Synthesis of new heterocyclic compounds via cycloaddition reaction

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Received 3 October 2000; accepted (revised) 20 November 2001

The reaction of bis-(p-3,5-dioxo-1,2,4-triazolin-4-yl)methane (diphenyl methanobistriazolinedione, DPMBTAD) with monomeric cyclopentadiene, 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, hexachlorocyclopentadiene, isoprene, 1,3-cyclohexadiene, and anthracene has been investigated. These reactions occurred via [4+2] Diels-Alder cycloaddition reaction and lead to the formation of novel heterocyclic bis-adducts in quantitative yields. The reaction of DPMBTAD with monomeric cyclopentadiene, 1,3-cyclohexadiene and isoprene are extremely fast even at -10 °C in methylene chloride solution.

4-Substituted-1,2,4-triazoline-3,5-diones as well as bis-triazolinediones are very powerful electron acceptors and thus are among the most reactive dienophiles1-12 and enophiles6-12 and electrophiles13-15. In a previous paper16 we reported the reaction of 1,6-bis(3,5-dioxo-1,2,4-triazolin-4-yl)hexane with some dienes which lead to the formation of novel heterocyclic bis-adducts in quantitative yields.

Bis-(p-3,5-dioxo-1,2,4-triazolin-4-yl)methane [diphenylmethanobistriazolinedione, DPMBTAD] 1 is very reactive bis-dienophile10-17-21, Bis-enophile10,17-24, and bis-electrophile13-15. Although the reaction of 1 with styrene17, isoegenol20, α-substituted esters22, β-dicarbonyl compounds23, N,N,N',N'-tetramethyl-phenylene diamine15, N-methylpyrrole31, trans-stilbene31, 1,1-diphenylethylene31, trans-3,3-dichloro-1-phenyl-1-propene30 and divinyl esters24 has been investigated, its reaction with simple dienes has not been reported so far. The purpose of this work was to examine the reactivity of 1 with some selected dienes.

Monomeric cyclopentadiene, 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopenta diene, hexachlorocyclopentadiene, isoprene, 1,3-cyclohexadiene, and anthracene were selected as dienes.

Freshly distilled monomeric cyclopentadiene 2 underwent reaction instantaneously with 1 via a [4+2] Diels-Alder reaction (Scheme I) when a methylene chloride solution of 1 was added at once to a methylene chloride solution of 2 at -10 °C in 1:2 molar ratio. The reaction was extremely fast even at -10 °C. The pale-yellow crystals were obtained after purification via reccrystallization. The yield is quantitative and the elemental analysis is in agreement with 1:2 adduct 3.

The 1H NMR spectrum of compound 3 showed signals at δ 1.93 (d, one of the protons of the bridge head CH2), 2.27 (d, the other proton of the bridgehead CH2), 4.00 (s, the proton of CH2 between two aromatic rings), 5.15 (s, bridged protons), 6.47 (s, olefinic protons), and 6.47 (s, aromatic protons). Similarly the reaction of 5,5-dimethoxy-1,2,3,4-tetra chlorocyclopentadiene 4 with DPMBTAD 1 was performed in methylene chloride solution at room temperature (2:1 molar ratio (Scheme I). The reaction was slow as compared to that of cyclopentadien
The reaction of 1 with 1,3-cyclohexadiene 10 was performed in methylene chloride at -10°C. The reaction was extremely fast even at temperature lower than -10°C. The completion of the reaction could be easily determined by the disappearance of the red colour of 1. The yield of cycloadduct was quantitative and elemental analysis and IR spectrum were in agreement with the assigned structure of 1:2 adduct 11 (Scheme III).

The 1H NMR spectrum of compound 11 showed signals which were in agreement with the assigned structure of 11.

The reaction of DPMBTAD 1 with anthracene 12 was carried out in methylene chloride at room temperature. Addition of the red solution of 1 to a methylene chloride solution of anthracene 12 produced a purple colour which after a few min turned into a light-pink colour and became pale-yellow after about 4 min. At the end of reaction the solvent was removed and a yellow solid was obtained. Recrystallization from ethyl acetate afforded yellow needle crystals of 13 (Scheme IV). Elemental analysis showed 13 to be a 1:2 adduct formed by [4+2] Diels-Alder cycloaddition reaction.

