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Supplementary Material Available: Spectroscopic data and physical constants for all synthetic intermediates (5 pages). Ordering information is given on any current masthead page.

Tetrahydrofurans via Isoxazoline: A Tandem 1,3-Dipolar Cycloaddition/Electrophilic Cyclization Sequence

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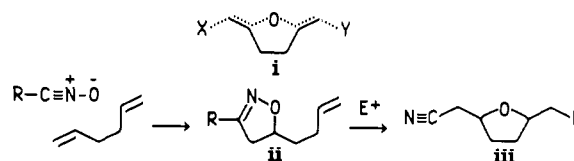
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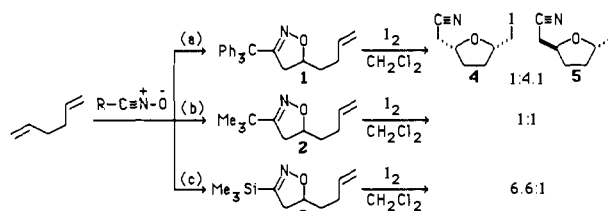
Development of methodology for the stereocontrolled synthesis of tetrahydrofuran containing natural products (e.g., polyether antibiotics) continues to receive significant attention.² Of the numerous strategies for tetrahydrofuran construction,³ bis addition of an oxygen nucleophile across a 1,5-diene moiety (i) (Scheme I) represents a particularly attractive approach. Noteworthy examples of this strategy include potassium permanganate promoted oxidative cyclizations of 1,5-dienes⁴ and epoxidation/oligoepoxide cascade cyclizations from 1,5-dienes.⁵ We reasoned that exposing 1,5-hexadiene to a tandem 1,3-dipolar cycloaddition⁶/electrophilic cyclization sequence would furnish 1,5-disubstituted tetrahydrofuran **iii** via the intermediacy of isoxazoline **ii**. To our knowledge, there are no reports of an isoxazoline moiety participating in electrophilic cyclization reactions. Clearly, the nature of R is important in this strategy, and, based on the assumption that cation stabilizing R groups would favor the 2 → 3 transformation, the first substrates investigated were those with R = triphenylmethyl and *tert*-butyl.

Cycloaddition of 1,5-hexadiene (5 equiv) and triphenylacetone nitrile oxide (prepared from triphenylmethyl chloride and silver fulminate)⁷ furnished isoxazoline **1** in quantitative yield (Scheme II). As hoped, treating this heterocycle with iodine resulted in electrophilic cyclization giving tetrahydrofurans **4** and **5** in a 1:4.1 ratio (capillary GLC)⁸ in 60% isolated yield. Apparently the triphenylmethyl moiety in **1** is initially lost as a triphenylcarbenium ion giving triphenylmethyl iodide which on aqueous workup undergoes solvolysis giving triphenylmethanol. *Cis/trans* stereochemical assignments for **4** and **5** were made in analogy with known 2,5-disubstituted tetrahydrofurans⁹ on the basis of ¹H data for the corresponding deiodinated derivatives¹⁰ (prepared by

Scheme I



Scheme II



(a) benzene, 25°C; (b) ^tBu-C(Cl)=N-OH, Et₃N, Et₂O; (c) Hg(CNO)₂, Me₃SiBr, benzene

Scheme III

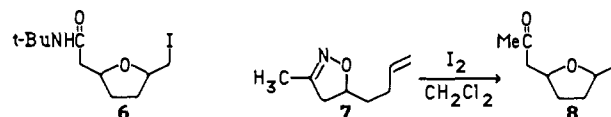


Table I. Electrophilic Cyclization of Isoxazoline **ii**

electrophile	R = () ^a	cis/trans ^b	yield (iiii, %) ^c
Br ₂	Ph ₃ C-(1)	1:2.8	66
PhSeBr	Ph ₃ C-(1)		<i>d</i>
PhSeBr	Me ₃ Si-(3)	5.7:1	40
I ₂	MeCH(OSiMe ₃)-(9)	1:1.4	59
I ₂	<i>i</i> -PrCH(OSiMe ₃)-(10)	1:1.6	55

^a Isoxazoline compound number. ^b Ratios determined by capillary GLC analysis of the crude reaction mixture. ^c Isolated, purified yields of **iii** from 1,5-hexadiene. ^d No tetrahydrofuran products were obtained.

