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Halogenated catechols from cycloaddition reactions of η^4-(2-ethoxyvinylketene)iron(0) complexes with 1-haloalkynes

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ABSTRACT

1-Chloroalkynes and 1-bromohexyne undergo cycloaddition reactions with ethoxyvinylketeneiron(0) complexes to form chloro and bromocatechols. With most substituents, the halogen is incorporated *ortho* to the phenolic hydroxyl group regioselectively. With chloroethyne, chlorohexyne, and methyl chloropropiolate, the reverse regioselection is observed. Ab initio calculations reveal that the products are, in most cases, nearly isoenergetic, which indicates that the intermediate ketene–alkyne adduct geometry must be important in determining the product distribution.

The efficient, regiospecific synthesis of highly substituted aromatic rings represents an important challenge in organic synthesis.[1] One convergent approach is the [4+2] cycloaddition of vinylketenes[2] with alkynes, however vinylketenes are usually unstable and undergo [2+2] cycloaddition upon reaction with alkynes as well as themselves. The parent compound, vinylketene (buta-1,3-dienone) dimerizes in a hetero [4+2] cycloaddition.[3] Masked vinylketenes have been used to carry out this transformation, but often require a deprotection step.[4] Danheiser used silicon-stabilized vinylketenes in Diels–Alder cycloaddition reactions with alkynes.[5] Electrocyclic ring closures of dienyl ketenes, generated in situ from cyclobutenones, have been developed by Moore,[6a] Danheiser,[6b] and Liebeskind.[6c] Danheiser also reported a formal [4+2] reaction of 2-silylvinylketenes with ynolates to form monosilylated resorcinol derivatives.[7]

Transition metals, through their ability to stabilize reactive intermediates, offer powerful alternatives for the synthesis of highly substituted aromatic systems. The reaction of Fischer carbene complexes with alkynes to form hydroquinones has been extensively studied and modified.[8] A wealth of evidence indicates that this important transformation proceeds through the intermediacy of vinylketene complexes. Chromium-promoted variants of the electrocyclization of dienylketenes have also been exploited by Merlic[9a,b] and Wulff,[9c] who first isolated an η^4-vinylketene chromium complex from the reaction of a Fischer carbene complex with an alkyne.[10] Liebeskind reported the synthesis of phenols from alkynes and cobalt-complexed vinylketenes, which were prepared from cyclobutenones,[11] and subsequently discovered a nickel-catalyzed variation.[12] Recently, Kondo and Mitsudo reported a rhodium-catalyzed reaction.[13] These methods use vinylketenes generated from cyclobutenones, limiting their utility. The availability of isolable η^4-vinylketene iron complexes from a variety of sources[14] provides a promising solution to the cycloaddition problem given the low cost of iron.[15] One noteworthy advantage of iron over chromium in benzannulation reactions is the fact that the product arenes are not complexed to the metal as they often are with chromium. Gibson prepared η^4-complexed vinylketene iron(0) complexes from η^4-vinylketone-iron(0) complexes,[16] however the major products of reactions of alkynes with these complexes were alkyne insertion products, which formed cyclopentenediones, and, rarely, phenols.[17] Treatment of the insertion products with $FeCl_3$ resulted in furan-3-(2*H*)-ones and reactions with CO produced cyclopentenediones and butenolides.[18]

Our early studies indicated that both electron-poor (i.e., ester, ketone, and trifluoromethyl substituted) and electron-rich alkynes (i.e., ynol ethers) readily undergo cycloadditions with vinylketene iron complexes to form catechol monoethyl ethers upon reaction with **1a** (Table 1, R^1 = Ph).[19] Tam recently reported ruthenium-catalyzed [2+2] cycloadditions[20a] of norbornenes with alkynyl halides, and rhodium-catalyzed intramolecular [4+2] cycloadditions[20b] of haloalkyne tethered dienes, which inspired us to examine the reactions of terminal haloalkynes with vinylketene iron(0) complexes. Our results are summarized in Table 1.