The 1H NMR spectrum of compound 13 showed signals at δ 3.95 (s, methylene protons between two aromatic rings), 6.35 (s, bridged C-H protons), 7.10 (s, aromatic protons of diphenylmethane moiety) and 7.45 (m, the other aromatic protons).

\[ \text{(monomer) even at room temperature. This can be explained in terms of frontier molecular orbitals theory. Replacement of four hydrogen atoms by four chlorine atoms in cyclopentadiene ring, lower the energy level of HOMO in diene 4, therefore energy gap between HOMO of diene 4 and LUMO of dienophile 1 increases causing a decrease in the reaction rate.} \]

The 1H NMR spectrum of compound 5 showed signals at δ 3.72 and 3.92 (each s) which were assigned to the methoxy group protons. The signals at δ 4.15 and 7.47 (each s) were assigned to the protons of CH₂ between two aromatic rings and the aromatic protons, respectively. The IR spectrum and elemental analysis agreed with 1:2 adduct 5.

The reaction of hexachlorocyclopentadiene 6 with 1 was also carried out in methylene chloride at room temperature (Scheme I). The Diels-Alder cycloaddition in this case was very slow compared to that of cyclopentadiene and it required almost 9 hr for completion. In this case, two more chlorine atoms further lowered the energy level of HOMO in diene 6 and leading further large energy differences between HOMO and LUMO, and thus, the rate of reaction decreased drastically. The yield of the cycloadduct was quantitative and the IR spectrum and elemental analysis agreed with 1:2 adduct 7. The 1H NMR spectrum of compound 7 was very simple and showed peaks only for protons of diphenylmethane moiety.

Isoprene 8 underwent reaction with 1 (Scheme II) when a methylene chloride solution of DPMBTAD was added to methylene chloride solution of compound 8. The reaction was extremely fast even at -10°C. The yield was quantitative and the IR spectrum and elemental analysis agreed with 1:2 adduct 9.

The 1H NMR spectrum of compound 9 showed signals at δ 1.90 (s, methyl protons), 4.10 (m, br, protons of CH₂ between two aromatic rings and the other 4 methylene protons), 5.65 (br, s, olefinic protons), and 7.42 (dd, aromatic protons).

The reaction of 1 with 1,3-cyclohexadiene 10 was performed in methylene chloride at -10°C. The reaction was extremely fast even at temperature lower than -10°C. The completion of the reaction could be easily determined by the disappearance of the red colour of 1. The yield of cycloadduct was quantitative and elemental analysis and IR spectrum were in agreement with the assigned structure of 1:2 adduct 11 (Scheme III).

The 1H NMR spectrum of 11 showed signals which were in agreement with the assigned structure of 11.

The reaction of DPMBTAD 1 with anthracene 12 was carried out in methylene chloride at room temperature. Addition of the red solution of 1 to a methylene chloride solution of anthracene 12 produced a purple colour which after a few min turned into a light-pink colour and became pale-yellow after about 4 min. At the end of reaction the solvent was removed and a yellow solid was obtained. Recrystallization from ethyl acetate afforded yellow needle crystals of 13 (Scheme IV). Elemental analysis showed 13 to be a 1:2 adduct formed by [4+2] Diels-Alder cycloaddition reaction.

The 1H NMR spectrum of compound 13 showed signals at δ 3.95 (s, methylene protons between two aromatic rings), 6.35 (s, bridged C-H protons), 7.10 (s, aromatic protons of diphenylmethane moiety) and 7.45 (m, the other aromatic protons).
Conclusion
From this investigation it is clear that 1 is extremely reactive dienophile. Its reaction with a wide variety of dienes gave novel heterocyclic compounds in quantitative yields. The reactivity of dienes towards this dienophile is in the order: isoprene ~cyclohexadiene > anthracene > 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene > hea-chlorocyclopentadiene. Furthermore, this dienophile is more reactive than its aliphatic analogue HMBTAD towards the above dienes. The resulted bis-cycloadducts are very interesting compounds for further studies.