tributyltin hydride reduction).¹¹

Employing dimethylpropionitrile oxide (generated in situ from the hydroxamic acid chloride with triethylamine)¹² gave isoxazoline **2** (70%) which, upon treatment with iodine, underwent electrophilic cyclization with concomitant loss of the *tert*-butyl moiety, again giving the anticipated tetrahydrofurans **4** and **5** (59% isolated yield). However, **2** also gave tetrahydrofuran **6**, a Beckmann rearrangement product, in 22% isolated yield (Scheme III). The fact that **1** gives no Beckmann rearrangement product while **2** does appears to reflect the ability of -R to serve as a stabilized cation source (ii → iii). Interestingly, treating a CH₂Cl₂ solution of isoxazoline **7** with iodine resulted in formation of ketone **8** (50%; 1:1 *cis/trans*): none of the corresponding nitrile or amide products were detected.

The next substrate investigated was (3-trimethylsilyl)isoxazoline **3**, prepared in a one-pot process by cycloaddition of 1,5-hexadiene (5 equiv) and trimethylsilylcarbonitrile oxide (generated in situ from trimethylsilyl bromide and mercury fulminate).¹³ Upon treatment with iodine, **3** underwent electrophilic cyclization, again furnishing **4** and **5** but this time with *cis* selectivity (*cis/trans*, 6.6:1; 40% isolated yield). This intriguing reversal in product selectivity is clearly a function of the R group in **ii**, yet each electrophilic cyclization (**1/2/3** → **4 + 5**) is certainly a kinetic process.

(11) Deiodination was accomplished by refluxing a benzene solution of **4 + 5**, 2 equiv of tributyltin hydride, and AIBN (15 mol %).

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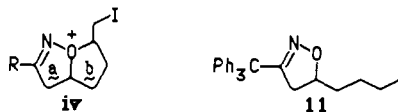
(8) With use of an HP 5930A, J & W Scientific Durabond-1701 capillary GLC column, an initial oven temperature of 80 °C, a final oven temperature of 250 °C, and programmed rate of +5°/min, the retention times were 18.9 min for *cis*-**4** and 19.2 min for *trans*-**5**.

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(10) In analogy with literature data,⁹ stereochemical assignments for the *cis* and *trans* isomers of 2-(cyanomethyl)-5-methyltetrahydrofuran were made on the basis of C₅-CH₃ chemical shifts (the -CH₃ doublet for the *trans* isomer resonating at higher field:^{9c} *cis* at δ 1.28 and *trans* at δ 1.24).

Bromine, like iodine, promotes electrophilic cyclization of isoxazoline **1**, whereas phenylselenyl bromide does not (Table I). In contrast, isoxazoline **3** does undergo phenylselenyl bromide promoted cyclization, again favoring the *cis* tetrahydrofuran product. Iodine promoted cyclizations of isoxazolines **9** (prepared from $\text{MeCH}(\text{OSiMe}_3)\text{CH}_2\text{NO}_2$ by dehydration with phenylisocyanate)¹⁴ and **10** (prepared from *i*-PrCH(OSiMe₃)CH₂NO₂ by dehydration with phenylisocyanate)¹⁴ also furnished tetrahydrofurans **4** and **5** but with disappointing diastereoselectivity.

While it is not clear how the R group in **ii** delegates stereoselectivity in the subsequent electrophilic cyclization, the observed chemistry is consistent with formation of isoxazolinium intermediate **iv**. Depending upon the R group, intermediate **iv** could then undergo a-ring fragmentation—either with loss (i.e., **iv** → **4** + **5**) or migration (i.e., **iv** → **6** or **8**) of R—to the observed iodocyclization products. The intermediacy of **iv** may also account

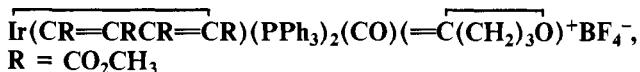


for the observed stereoselectivities: for example, the triphenylmethyl group may accommodate reversible addition of the isoxazoline moiety to an initially formed iodonium ion, whereas the (3-trimethylsilyl)isoxazoline may undergo nonreversible addition. As demonstrated with **11**, isoxazolines lacking the pendant C=C are stable to the iodocyclization conditions employed ($\text{I}_2/\text{CH}_2\text{Cl}_2$, 25 °C or 40 °C, 8 h) indicating that iodonium ion formation precedes a-ring fragmentation in these iodocyclizations. Current efforts are directed toward elucidating the relative importance of these and other effects in determining the stereochemical course of this novel transformation.

