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(4+2) Cycloaddition to tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron for the rapid construction of a spiro[5.5]undecane system

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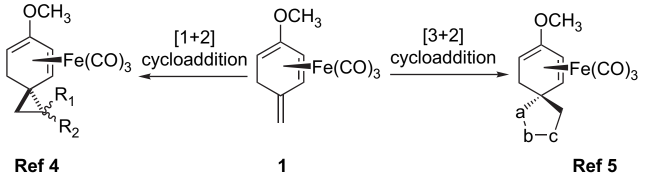
Abstract—Diels–Alder reactions of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** with 1,2,4,5-tetrazine-3,6-disubstituted derivatives **2a**,**b**,**d** and 2,3,4,5-tetrabromothiophene-1,1-dioxide **5** are reported. The (4+2) cycloaddition reactions took place exclusively with highly electron deficient dienes to form spiro[5.5]undecane system in good yield. The more electron rich nature of the 1,2,4,5-tetrazine-3,6-disubstituted derivatives **2b** did not react. The reaction also took place stereospecifically *exo* to the Fe(CO)$_3$ moiety.

1. Introduction

Development of effective methodology for the synthesis of spirocycles has been extensively reported because of their wide occurrence in a large number of natural products.[1] Among the numerous approaches for synthesizing spirocycles, the cycloaddition to an exocyclic double bond is one of the most rapid methods. Whereas the use of (3+2) cycloaddition to exocyclic double bond for the synthesis of spiro[4.*n*]alkanes has been widely reported,[2] and the use of (4+2) cycloaddition to exocylic double bond is more restricted.[3] In our previous work, we investigated the (2+1) and (3+2) cycloaddition reactions to the exocyclic double bond of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** for the synthesis of spiro[5.2]octane and spiro[5.4]decane skeletons[4,5] (Scheme 1).



Scheme 1.

We envisioned that an efficient entry to the spiro[5.5]undecane skeleton can be similarly achieved by the use of (4+2) cycloaddition reactions to tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1**. More importantly, the lateral coordination of the bulky Fe(CO)$_3$ group should provide a high degree of regio-, stereo- and chemo-control during the (4+2) cycloaddition reaction with the 4π components. Herein we wish to report an efficient and practical method of constructing spiro[5.5]undecane skeletons with high regiospecific and stereospecific *exo*-selective Diels–Alder reactions.

2. Results and discussion

Initially, the exocyclic double bond of complex **1** was screened for its ability to react with electron rich dienes. The reaction of complex **1** with cyclopentadiene and 2,3-dimethylbutadiene did not afford any (4+2) cycloaddition products. This is consistent with our earlier findings that the exocyclic double bond in complex **1** behaves more like an electron rich double bond and undergoes electrophilic addition readily.[6] We next envisioned that the exocyclic double bond of complex **1** behaved as an electron rich dienophile and this required the use of electron deficient dienes for an inverse-electron demand (4+2) cycloaddition reaction. Surprisingly, complex **1** did not undergo (4+2) cycloaddition with hexa-2,4-dienedioic acid dimethyl ester.

Cycloheptatriene–tricarbonyliron complexes have been reported to undergo an inverse-electron demand (4+2) cycloaddition[7] with methyl 1,2,4,5-tetrazine-3,6-dicarboxylate. We first synthesized methyl 1,2,4,5-tetrazine-3,6-dicarboxylate **2a** according to the literature method.[8] The reaction of complex **1** with tetrazine **2a** afforded the (4+2) cycloaddition product **3a** that rapidly isomerizes into **4a** as the sole isolated product in 65% yield. The formation of **4a** can be attributed

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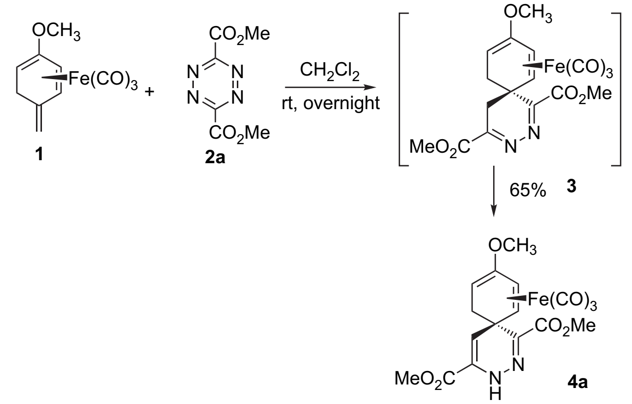
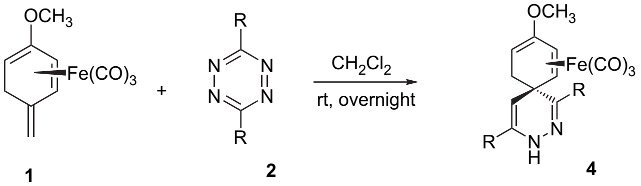
to the release of steric strain or perhaps the formation of a homoaromatic ring through intermediate **3** (Scheme 2). The structure of **4a** was assigned on the basis of IR and ^{1}H NMR spectroscopic data. The IR spectrum of **4a** exhibited an NH band at 3415 cm^{-1}. Particular diagnostic signals present in the ^{1}H NMR spectrum of **4a** include the presence of a C-5 methine proton at δ 5.61 and an NH peak at δ 8.33; whereas the C-5 methylene protons signal for **3a** was not observed. According to our previous study, cycloaddition reaction to the exocyclic double bond of complex **1** generally take place stereospecifically *exo* to the Fe(CO)$_3$ moiety and this was tentatively assigned.



