), 3.45 (m, 1H), 3.36 (dd, 1H,J=2.5 Hz) and 3.28 (d, 1H,J=2.5Hz) ^{13}C NMR (acetone- d_6) δ_{C} 203.60, 198.80, 170.20, 145.60, 138.60, 78.80, 58.40 and 52.90. Anal calcd for

C₁₁H₈O₄; C, 64.71, and H, 3.95%. Found; C, 64.00, and H, 3.54%

Bis-Adduct (12a)

To a mixture of a pure p-benzoquinone (1.35 g, 0.0125 mol) in a dry 1,4-dioxane (15 ml) was added freshly distilled pyrrole (1.68 g, 0.025 mol) with 1,4-dioxane (15 ml). The reaction mixture was stirred at room temperature for 10 days. Monitoring and workup proceeded as previously described. The crude adduct was filtered to remove any insoluble material, 0.235 g (13.99%) of a bright black crystalline was obtained, mp 168-174° (lit. 171°)¹⁰ as a quinhydrone. Filtrate was treated with charcoal, filtered and evaporated to give a bis-adduct in 0.583 g (43.18%), and 0.77 g (45.60%) on using AlCl₃ as a catalyzed, mp 293.295° upon recrystallization from ether/hexane (1:1 v/v) as a crystallization mixed solvent: IR_{vmax}(KBr), 3800-3500, 3350, 3040, 2900, 1720, 1645, 1645, 1420, 1300, 1230, 1010, 950, 900, 740 and 735 cm⁻¹. ¹H nmr (250 MHz) (DMSO) δ_H 6.72 (dd, 2H, J = 2.0Hz), 6.65 (dd, 2H, J = 20Hz), 3.96 (dd, 2H, J = 20Hz), 3.95-3.86 (brs, 2H), 3.85 (dd, 2H, J = 20Hz), 3.70 (dd, 1H, J = 2.0Hz), 3.68 (dd, 2H, J = 2.0Hz) and 3.603.4 (dd, 2H, J = 2.0Hz). ¹³C nmr (DMSO) δ_C 195.80, 172.60, 142.80, 134.90, 73.20, 52.40, 49.80, 48.90 and 48.60. Anal calcd for C₁₄H₁₄N₂O₂; C, 69.41; H, 5.83 and N, 11.56% Found C, 70.02; H, 5.49 and N, 12.04%

7-Oxabicyclo[2.2.1]heptan-5-ene-1-carboxyaldehyde-2,3-dicarboxylic Acid (14)

To (0.32 g, 1.65 mmol) of 7-oxabicyclo[2.2.1]heptan-5-ene-1-carboxyaldehyde-2,3-dicarboxylic anhydride (6a) in (250 ml) round bottle flask was added (34 ml) of water. The reaction mixture was refluxed to boiling and continued to reflux until the organic compounds went into solution. The hot solution was filtered and allowed it cool to give 1.3 g of crude product which was purified as previously described to yield 0.09 g (28.13%) of a white crystalline material, mp 218-220° upon recrystallization from 1-propanol/ethylacetate (1:1 v/v) as a mixed solvent. IR_{vmax}(KBr), 3600-3400, 3050, 2800, 1715, 1650, 1450, 1250, 1230, 1050, 920, 900, 745 & 730 cm⁻¹. ¹H nmr (250 MHz) (Acetone-d₆) δ_H 10.10 (s, 1H), 9.80 (s, 1H), 6.89 (s, 1H), 6.80 (s, 1H), 3.86 (m, 1H), 3.70-3.10(m, 2H), ¹³C nmr (Acetone-d₆) δ_C 203.20, 189.20, 140.60, 79.80, 78.20, 76.20, 57.60 and 54.20. Anal calcd for C₉H₈O₆; C, 50.95 and H, 3.80% Found; C, 51.10 and H, 4.10%. Note similar compound was obtained by using fumaric acid as a dienophile.

7-Thiobicyclo[2.2.1]heptan-5-ene-2,3-dicarboxylic Acid (15)

Monitoring and workup proceeded as described above, yield 0.12 g (31.30%), mp 18991°. IR_{vmax}(KBr), 3850, 3700, 2900, 2850, 1710, 1650, 1450, 1210, 1020, 908, 820, 790 and 730 cm⁻¹. ¹H nmr

(DMSO) δ_H (250 MHz) 6.70(s, 1H), 6.69(s, 1H), 3.92-3.10(m, 6H). ¹³C nmr (DMSO) δ_C 178.90, 138.80, 79.20, 78.40, 75.60, 58.20 and 56.40. Anal calcd for C₈H₈O₄S; C, 48.03; H, 4.00, and S, 16.01 Found C, 48.43; H, 3.72, and S, 15.63.

(DMSO) δ_H (250 MHz) 6.70(s, 1H), 6.69(s, 1H), 3.92-3.10(m, 6H). ¹³C nmr (DMSO) δ_C 178.90, 138.80, 79.20, 78.40, 75.60, 58.20 and 56.40. Anal calcd for C₈H₈O₄S; C, 48.03; H, 4.00, and S, 16.01 % Found C, 48.43; H, 3.72, and S, 15.63.

7-Azabicyclo[2.2.1]heptan-5-ene-2,3-dicarboxylic Acid (16)

Monitoring and workup proceeded as described above, yield 0.12 g (37.50%), mp 218-221°. IR_{vmax}(KBr), 3800-3600, 2950, 2850, 1710, 1640, 1400, 1210, 1010, 900, 800, 790 and 730 cm⁻¹. ¹H nmr (250 MHz) (CDCl₃) δ_H 10.20 (s, 2H), 6.72(m, 1H), 6.70(m, 1H), 3.90-3.00(overlapping signals, 5H). ¹³C NMR (CDCl₃) δ_C 179.60, 139.20, 78.90, 78.20, 75.80, 58.60 and 56.20. Anal calcd for C₈H₉N₂O₄; C, 52.46, H, 4.95 and N, 7.65% Found; C, 53.20; H, 5.35 and N, 7.30%

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