ACS Combinatorial Science

Letter

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Development and Evaluation of a Solid-Supported Cyclobutadieneiron Tricarbonyl Complex for Parallel Synthesis Applications

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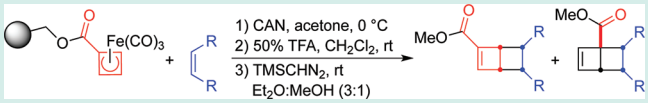
Supporting Information

ABSTRACT: Cycloadditions of cyclobutadiene can offer rapid access to rigid polycyclic ring systems. Further functionalization of these strained-ring cycloadducts can lead to unique scaffolds for probing unexplored regions of chemical space. Along these lines, opportunities for high-throughput syntheses of these novel systems could be facilitated with the introduction of an immobilized cyclobutadiene reagent. Reported herein are preliminary studies of an iron tricarbonyl cyclobutadiene complex attached to solid support. Oxidative unmasking of the immobilized cyclobutadiene in the presence of various dienophiles is shown to produce a small collection of substituted bicyclo[2.2.0]hexene derivatives. The solid support cycloaddition strategy is shown to be comparable, but lower in efficiency to solution phase methods for generating these cycloadducts.



KEYWORDS: *cyclobutadiene, cycloaddition, cyclobutene, solid support, parallel synthesis*

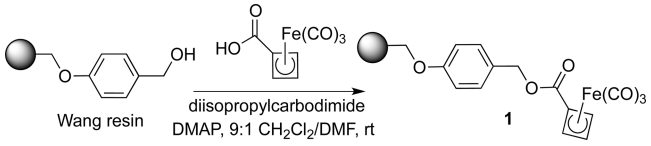
The creation of new structural diversity is important for identifying novel chemical leads for applications in materials science, catalysis, chemical biology, and medicinal chemistry.[1] Reactions that generate novel structures can allow for the exploration of untapped regions of chemical space[2] with the expectation of finding new compounds with desirable properties. In chemical biology and medicinal chemistry, for example, the unusual presentation of hydrogen bond donors and acceptors can access new pharmacophores providing opportunities in the discovery of new tools to probe biological systems or unique leads for pharmaceutically important targets.[3]

Cyclobutadiene, with its antiaromatic ring system, has long been of interest from a theoretical standpoint.[4] The ability to stabilize this reactive functionality through complexation with iron tricarbonyl[5] has led to the use cyclobutadiene as a versatile reagent for synthetic applications.[6,7] The adducts generated from the cycloaddition of cyclobutadiene possess multiple strained rings in a stereochemically well-defined, rigid framework. This remarkably compact molecular geometry allows for the unique presentation of substituents, and therefore could be used to probe underexplored regions of chemical diversity space.[8]

Library strategies using immobilized reagents or substrates often promise to yield practical advantages regarding product purification and isolation. In addition to facilitating isolation, cycloadditions of cyclobutadiene on a solid support could also improve efficiency by allowing for the use of excess dienophile, while minimizing the often-competitive dimerization of cyclobutadiene. Interestingly, iron complexes of cyclobutadiene, coordinated to polystyrene through an immobilized phenanthroline ligand played an important role in early studies on the nature of cyclobutadiene.[9] Perhaps these or related solid support systems could provide a practical synthetic advantage in the generation of unique, small molecule libraries as well.

Because of the acid lability of its benzyl alcohol tether and its general availability, Wang Resin[10] was chosen as the solid support for this study. The tether was esterified with (cyclobutadienecarboxylic acid)iron tricarbonyl complex[11] to provide the solid-supported cyclobutadiene ester **1** (Scheme 1).

Scheme 1. Synthesis of Cyclobutadiene Resin



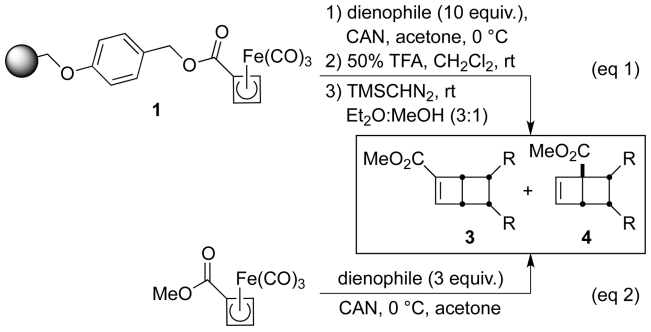
Several analytical strategies were explored to determine the coupling efficiency of the complex onto the beads. Direct measurement of iron content through atomic emission spectroscopy proved convenient and provided results most consistent with the more cumbersome, but reliable resin hydrolysis studies. This assay indicated that for a typical batch of resin, approximately 77% of the theoretical loading of the cyclobutadiene complex onto the bead is achieved.