Scheme 2. Inverse-electron demand (4+2) cycloaddition reaction.

We also synthesized other tetrazine derivatives **2b–d**[9,10] as the diene to react with complex **1**. Complex **1** was found to undergo cycloaddition reaction with tetrazine **2b** and **2d** to afford product **4b** and **4d** in 55% and 45%, respectively. Interestingly, **2c** did not undergo cycloaddition reaction with complex **1**. This can be attributed to the more electron rich nature of **2c** that possesses a methoxyphenyl substituent (Scheme 3).



R=	Yield
b. -Phenyl	45%
c. -4-Methoxyphenyl	no reaction
d. -Pyridiyl	55%

Scheme 3. Influence of substituent at the 1,2,4,5-tetrazine-3,6-derivatives **2** on the (4+2) cycloaddition reaction with complex **1**.

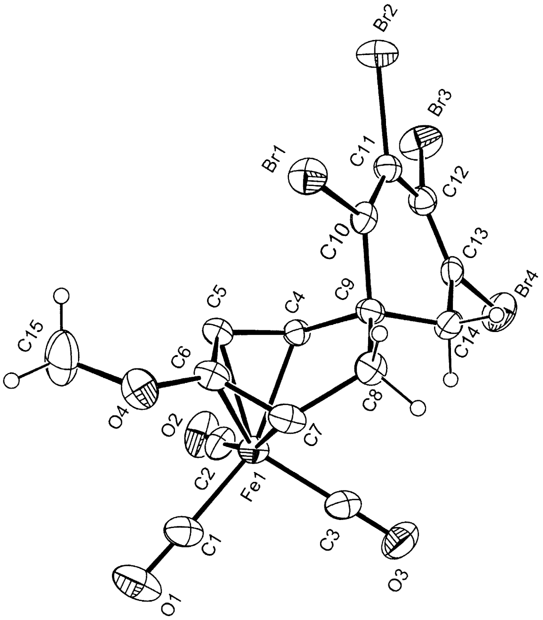
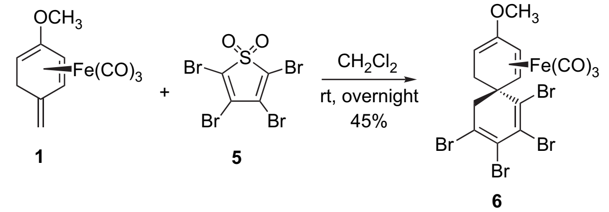


Figure 1. Single-crystal X-ray analysis and the ORTEP plot.

Another highly electron deficient diene that showed good reactivity with many electron rich dienophiles is 2,3,4,5-tetrabromothiophene-1,1-dioxide **5**.[11] 2,3,4,5-Tetrabromothiophene-1,1-dioxide **5** was prepared from thiophene via bromination followed by oxidation with *m*-chloroperoxybenzoic acid. When complex **1** was reacted with 2,3,4,5-tetrabromothiophene-1,1-dioxide **5**, at room temperature overnight, crystalline cycloaddition product **6** was obtained in 45% yield (Scheme 4). The structure of complex **6** was assigned on the basis of ^{1}H NMR spectrum and further confirmed through single-crystal X-ray diffractometry, and the ORTEP plot[12] (Fig. 1) shows that the diene has approached the exocyclic double bond in complex **1** stereospecifically from less hindered *exo*-face.



Scheme 4. (4+2) Cycloaddition reaction of complex **1** with **5**.

In summary, the rapid methodology for the construction of spiro[5.5]undecane system from tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** has been successfully developed. The reaction of complex **1** requires the use of highly electron deficient diene and take place stereospecifically *exo* to the Fe(CO)$_3$ moiety.