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The First Stable Metallacycle-Carbene Complexes: Structural Characterization of



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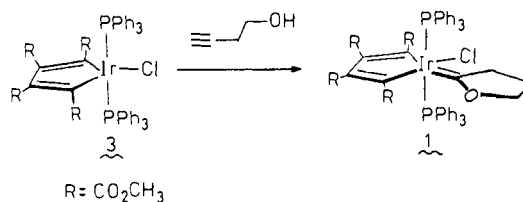
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Metallacyclopentadiene complexes are demonstrated or proposed intermediates in numerous metal-mediated cyclization reactions of acetylenes.¹ Although metallacycles have been extensively utilized as synthetic intermediates, surprisingly little is

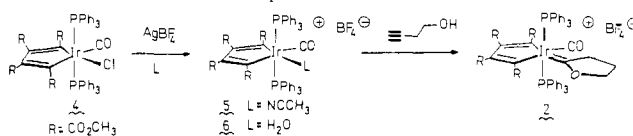
known about the structure and properties of metallacycles which contain an additional η^1 -bonded carbon ligand.² Such species have potential for the development of new modes of metallacycle reactivity.

We recently initiated a program designed to combine the metallacycle and carbene compound classes into a single mononuclear material in an effort to modify and/or couple their unique reactivities.³ Of particular interest in this regard is insertion of a carbene ligand into a metallacycle and subsequent reductive-elimination to give cyclopentadiene products. We report herein the synthesis and structural characterization of the first isolable metallacycle-carbene complexes: $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{Cl})(=\text{C}(\text{CH}_2)_3\text{O})$, **1** ($\text{R} = \text{CO}_2\text{CH}_3$)⁴ and $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{CO})(=\text{C}(\text{CH}_2)_3\text{O})^+\text{BF}_4^-$, **2** ($\text{R} = \text{CO}_2\text{CH}_3$).



When a chloroform solution of 3-butyn-1-ol (0.94 mmol) and the coordinatively unsaturated metallacycle $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{Cl})$, **3** ($\text{R} = \text{CO}_2\text{CH}_3$)⁴ [0.8 mmol, 0.02 M], is stirred at 23 °C for 15 h, the neutral metallacycle-carbene complex $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{Cl})(=\text{C}(\text{CH}_2)_3\text{O})$, **1**, is formed in good yield (81% isolated).⁵ In the ¹³C{¹H} NMR spectrum of **1** a triplet at δ 286 ($J_{\text{PC}} = 6$ Hz) is assigned to the carbene carbon and two pseudo triplets at δ 152.4 ($J = 7.0, 6.6$ Hz) and 148.8 ($J = 12.0, 12.6$ Hz) are attributed to the metallacycle carbons bonded to iridium.⁶

Treatment of an acetonitrile solution of the coordinatively saturated metallacycle $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{CO})(\text{Cl})$, **4** ($\text{R} = \text{CO}_2\text{CH}_3$),⁴ with AgBF_4 leads to formation of the cationic metallacyclopentadiene complex $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{CO})(\text{CH}_3\text{CN})^+\text{BF}_4^-$, **5**, in 90% isolated yield.⁷ In a similar manner, reaction of **4** with AgBF_4 in THF (aqueous) gives the aquo complex $\text{Ir}(\text{CR}=\text{CRCR}=\text{CR})(\text{PPh}_3)_2(\text{CO})(\text{H}_2\text{O})^+\text{BF}_4^-$, **6**, in 70% isolated yield.⁷ In the presence of H_2O , **5** exists in equilibrium with **6** ($K_{\text{eq}}^{23^\circ\text{C}} = 4.2 \times 10^{-3}$).



When a methylene chloride solution of **5** (0.5 mmol, ~0.02 M) and 3-butyn-1-ol (0.6 mmol) is refluxed for 12 h, a nearly quantitative yield (96%) of the cationic metallacycle-carbene

(2) Metallacycle complexes which contain an additional η^1 -bonded carbon ligand are very rare. For an example, see: Baddley, W. H.; Tupper, G. B. *J. Organomet. Chem.* **1974**, *67*, C16.

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