Incorporation of hexafluorobutyne into furans or phenols via reaction with iron(0) carbene or vinylketene complexes

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ARTICLE INFO

ABSTRACT

Reaction of iron(0) carbene complexes with hexafluorobut-2-yne produces 3,4-bis(trifluoromethylated)furans in a process that is favored for electron-rich carbenes. No traces of furannulation or benzannulation are observed with Group 6 Fischer carbenes. Reaction of hexafluorobut-2-yne with a vinylketene iron(0) complex gives a 2,3-bis-trifluoromethylated phenol.

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Furans represent a class of heterocycles that are widely found in nature in numerous natural products, and their synthetic derivatives have found wide application in medicinal chemistry.[1] Trifluoromethylated organic compounds, by virtue of the special electronic and steric properties associated with the trifluoromethyl group, occupy a special niche in organic chemistry. New methods of the preparation of fluorinated organic compounds, especially trifluoromethylated species, are always in demand.[2] We report herein our preliminary results in the preparation of bis-trifluoromethylated furans through the reaction of hexafluorobutyne with iron(0) carbene complexes, which is believed to take place via the intermediacy of a vinylketene complex. Extension of the reaction to an isolable η[4]-vinylketene complex resulted in the formation of a 2,3-bis-trifluoromethylated phenol.

The benzannulation reaction of chromium(0) carbene complexes[3] with alkynes is a well-established process that has been exploited extensively in the synthesis of phenols.[4] Mechanism-based planning has lead to the discovery of routes to numerous alternative products such as furans, vinylketenes, cyclobutenones, and cyclohexadienones among others. Reaction of hexafluorobutyne in THF with phenyl(ethoxy)methylene chromium(0) **1a** in a sealed tube at 60 °C for 48 h formed a large number of products with none predominating. We were unable to detect the expected naphthol, or any of the aforementioned products. Additional studies with the molybdenum(0) carbene complex **1b** and the tungsten(0) carbene complex **1c** revealed that the carbene complex was recoverable (crude NMR analysis) and the solution viscosity increased, dramatically with **1c**, presumably due to polymerization.

Since the Group 6 complexes were not immediately useful, we assayed the reaction with iron(0) carbene complexes, because earlier studies indicated that these should exhibit substantially differ-
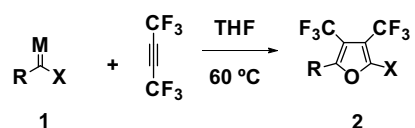
ent reactivities from their Group 6 counterparts. These complexes, first reported by Fischer in 1972,[5] have yet to stimulate the level of interest seen for the chromium analogues. Aumann has examined the fundamental properties of the prototype complexes in a wide range of reactions with cumulene systems.[6] Dvorak reported the intramolecular cyclizations of *N*-allyl iron(0) complexes.[7] The study of reactions of iron carbene complexes with alkynes is extremely limited. Semmelhack observed the formation of η[4]-pyrone iron tricarbonyl complexes upon the reaction of a variety of alkynes with alkoxycarbene iron(0) complexes under modest CO pressure.[8] Subsequent studies with ((dimethylamino)-phenylmethylidene)tetracarbonyliron(0)[9] showed that furan formation predominates. Our own work with electron-poor alkynes[10] demonstrated the delicate balance between benzannulation and furan ring formation with alkoxycarbene iron complexes. This situation was paralleled in Wulff's work, where it was observed that a cyclohexenyl alkoxycarbene chromium complex reacted with 1,3,5-triynes to undergo benzannulations while a phenyl carbene complex produced the furan. In both cases, the central alkyne of the triyne was incorporated into the aromatic ring.[11]

We chose a carefully selected group of complexes for this preliminary work. The phenyl carbene complex **1e** serves as a reference for electronic effects (Table 1). The *para*-methoxy complex **1f** and the *para*-*N,N*-dimethylamino complex **1g** are both relatively electron rich and both provide the furan in good yield. The furan is easily distinguished from the most likely alternative product, the naphthol by the proton NMR, and was the only product that incorporated atoms from both the carbene complex and the alkyne. The electron-rich amino carbene complex **1i** also gave a good yield of furan. The *meta*-methoxy compound **1d** is relatively electron-poor and gave a low yield of furan, as did the sterically congested *tert*-butyl complex **1h**, for which benzannulation is not a possibility. In this case, the low thermal stability of the carbene complex may have contributed to the low yield. The furans were hydrolytically sensitive, and reduced yields can be attributed to some