3. Experimental section

All reactions were performed under an atmosphere of dry nitrogen. IR spectra were measured with a Hitachi I-2001 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini-200 MHz or Varian UNITY INOVA 500 MHz using CDCl$_3$ as solvent and internal standard. Low- and high-resolution mass spectra were measured with a Hitachi M-52-Instrument or Bruker APEX II mass spectrometer. Melting points are uncorrected. Compounds **1**,[4,5] **2a–d**[7,8,9] and **5**[10] were prepared according to literature method.

3.1. General procedure for the (4+2) cycloaddition of triene complex 1 with diene

To a solution of triene complex **1** (1 mmol) in CH_2Cl_2 (10 mL) was added compound **3** or **4** (3 mmol). After stirring at room temperature overnight, the mixture was concentrated in vacuo and purified by preparative TLC to give the desired compound.

3.1.1. Tricarbonyl{(7-9-η)-9-methoxy-2,3-diaza-spiro-[5.5]undeca-1,4,7,9-tetraene-1,4-dicarboxylic acid dimethyl ester}iron 4a. Eluent: CH_2Cl_2. Yield: 65% as yellow solid. Mp: 142–143 °C. R_f: 0.22 (CH_2Cl_2). IR ν_{max} (CH_2Cl_2): 3415, 2047, 1972, 1719 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (br s, N-H, 1H), 5.61 (d, *J*=2.5 Hz, 5-H, 1H), 4.95 (dd, *J*=6, 2.5 Hz, 8-H, 1H), 3.88 (s, –CO_2Me, 3H), 3.80 (s, –CO_2Me, 3H), 3.70 (s, –OCH_3, 3H), 3.39 (m, 10-H, 1H), 2.55 (dd, *J*=15, 2.5 Hz, *endo*-11-H, 1H), 2.33 (d, *J*=6 Hz, 7-H, 1H), 1.58 (dd, *J*=15, 2.5 Hz, *exo*-11-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.3 (CO), 163.8 (*C*O_2Me), 161.8 (*C*O_2Me), 141.9 (9-C), 135.3 (1-C), 126.9 (4-C), 115.7 (5-C), 62.7 (8-C), 56.7 (10-C), 54.7 (–OCH_3), 52.7 (7-C), 52.6 (CO_2*C*H_3), 52.3 (CO_2*C*H_3), 43.1 (11-C), 37.6 (6-C). Mass (FAB): *m*/*z* 433 (M^++1), 432 (M^+), 404 (M^+-CO), 376 (M^+-2CO), 348 (M^+-3CO). HRMS (ESI) Calcd for $C_{17}H_{17}N_2O_8Fe$ (M^++1): 433.0334; found: 433.0338. Anal. Calcd for $C_{17}H_{16}N_2O_8Fe$: C, 47.26; H, 3.73; N, 6.48. Found: C, 47.09; H, 3.83; N, 6.47.

3.1.2. Tricarbonyl{(7-9-η)-9-methoxy-1,4-diphenyl-2,3-diaza-spiro[5.5]undeca-1,4,7,9-tetraene}iron 4b. Eluent: CH_2Cl_2. Yield: 45% as yellow solid. Mp: 147–148 °C. R_f: 0.31 (CH_2Cl_2). IR ν_{max} (CH_2Cl_2): 3440, 2041, 1971 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (br s, N-H, 1H), 7.33–7.51 (m, Ph, 10H), 4.84 (d, *J*=2 Hz, 5-H, 1H), 4.77 (dd, *J*=6.5, 2.5 Hz, 8-H, 1H), 3.45 (s, –OCH_3, 3H), 3.24 (m, 10-H, 1H), 2.63 (d, *J*=6.5 Hz, 7-H, 1H), 2.30 (dd, *J*=15, 2.5 Hz, *endo*-11-H, 1H), 1.77 (dd, *J*=15, 2.5 Hz, *exo*-11-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.2 (CO), 149.0 (1-C), 140.0 (9-C), 137.9 (4-C), 137.8 (Ph 1′-C), 134.5 (Ph 1-C), 129.7 (Ph 4-C), 128.9 (Ph 2-C), 128.8 (Ph 3′-C), 127.9 (Ph 3-C), 127.8 (Ph 2′-C), 125.5 (Ph 4′-C), 102.9 (4-C), 65.2 (8-C), 57.5 (10-C), 54.3 (–OCH_3), 52.9 (7-C), 43.4 (11-C), 40.8 (6-C). Mass (FAB): *m*/*z* 469 (M^++1), 441 (M^++1-CO), 412 (M^+-2CO), 384 (M^+-3CO). HRMS (FAB) Calcd for $C_{25}H_{21}N_2O_4Fe$ (M^++1): 469.0852; found: 469.0840. Anal. Calcd for $C_{25}H_{20}N_2O_4Fe$: C, 64.15; H, 4.31; N, 5.98. Found: C, 64.13; H, 4.45; N, 6.04.