With cyclobutadiene iron tricarbonyl-functionalized resin **1** in hand, its cycloaddition chemistry could be explored (Scheme 2, eq 1). Symmetrically substituted dienophiles **2a–g** were chosen to limit the formation of regioisomeric products. A variety of dienophiles were examined to test the impact of

Received: December 10, 2011
Revised: March 6, 2012
Published: May 14, 2012

 © 2012 American Chemical Society dx.doi.org/10.1021/co2002069 | *ACS Comb. Sci.* 2012, 14, 343–346

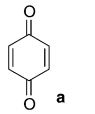
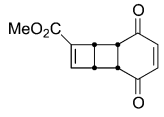
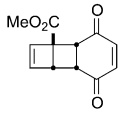
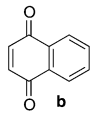
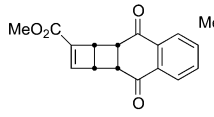
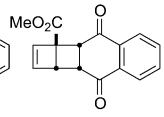
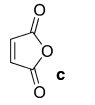
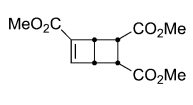
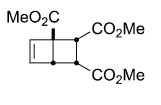
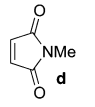
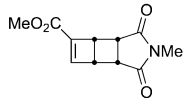
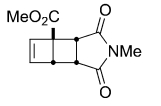
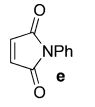
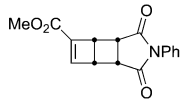
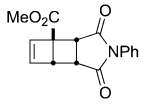
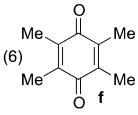
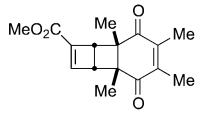
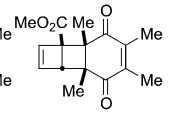
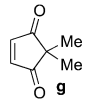
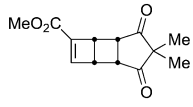
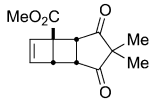
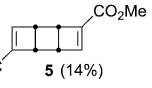
Scheme 2. Solid-Support and Solution Phase Cycloadditions



sterics on the course of the reaction. For comparison, the cycloadditions of iron tricarbonyl methylcyclobutadienoate[7] were also examined under typical solution phase conditions (Scheme 2, eq 2).

As shown in Table 1, the solution phase reactions generated regioisomeric cycloadducts **3a–b**, **d–f** and **4a–b**, **d–f** in yields

Table 1. Cycloaddition Results

Entry	Dienophiles 2a-g	Cycloadducts 3a-g	Cycloadducts 4a-g	Solution Phase Yield (ratio 3:4)	Solid Support Yield (ratio 3:4)
(1)	 a			59% (2.4:1)	36% (1.1:1)
(2)	 b			93% (1.9:1)	40% (1.7:1)
(3)	 c			–[a]	14% (1:1.3)
(4)	 d			63% (3.2:1)	29% (1.6:1)
(5)	 e			56% (1:1)	61% (1:1.8)
(6)	 f			98% (4.3:1)	24% (3:1)
(7)	 g		  5 (14%)	0%	0%

[a]Desired products were observed by crude ^{1}H NMR but could not be isolated free of metal salts, even after esterification using $TMSCHN_2$.

ranging from 56% to 93%, with the exception of dienophiles **2c**, **g**. Figure 1 illustrates the ORTEP of the X-ray crystal structures of the two regioisomers isolated when *N*-methylmaleimide (**2d**) was used as the dienophile. It is noteworthy that in all these cyclobutadiene cycloadditions only the endo products are observed. When **2c** was used as a dienophile, the desired

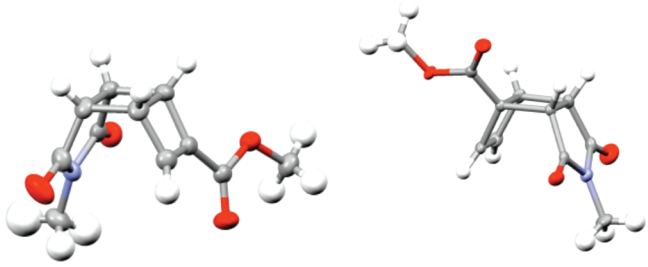


Figure 1. ORTEP of **3d** and **4d**.

cycloadducts **3c** and **4c** were not isolated under a variety of workup conditions, likely due to the aqueous solubility of the products and potential sensitivity of the anhydride adducts. For **2g**, only a mixture of cyclobutadiene dimers **5** (tricycloctadiene diesters) was isolated, suggesting that the more hindered dienophile **2g** reacted too slowly to compete with the facile dimerization of cyclobutadiene.