Initially, we compared the reactions of 1-iodohexyne, 1-bromohexyne, and 1-chlorohexyne with **1a**. Heating **1a** with iodohexyne for 96 h in DMF at 120 °C provided mostly unreacted iodohexyne with two putative cycloadducts (*m*/*z* = 396), which were detected by GC–MS. Bromohexyne was more promising, giving **3a** in 5% yield after refluxing in THF for 24 h. Heating **1a** with bromohexyne in DMF at reflux for 48 h produced the bromocatechol **3a** in 28% yield. A NOESY experiment was used to verify the

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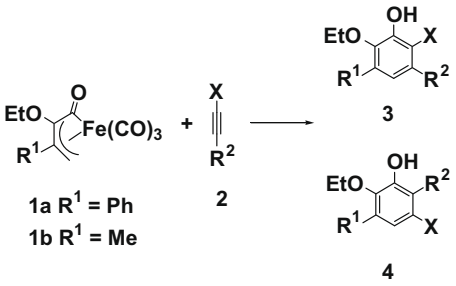
Table 1
Cyclization of vinylketeneiron(0) complexes with 1-haloalkynes[a]



Entry	Complex	R^2	X	Product (%)	ΔE^b (kcal/mol)
1	**1a**	Bu	Br	**3a** (28)[c]	
2	**1a**	H	Cl	**4b** (33)[d]	**3b** 1.1
3	**1a**	Cl	Cl	**3c** (45)[d]	
4	**1a**	*cyc*-Pr	Cl	**3d** (62)	**4d** 0.2
5	**1a**	*t*-Bu	Cl	**3e** (55)	
6	**1a**	*t*-Bu	Cl	**3e** (44)	
				4e (11)[e]	
7	**1a**	Bu	Cl	**4f** (72)	
8	**1a**	Ph	Cl	**3g** (62)	**4g** −0.8
9	**1a**	$SiMe_3$	Cl	**3h** (42)	**4h** −3.5
10	**1a**	COOMe	Cl	**3i** (14)	**3i** 5.6
				4i (23)[f]	
11	**1b**	Bu	Cl	**3j** (49)	
12	**1b**	Ph	Cl	**3k** (43)	

[a] Unless otherwise stated all reactions were carried out with 0.3–1.5 mmol of vinylketene complex with 1.0 equiv of haloalkyne in 3–15 mL THF heated at reflux for 24–48 h.
[b] Positive (negative) value indicates **3** (**4**) is more stable.
[c] DMF, reflux 48 h.
[d] Volatile alkynes were used in excess as solutions that were heated at 70 °C in pressure vessels equipped with Young valves.
[e] Reaction was carried out at 90 °C.
[f] Dechlorinated product, **4i** with X = H, was also obtained in 39% yield.

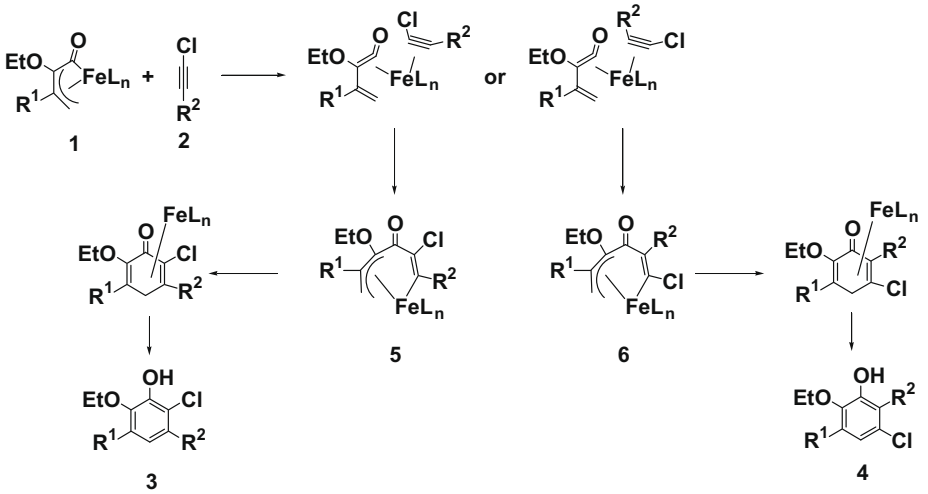
structure. Reaction of one equivalent of chlorohexyne with **1a** in THF produced **4f** in 72% yield. Cyclotrimers were not a significant contributor to the mass balance of the reactions, although detectable quantities of cyclotrimerization products were found with GC–MS in the Single Ion Monitoring (SIM) mode.