3.1.3. Tricarbonyl{(7-9-η)-9-methoxy-1,4-dipyridyl-2,3-diaza-spiro[5.5]undeca-1,4,7,9-tetraene}iron 4d. Eluent: CH_2Cl_2. Yield: 55% as yellow solid. R_f: 0.40 (CH_2Cl_2: EA = 10:1). IR ν_{max} (CH_2Cl_2): 3392, 2047, 1972 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (br s, N-H, 1H), 8.56 (d, *J*=5 Hz, Py 2-H, 1H), 8.54 (d, *J*=5 Hz, Py 2′-H, 1H), 7.65–7.75 (m, Py-H, 4H), 7.20–7.25 (m, Py-H, 2H), 5.27 (d, *J*=1.5 Hz, 5-H, 1H), 4.84 (dd, *J*=6.5, 2.5 Hz, 8-H, 1H), 3.61 (s, –OCH_3, 3H), 3.36 (m, 10-H, 1H), 2.85 (dd, *J*=15, 2.5 Hz, *endo*-11-H, 1H), 2.68 (d, *J*=6.5 Hz, 7-H, 1H), 1.71 (dd, *J*=15, 2.5 Hz, *exo*-11-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9 (CO), 156.5 (1-C), 150.3 (Py 2′-C), 148.3 (Py 6-C), 147.6 (Py 6′-C), 144.4 (Py 2-C), 141.9 (9-C), 136.7 (Py 4′-C), 136.0 (Py 4-C), 134.9 (4-C), 124.0 (Py 3-C), 123.0 (Py 5-C), 122.3 (Py 5′-C), 119.1 (Py 3′-C), 105.3 (5-C), 64.3 (8-C), 58.0 (10-C), 54.4 (–OCH_3), 53.2 (7-C), 42.9 (11-C), 39.6 (6-C). Mass (FAB): *m*/*z* 471 (M^++1), 442 (M^++1$-$CO), 414 (M^+-2CO), 386 (M^+-3CO). HRMS (FAB) Calcd for $C_{23}H_{19}N_4O_4Fe$ (M^++1): 471.0757; found: 471.0762.

3.1.4. Tricarbonyl{(7-9-η)-9-methoxy-1,2,3,4-tetra-bromo-spiro[5.5]undeca-1,3,7,9-tetraene}iron 6. Eluent: hexane. Yield: 45% as yellowish crystals. Mp: 158–159 °C. R_f: 0.32 (hexane). IR ν_{max} (CH_2Cl_2): 2053, 1978 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.03 (dd, *J*=6.5, 2.5 Hz, 8-H, 1H), 3.70 (s, –OCH_3, 3H), 3.31 (m, 10-H, 1H), 2.82 (s, 5-H, 2H), 2.81 (d, *J*=6.5 Hz, 7-H, 1H), 2.33 (dd, *J*=15.5, 2.5 Hz, *endo*-11-H, 1H), 1.51 (dd, *J*=15.5, 2.5 Hz, *exo*-11-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4 (CO), 142.0 (9-C), 137.7 (4-C), 122.3 (1-C), 120.7 (2-C), 119.3 (3-C), 62.8 (8-C), 54.8 (–OCH_3), 52.6 (10-C), 52.4 (7-C), 49.0 (5-C), 46.8 (6-C), 43.3 (11-C). Mass (FAB): *m*/*z* 630 (M^+: $C_{15}H_{10}{}^{79}Br_2{}^{81}Br_2O_4Fe$), 602 ($M^+-CO$), 574 ($M^+-2CO$), 546 ($M^+-3CO$). HRMS (FAB) Calcd for $C_{15}H_{10}{}^{79}Br_2{}^{81}Br_2O_4Fe$ (M^+): 629.6619; found: 629.6635. Anal. Calcd for $C_{15}H_{10}Br_4O_4Fe$: C, 28.79; H, 1.61. Found: C, 28.75; H, 1.35.

Acknowledgements

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12. Crystal data for **6**: yellow crystal of $C_{15}H_7Br_4FeO_4$, MW= 626.70, monoclinic, space group *P*-1 (no. 2), $a=9.64(19)$ Å, $b=13.82(3)$ Å, $c=14.22(3)$ Å, $\alpha=90.0°$, $\beta=99.8(3)°$, $\gamma=90.00°$, $V=1867(6)$ Å^3, $Z=4$, $Dc=2.230\ g\ cm^{-3}$, $R=0.052$, Rw=0.134, GOF=1.03 for 3657 reflections with $I>2.00\sigma$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center under the following numbers: CCDC-605320.