Table 1
Furan formation from hexafluorobutyne and carbene complexes

Entry	M	R	X	Yield **2** (%)
1	**1a** Cr(CO)$_5$	Ph	OEt	0
2	**1b** Mo(CO)$_5$	4-MeOPh	OEt	0
3	**1c** W(CO)$_5$	4-MeOPh	OEt	0
4	**1d** Fe(CO)$_4$	3-MeOPh	OEt	19
5	**1e** Fe(CO)$_4$	Ph	OEt	42
6	**1f** Fe(CO)$_4$	4-MeOPh	OEt	56
7	**1g** Fe(CO)$_4$	4-Me$_2$NPh	OEt	48
8	**1h** Fe(CO)$_4$	t-Bu	OEt	12
9	**1i** Fe(CO)$_4$	4-MeOPh	NMe$_2$	41

decomposition upon column chromatography. The *tert*-butyl furan was not purified to homogeneity (some solvent remained in the sample) because of its low yield, hydrolytic sensitivity, relatively high vapor pressure, and low polarity.

With hexafluorobutyne and iron(0) carbene complexes, furan formation appears to be extremely selective. Gas chromatographic–mass spectrometric analysis of crude reaction mixtures revealed the formation of nearly exclusively single products, the furans. Even when the yields were low, no other products were isolated in significant quantities. Although hexafluorobutyne cyclotrimerizes readily upon reaction with transition metal reagents,[12] GC–MS analysis of crude reaction mixtures failed to show the presence of trimer at the detection limit of the instrument even though hexakis(trifluoromethyl)benzene has been fully characterized.[13] The photochemical reaction of hexafluorobutyne with tricarbonyliron complexes has been reported to form tetrakis(trifluoromethyl)cyclopentadienone iron complexes.[14] The products formed with other metal complexes depended on the metal complex employed.[15]

There are many examples of furan formation upon the reaction of Group 6 carbene complexes with alkynes. Initially, Dötz et al. discovered that furans were a minor side product formed when chromium carbene complexes were reacted with diphenylacetylene in heptane.[16] Wulff subsequently showed that cobalt(I) carbene complexes preferentially formed furans upon reaction with several alkyl and aryl acetylenes.[17] A recent study by Zora and Güngör demonstrated that chromium, molybdenum, and tungsten carbenes produced furans when ferrocenyl carbene complexes were allowed to react with aryl and alkyl alkynes.[18]

There appears to be a strong propensity for furans to form as alternative products of reactions of transition metal derivatives with alkyne systems with carbonyl groups already present. For example, Herndon and Wang reported the formation of furans upon reaction of enynals with the methyl carbene complex of chromium, a process that takes place through a different mechanism, but one which illustrates the ability of chromium complexes to promote furan ring formation.[19] Casey observed the conversion of *o*-ethynylbenzoyl rhenium complexes to isobenzofurans,[20] a process similar to the chromium-catalyzed cyclizations of *cis*-2-penten-4-yne-1-ones to furans developed by Uemura and co-workers.[21] A copper-catalyzed synthesis of furans has been studied by Barluenga et al.[22] O'Connor and co-workers discovered an intriguing electrochemical conversion of an ester-substituted cobaltacyclobutene to form a furan through a 2 electron oxidation, in which the ester carbonyl oxygen is incorporated into the furan as the ring oxygen.[23] Furans appear to be the preferred products of reaction of carbene complexes with alkynes when benzannulation

is thwarted by stereochemical, structural (i.e., lack of a π-system upon which to benzannulate) or electronic factors. Since dimethylacetylene dicarboxylate is the only alkyne reported to undergo benzannulation with iron carbene complexes,[10] we originally believed that the symmetry of the electron-withdrawing groups was a critical feature of this process. Our results with hexafluorobutyne now indicate the flawed reasoning in this argument and instead suggest that the carbonyl groups of the ester are apparently critical in establishing the stereochemistry of the intermediates that lead to the bifurcation of mechanism, which is responsible for the formation of furan over naphthol or phenol.

Mechanisms to account for furan formation have been suggested for alkoxy chromium carbene complexes[24] and for amino chromium carbene complexes.[25] Park has proposed the intermediacy of an η^4-furan iron complex during the reaction of an alkynyl iron(0) carbene complex to produce a vinylcarbene complex.[26] Semmelhack gave a similar mechanism to account for the formation of furans from amino carbene complexes of iron.[9] The critical intermediate is the vinylketene complex **A** that determines whether furan or benzene rings form. Benzannulation results from a metal-directed electrocyclic ring closure. In our case, we suggest that a nucleophilic addition of the carbonyl group leads to an anion that is stabilized by the powerful electron-withdrawing effect of the trifluoromethyl group. Migration of the alkoxy or amino group, presumably assisted by the iron carbonyl moiety, leads ultimately to the furan. In the absence of a transition metal, these intermediates would be unlikely to form under the mild conditions employed in our protocols (Fig. 1).