Experimental Section

General. IR spectra in cm⁻¹ were recorded on a Shimadzu 435 IR spectrophotometer using KBr pellets, and ¹H NMR spectra (90MHz) on a Varian EM-390 instrument, using TMS as internal standard (chemical shifts in δ, ppm). All melting point were taken with a Gallenhamp melting point apparatus and are corrected. Elemental analysis were performed by Research Institute of Petroleum Industry, Tehran, I.R.Iran.

TLC on commercial plates of silica gel 60 F₂₅₄ on aluminium was used to determine Rₛ. Column chromatography was carried out using silica gel 60 (Riedel-DeHaeen AG).

Reagents were purchased from Aldrich Chemical Co., Fluka Chemical Co., or Riedel-deHaen AG. Bis-(p-3,5-dioxo-1,2,4-triazolin-4-yl)methane (diphenylmethane 7. Hexachlorocyclopentadiene and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene were prepared. To this solution und stirring a red solution of 0.30g (8.28x10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once at room temperature. The solution developed a deep-purple colour and after 2 hr turned to pale yellow. The solvent was removed in vacuo and 0.74 g (100%) of yellow solid. This solid was chromatographed over silica gel using ethyl acetate–cyclohexane (50:50) as eluent and 0.70 g solid (I 0.84) was collected. Recrystallization from ethane gave pale-yellow crystals; mp 200°C(dec); IR (KBr): 3050 (w), 2950 (w), 2850 (w), 1710 (s), 1570 (w), 1400 (s) cm⁻¹; ¹H NMR (CDCl₃, TMS): δ 1.93 (d, 2H, J= 10.5 Hz), 2.27 (2H, J= 10.5 Hz), 4.00 (s, 2H), 5.15 (s, 4H), 6.47 (s, 4H), 7.25 (s, 8H); Anal. Calcd for C₁₁₁H₂₂N₄O₂: 65.57; H, 4.48; N, 17.00. Found: C, 65.30; H, 4.70; N, 17.40%.

Preparation of bis-[5,6,7,8-tetrachloro-9,10-dimethoxy-5,8-methano-s-triazolo[1,2-a]pyridazin-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 5. In a 2 mL round-bottomed flask, equipped with a magnet stirrer and a constant-pressure dropping funnel, a solution of 0.44 g (1.67x10⁻³ mole) of 5,5-dimethox-1,2,3,4-tetrachlorocyclopentadiene and 10 mL of methylene chloride was prepared. To this solution und stirring a red solution of 0.30g (8.28x10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once at room temperature. The solution developed a deep-purple colour and after 2 hr turned to pale yellow. The solvent was removed in vacuo and 0.74 g (100%) of yellow solid. This solid was chromatographed over silica gel using ethyl acetate–cyclohexane (50:50) as eluent and 0.70 g solid (I 0.84) was collected. Recrystallization from ethane gave pale-yellow crystals; mp 200°C(dec); IR (KBr): 3050 (w), 2950 (w), 2850 (w), 1710 (s), 1570 (s), 1400 (s) cm⁻¹; ¹H NMR (CDCl₃, TMS): δ 3.72 (6H), 3.92 (s, 6H), 4.15 (s, 2H), 7.47 (s, 8H); Anal. Calcd for C₁₁₁H₂₂N₄O₂Cl₂: C, 41.82; H, 2.49; N, 9.44. Found: C, 41.90; H, 2.60; N, 9.60.

Preparation of bis-[5,6,7,8,9,9-hexachloro-5,8-dimethano-s-triazolo[1,2-a]pyridazin-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 7. Hexachlorocyclopentadiene (0.53 g, 1.94x10⁻³ mole) and 20 mL of methylene chloride were placed into a 250 mL round-bottomed flask. A solution of 0.35g (9.66x10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once at room temperature. The solution became deep-purple which turned to pink. After 9 hr a pale-yellow solution was obtained. Methylene chloride was removed in vacuo to yield 0.88 g (100%) of pale-yellow solid. This solid was chromatographed over silica gel using methylene chloride–cyclohexane (20:80) as eluent and 0.85 g solid (Rₛ 0.68) was collected. Recrystallization from methanol gave pale-yellow crystals; mp 170°C(dec); IR (KBr): 3050 (w), 2950 (m), 17 (s), 1710 (s,br), 1570 (w), 1400 (s) cm⁻¹; ¹H NMR (CDCl₃, TMS): δ 1.93 (d, 2H, J= 10.5 Hz), 2.27 (2H, J= 10.5 Hz), 4.00 (s, 2H), 5.15 (s, 4H), 6.47 (s, 4H), 7.25 (s, 8H); Anal. Calcd for C₂₇H₂₇N₆O₄: 59.57; H, 4.48; N, 17.00. Found: C, 59.30; H, 4.70; N, 17.40%.