For the solid-supported studies, cyclobutadiene iron tricarbonyl functionalized resin **1** was oxidized with ceric ammonium nitrate in the presence of excess dienophile (Scheme 2, eq 2). Trimethylamine N-oxide was also examined as an oxidant, but the resin proved unstable to these conditions. The resulting cycloadducts were then cleaved from the solid-support under standard acidic conditions. To aid in the purification, the freed cyclobutene carboxylic acids were esterified using trimethylsilyldiazomethane.[12] For each reaction, a pair of regioisomeric cycloadducts resulting from an endo cycloaddition was isolated in 14% to 61% overall yield (**3a–f** and **4a–f**). It is important to note that the solid supported yields shown in Table 1 encompass not only the cycloaddition, but also the four-step overall sequence beginning with the functionalization of the Wang resin and including cleavage and esterification.

Interestingly, the ratio of regioisomers observed in the solid supported cycloadditions differed in some cases from those obtained in the analogous solution phase reactions. The same overall selectivity was observed favoring the conjugated esters (**3**); however, in general, the selectivities were not as high. Reaction with **2c**,**e** provided an apparent reversal of selectivity favoring the bridgehead ester **4c**,**e**. Although the yield of **3c–4c** is low, it is noteworthy that this compound was not isolated in the corresponding solution phase reaction. In entry 7, the desired products were again not observed for the sterically encumbered dienophile **2g**. Also, as expected for the solid support, no cyclobutadiene dimers were isolated.

Since the attachment of cyclobutadiene to a resin should limit diffusion-controlled dimerization of this reactive species, it might be possible that immobilized cyclobutadiene will display a longer lifetime than the corresponding solution phase version. Unfortunately, efforts to unveil the cyclobutadiene in the absence of dienophile, followed by a subsequent trapping step through the addition of a dienophile were unsuccessful. This suggests that the lifetime of cyclobutadiene on solid support is not significantly extended relative to its solution phase counterpart. Given that no dimeric products are isolated, the cyclobutadiene must be consumed through alternate reaction pathways, perhaps involving the aromatic functionality of the resin.[13]

The newly developed cyclobutadieneiron tricarbonyl complex resin **1** provides a convenient source of the highly reactive diene. Cycloadditions with this reagent lead to a mixture of

dx.doi.org/10.1021/co2002069 | *ACS Comb. Sci.* 2012, 14, 343–346

regioisomers that can be purified rapidly in parallel. Cycloadditions producing unstable or highly polar products can be completed successfully without the need for traditional purification. The products generated represent a unique, small library of solid-supported bicycle[2.2.0]hexene-derivatives with useful handles for the development of further functionalized daughter libraries and exploration of the rich chemistry of rearrangements afforded by these highly strained cycloadducts.[7b−e,f,g,i−k]

EXPERIMENTAL PROCEDURES

Cyclobutadieneiron Tricarbonyl Wang Resin (1). An oven-dried 25 mL Schlenk flask was charged with 1.13 g of Wang Resin (0.9 mmol/g, 1.0 equiv, 1.02 mmol) and 600 mg of (cyclobutadiene carboxylic acid)iron tricarbonyl (2.5 equiv, 2.54 mmol) under a nitrogen atmosphere and the beads suspended in 15 mL 9:1 CH_2Cl_2/DMF. The resin was allowed to swell for 1.5 h. Diisopropylcarbodiimide (5.0 equiv., 5.1 mmol, 199 μL) was added via syringe, followed by a solution of dimethylaminopyridine (0.10 equiv., 0.102 mmol, 12.5 mg) in DMF (500 μL). The flask was sealed with a glass stopper and stirred at ambient temperature for 12 h. Resin was collected by filtration and washed successively with DMF, CH_2Cl_2 and methanol (3 portions of 10 mL each per solvent) then dried under high vacuum for 12 h. Recovered 1.45 g red/orange resin.

^{13}C NMR (101 MHz, $CDCl_3$, gel phase[14]): δ 211.8, 166.7, 145.1, 130.1, 127.7, 114.7, 69.9, 67.7, 65.1, 62.3, 40.5. IR (KBr pellet) 3466 (br), 3399 (br), 3063 (m), 3033 (m), 2940 (m) 2918 (m), 2901 (m), 2886 (m), 2856 (m), 2058 (s), 1977 (s), 1711 (s), 1609 (m), 1511 (m), 1440 (m), 1368 (w), 1307 (w), 823 (w), 764 (w), 752 (w), 694 (w), 611 (m), 586 (m), 538 (m). ICP-Fe Anal: found 4.25%; calcd 5.52% (indicates 77% loading of resin hydroxyl groups)

General Solution Phase Cycloaddition Procedure. To a stirring solution of (methylcyclobutadienoate)iron tricarbonyl (250 mg, 1 mmol, 1 equiv) and dienophile (**2**) (3 mmol, 3 equiv) in acetone (10 mM, 100 mL) at 0 °C was added ceric ammonium nitrate (2.7 g, 5 mmol, 5 equiv). The reaction was stirred loosely capped for 3 h[15] and then quenched with saturated aqueous $NaHCO_3$ (7 mL). Solution was decanted from the precipitated salts and the salts washed three times with CH_2Cl_2. Combined organics were then concentrated and the residue purified by gradient silica gel flash chromatography.