We focused our subsequent efforts in this preliminary study on 1-chloroalkynes. For chloroethyne (entry 2), chlorohexyne (entry 7), and methyl chloropropiolate (entry 10), the chlorine of the major product was incorporated *meta* to the phenolic hydroxyl group. An intermediate was isolated from the reaction of chloroethyne with **1a**, which exhibited proton and carbon NMR spectra consistent with the alkyne insertion product, (Scheme 1, compound **6**, R^1 = Ph, R^2 = Et, R^3 = H). Injection (300 °C) into the GC–MS provided a peak with retention time and mass coincident with **4b**. Thermolysis of a sample at 110 °C for 24 h in THF resulted in complete conversion to **4b**. In the other compounds studied to date the chlorine was found *ortho* to the phenolic hydroxyl. Reaction with chloroethynyl cyclopropane (entry 4) did not produce any ring opening product, suggesting that a slow radical reaction is unlikely. Although most reactions were carried out in refluxing THF, reaction with *tert*-butylethynyl chloride at 90 °C (entry 6) produced both isomers of the cycloadduct in a 1:4 ratio, indicating that regioselection is temperature dependent. GC–MS analysis of aliquots taken from a reaction of **1a** with chlorohexyne (entry 7) revealed that formation of the product **4f** was detectable after a few minutes at room temperature.

The reaction with methyl chloropropiolate (entry 10) was complicated by dechlorination resulting in a lower yield of halocatechol. GC-MS studies are consistent with the observation that the dechlorination occurs after incorporation of the chloroalkyne. Reaction of **1a** with methyl propiolate provided large amounts of the two cyclotrimers, neither of which was observed in this reaction, suggesting that dechlorination may not be occurring prior to reaction with the vinylketene complex. GC–MS analysis of aliquots taken from this reaction showed initial formation of the desired product soon after the reaction was started. The dechlorinated catechol was not detected until after 24 h and then increased at the expense of the desired product. Trace amounts of dechlorination product were detected (GC–MS) with chloroethynyltrimethylsilane, chlorohexyne, and chloroethyne.

Complex **1b** behaved similarly, but it was noted that under the reaction conditions similar to those used with the phenyl complex, unreacted **1b** was isolated along with pyrocatechols even after extended reaction times. Again, the regioselectivity appears to be controlled primarily by steric effects. The regioselectivity exhibited in this study is most often precisely the opposite exhibited by the Dötz benzannulation[8] of chromium carbene complexes: the more sterically demanding substituent is incorporated *meta* rather than *ortho* to the inserted carbonyl group which forms the phenol.

A mechanism is suggested in Scheme 1. Formation of a coordinatively unsaturated iron complex through decomplexation of one of the π bonds of the diene leads to formation of the η^2 alkyne complex.[21] It seems most likely that the regioselectivity is established when the η^2-complex forms the insertion product. Analogy with the work of Gibson[17,18,22] suggests that insertion occurs first



Scheme 1. Proposed mechanism of the formation of chlorocatechols.

at the ketene carbonyl rather than at the terminal allylic carbon of the vinylketene. Reductive elimination to form a cyclohexadienone, followed by tautomerization provides the catechol.

In an attempt to understand the regioselectivity of the products, ab initio calculations are performed for various alkynes and some of the products. The Löwdin population analysis on the chloroalkyne at the various levels of the theory shows the general trend for the alkyne carbon connected to R^2 is electron-rich or electron-deficient in accordance with the electronegativity difference between chlorine and the R^2 group. Therefore, the product distribution in Table 1 cannot be understood by the alkyne electronic structure. The thermodynamic stability of the products alone does not explain the product distribution, either. As shown in Table 1, using the MP2/6-31G(d,p) level of theory including the zero-point energy from the RHF/6-31G(d,p) level, R^2 = H, *cyclo*-Pr, and Ph substituted model products are nearly isoenergetic. In the case of $R^2 = SiMe_3$, **4h** is more stable than **3h** by 3.5 kcal/mol. The largest difference among the calculated products is R^2 = COOH, and **3i** is 6 kcal/mol more stable than **4i**. The major products of the latter two substitutions are in fact opposite of what thermodynamic stability of the products should be. From these considerations, it is likely that steric factors in the formation of reactive intermediates play a more important role in the formation of the observed products. Hence the ketene-alkyne adduct geometry must be important in determining the product distribution, and we are currently investigating this aspect computationally. We are actively probing the electronic and steric parameters that influence the regioselectivity.

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Supplementary data

Supplementary data (detailed experimental procedures, spectroscopic data, NMR spectra, and details of ab initio calculations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.029.

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