Preparation of bis-[5,6,7,8-tetrachloro-9,10-dimethoxy-5,8-methano-s-triazolo[1,2-a]pyridazin-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 5. In a 2 mL round-bottomed flask, equipped with a magnet stirrer and a constant-pressure dropping funnel, a solution of 0.44 g (1.67x10⁻³ mole) of 5,5-dimethox-1,2,3,4-tetrachlorocyclopentadiene and 10 mL of methylene chloride was prepared. To this solution und stirring a red solution of 0.30g (8.28x10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once at room temperature. The solution developed a deep-purple colour and after 2 hr turned to pale yellow. The solvent was removed in vacuo and 0.74 g (100%) of yellow solid. This solid was chromatographed over silica gel using ethyl acetate–cyclohexane (50:50) as eluent and 0.70 g solid (I 0.84) was collected. Recrystallization from ethane gave pale-yellow crystals; mp 200°C(dec); IR (KBr): 3050 (w), 2950 (w), 2850 (w), 1710 (s), 1570 (s), 1400 (s) cm⁻¹; ¹H NMR (CDCl₃, TMS): δ 3.72 (6H), 3.92 (s, 6H), 4.15 (s, 2H), 7.47 (s, 8H); Anal. Calcd for C₁₁₁H₂₂N₄O₂Cl₂: C, 41.82; H, 2.49; N, 9.44. Found: C, 41.90; H, 2.60; N, 9.60%.

Preparation of bis-[5,6,7,8,9,9-hexachloro-5,8-dimethano-s-triazolo[1,2-a]pyridazin-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 7. Hexachlorocyclopentadiene (0.53 g, 1.94x10⁻³ mole) and 20 mL of methylene chloride were placed into a 250 mL round-bottomed flask. A solution of 0.35g (9.66x10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once at room temperature. The solution became deep-purple which turned to pink. After 9 hr a pale-yellow solution was obtained. Methylene chloride was removed in vacuo to yield 0.88 g (100%) of pale-yellow solid. This solid was chromatographed over silica gel using methylene chloride–cyclohexane (20:80) as eluent and 0.85 g solid (Rₛ 0.68) was collected. Recrystallization from methanol gave pale-yellow crystals; mp 170°C(dec); IR (KBr): 3050 (w), 2950 (w), 1800 (m), 1745 (s,br), 1630 (m), 1580 (s), 1510 (s), 1390 (s) 1210 (s, br) cm⁻¹; ¹H NMR (CDCl₃, TMS): δ 1.93 (d, 2H, J= 10.5 Hz), 2.27 (2H, J= 10.5 Hz), 4.00 (s, 2H), 5.15 (s, 4H), 6.47 (s, 4H), 7.25 (s, 8H); Anal. Calcd for C₂₇H₂₇N₆O₄: 65.57; H, 4.48; N, 17.00. Found: C, 65.30; H, 4.70; N, 17.40%.
Preparation of bis-[7-methyl-5,8-dihydro-s-triazolo[1,2-a]pyridazine-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 10. Into a 500 mL two-necked round-bottomed flask, equipped with a magnetic stirrer and a thermometer, 0.18 g (2.76×10⁻³ mole) of freshly distilled isoprene and 20 mL of methylene chloride were added. The solution was stirred and cooled to -10°C in an ice-salt bath. A solution of 0.5 g (1.37×10⁻³ mole) of DPMBTAD in 300 mL of methylene chloride was added all at once. The red colour of DPMBTAD disappeared as soon as the solution was added to give a pale-yellow solution. The solvent was removed in vacuo to give 0.68 g (100%) of pale-yellow solid. This solid was chromatographed over silica gel using hexane fraction-cyclohexane (50:50) as eluent and 0.65 g of solid (Rf 0.58) was collected. Recrystallization from methanol gave pale-yellow crystals; mp 235°C (dec); IR (KBr): 3300 (w), 2950 (m), 1770 (w), 1710 (s, br), 1510 (s), 1420 (s, cm⁻¹); ¹H NMR (CDCl₃, TMS): δ, 1.90 (s, 6H), 4.10 (m, 10H), 5.65 (s, br, 2H), 7.42 (dd, 8H, J₁ = 20.0 Hz, J₂ = 10.5 Hz). Anal. Calcd for C₂₇H₂₉N₆O₄: C, 75.19; H, 6.40%; N, 11.60%. Found: C, 75.19; H, 6.40%; N, 11.60%.