General Solid-Supported Cycloaddition Procedure. Cyclobutadiene resin **1** (400 mg, 0.36 mmol, 1.0 equiv.) was suspended in wet acetone (10 mL) in a loosely capped scintillation vial. The suspension was agitated via magnetic stirring at ambient temperature for 1 h to allow swelling of the resin and then cooled to 0 °C. The dienophile (**2**) was added to the suspension (3.6 mmol, 10 equiv), followed by ceric ammonium nitrate (990 mg, 1.8 mmol, 5 equiv), and the reaction was stirred for 2 h at 0 °C.[15] The resin was then collected by filtration in a fritted 4 cm polypropylene chromatography column and washed successively with water, acetone, dichloromethane, and methanol (3 portions of 5 mL each) and dried under high vacuum for 12 h. Infrared spectroscopy (KBr pellet) of the resin indicated complete consumption of the cyclobutadiene complex as monitored by the iron carbonyl absorbances.

Cleavage of the cycloadduct from the resin was accomplished by suspending the resin in a 50% v/v solution of trifluoroacetic acid in dichloromethane and agitating the polypropylene chromatography column on a rotary shaker for 1 h at room temperature. The resin was removed by filtration and washed with dichloromethane (3 portions of 5 mL). Combined filtrates were concentrated.

The crude residue from product cleavage was dissolved in a 3:1 mixture of anhydrous diethyl ether and methanol and cooled to 0 °C under a nitrogen atmosphere. A solution of trimethylsilyldiazomethane (2.0 M) in diethyl ether (200 μL, 0.40 mmol, 1.1 equiv) was added dropwise and the solution was stirred while warming to room temperature over 12 h. Products were purified as for the solution phase cycloadditions and spectral data matched that for previously reported compounds.

Benzoquinone Cycloaddition. Purification by silica gel flash chromatography (eluting with a gradient from hexanes to 30% then 50% diethyl ether in hexanes and finally 100% diethyl ether) afforded two regioisomeric cycloadducts in a combined yield of 59% (183 mg **3a** as a pale yellow solid and 76.4 mg **4a** as a pale yellow solid (2.4:1 ratio **3a**:**4a**)).

*7,10-Dioxo-tricyclo[4.4.0.0^{2,4}]deca-3,8-diene-3-carboxylic Acid Methyl Ester (**3a**).* mp: 109−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, J = 2.4 Hz, 1H), 6.73 (s, 2H), 4.13−4.00 (m, 1H), 3.82 (t, J = 5.5 Hz, 1H), 3.75−3.64 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.4, 196.3, 161.3, 147.3, 144.3, 144.1, 141.2, 51.9, 45.6, 43.1, 42.3, 41.3. IR (KBr, thin film): 3081 (w), 3059 (m), 3029 (s), 1722 (m), 1674 (m), 1600 (w), 1447 (w), 1316 (w), 1291 (w), 1251 (m), 1252 (w), 1127 (w), 1101 (w), 750 (m), 697 (m). DART-HRMS (m/z) Calcd for $[M + H]^+$: 219.0657; found 219.0656.

*7,10-Dioxo-tricyclo[4.4.0.0^{2,4}]deca-3,8-diene-2-carboxylic Acid Methyl Ester (**4a**).* mp: 51−57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 2H), 6.31 (d, J = 2.5 Hz, 1H), 6.25 (t, J = 2.4 Hz, 1H), 4.11 (d, J = 10.0 Hz, 1H), 3.94 (dd, J = 9.0, 2.2 Hz, 1H), 3.76 (s, 3H), 3.75−3.68 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.3, 196.3, 170.6, 144.1, 144.0, 140.4, 138.3, 56.9, 52.9, 49.9, 43.4, 41.1. IR (KBr, thin film): 2955 (m), 2892 (w), 2870 (w), 1727 (s), 1676 (s) 1599 (w), 1459 (w), 1436 (m), 1377 (w), 1318 (w), 1275 (s), 1241 (m), 1199 (m), 1180 (m), 1129 (m), 1103 (w), 1072 (w), 1060 (w), 1021 (w), 864 (w), 779 (w), 410 (w). DART-HRMS (m/z) Calcd for $[M + H]^+$: 219.0657; found 219.0655.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds, as well as X-ray crystallographic data for **3d** and **4d** is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

Financial support was provided by the National Institutes of Health (R56-GM062824).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to Schering-Plough for support of the X-ray facilities at Boston College.

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