Preparation of bis-[5,8-dihydro-5,8-ethano-s-triazolo[1,2-a]pyridazine-1,3-(2H)-dion-2-yl-(p-phenyl)] methane 11. Into a 500 mL two-necked round-bottomed flask, equipped with a magnetic stirrer and a thermometer, 0.22 g (2.74×10⁻³ mole) of 1,3-cyclohexadiene and 10 mL of methylene chloride were added. The solution was stirred and cooled to -10°C with an ice-salt bath. A solution of 0.50 g (1.73×10⁻³ mole) of DPMBTAD in 300 mL of methylene chloride was added all at once. The red colour of DPMBTAD disappeared as soon as the solution was added and pale-yellow solution was obtained. The solvent was removed to give pale-yellow solid, yield 0.72 g (100%). This solid was chromatographed over silica gel using ethyl acetate as eluent and 0.70 g of solid (Rf 0.74) was collected. Recrystallization from methanol gave pale-yellow crystals; mp 235°C (dec); IR (KBr): 3400 (w,br), 3050 (w), 2950 (w), 1780 (m), 1700 (s, br), 1520 (m), 1400 (s, cm⁻¹); ¹H NMR (CDCl₃, TMS): δ, 1.92 (d, 4H, J = 10.5 Hz), 2.22 (d, 4H, J = 9.0 Hz), 4.10 (s, 2H), 4.95 (s, br, 4H), 6.57 (t, 4H, J = 4.5 Hz), 7.30 (dd, 8H, J₁ = 15.5 Hz, J₂ = 10.5 Hz). Anal. Calcd for C₂₇H₂₉N₆O₄: C, 66.65; H, 5.02%; N, 16.68. Found: C, 66.50; H, 5.10%; N, 16.40%.

Preparation of bis-[13,15-dioxo-9,10-[1',2']-(1,2,4-triazolidino) anthracene-14-yl-(p-phenyl)] methane. Into a 250 mL round-bottomed flask fitted with a magnetic stirrer were placed 0.34g (1.93×10⁻³ mole) of anthracene and 30 mL of methylene chloride and the mixture was stirred. To this 0.35 g (9.66×10⁻⁴ mole) of DPMBTAD in 200 mL of methylene chloride was added all at once. A deep-purple colour appeared which later on turned to a light-pink colour. After about 4 min a pale yellow solution was obtained. The solvent was evaporated in vacuo to give pale-yellow solid, yield 0.69 g (100%). This solid was chromatographed over silica gel using carbon tetrachloride-methanol (80:20) as eluent and 0.65 g of solid (R₁ 0.80) was collected. Recrystallization from ethyl acetate gave pale-yellow crystals; mp 238°C (dec); IR (KBr): 3400 (w), 3050 (w), 2950 (w), 1770 (m), 1710 (s, br), 1510 (m), 1510 (s), 1460 (s), 1400 (s, cm⁻¹); ¹H NMR (CDCl₃, TMS): δ, 3.95 (s, 2H), 7.10 (s, 4H), 7.45 (m, 24H). Anal. Calcd for C₃₅H₂₇N₆O₄: C, 75.19; H, 4.20%; N, 11.69. Found: C, 74.20; H, 4.50%; N, 11.60%.

Acknowledgement

The financial support of this work from Center of Excellency in Chemistry Research, Isfahan University of Technology (IUT), Isfahan, I.R.Iran, is gratefully acknowledged. We thank professor Ali A. Entezami (University of Tabriz) for a gift of isoprene.

References