3,4-Bis-(trifluoromethyl)furans have been prepared by a variety of alternative methods, including Diels–Alder cycloaddition of hexafluorobutyne with a furan followed by retro-Diels–Alder to provide the trifluormethylated furan,[27] treatment of 3,4-dimethylfurans with SF$_4$,[28] alkylation with trifluoromethyliodide,[29] cyclization of trifluoromethylated-1,4-diketones),[30] reactions of 2-lithiobis(trifluoromethyl)furan with electrophiles,[31] and reaction of aldehydes with hexafluorobutyne under γ-ray irradiation.[32] Ours is the first method to utilize an iron carbene complex with hexafluorobutyne and is especially useful for preparing furans with amine or alkoxy groups in position 2 of the furan.

Since vinylketene iron complexes[33] often exhibit reactivity indicating an equilibrium with the vinylcarbene form, we investigated the reaction of the prototype vinylketene complex **3** with hexafluorobutyne and observed, not the formation of a furan, but a catechol derivative in 42% yield. (Fig. 2) This represents an additional example of our earlier work on vinylketene complexes to form catechols, which was somewhat limited in scope.[34] The alkyne cyclotrimer was not a significant problem in this specific example.

We report the first syntheses of 3,4-bis(trifluoromethylated)furans through the reaction of iron(0) carbene complexes and hexafluorobutyne.[35,36] In our studies (Table 1) we found that the
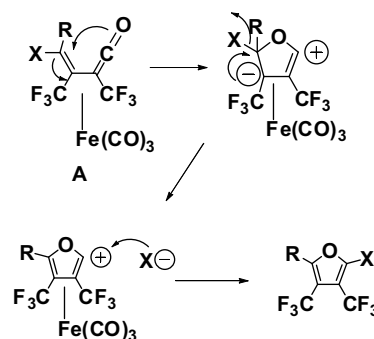

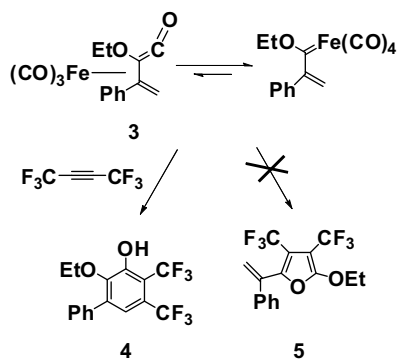**Figure 1.** Proposed mechanism of furan formation.

Figure 2. Reaction of hexafluorobutyne with vinylketene complex **3**.

more electron-rich carbene complexes provide higher yields of furan. This may not be a reflection of faster reactivity, but may be due to increased stability of the product to oxidation or hydrolysis. We furthermore observed benzannulation upon reaction of hexa-fluoro-butyne with a vinylketene iron complex.[35,37] In future work, unsymmetrical trifluoromethylacetylenes will be examined in both processes to establish the regioselectivity that might be exhibited. The process reported here has significant implications on the mechanism of reaction of alkynes with iron(0) carbene complexes as well as on the establishment of synthetically useful protocols for the preparation of trifluoromethylated furans and phenols.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.037.

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35. General procedure: A heavy-walled Schlenk tube equipped with a Young Valve and small stir bar was cooled to −78 °C and evacuated and filled with argon. A quantity of hexafluorobutyne (500–1300 mg; 3–8 mmol) was allowed to distill into the tube and then weighed. The tube was recooled and a solution of carbene or vinylketene complex (0.5–6 mL) in anhydrous THF (5–6 mL) was added slowly. The mixture was placed under argon and the tube sealed tightly. The biphasic mixture was allowed to warm to room temperature slowly and was gradually heated at 60 °C for 48 h. The tube was then cooled to −78 °C, the Young valve opened, and then the solution was allowed to warm to room temperature. The crude product was filtered through Celite and then purified via flash chromatography on triethylamine-doped silica.
36. Spectroscopic data (**2g**): From tetracarbonyl[4-N,N-dimethylaminophenyl(ethoxy)methylene] iron (243 mg; 0.73 mmol) and hexafluorobutyne (1.2 g; 7.4 mmol) in THF (5 mL) was obtained **2g** (yield: 128 mg; 48%) ^{1}H NMR (400 MHz, acetone-d_6) δ 7.40 (2H, d, J = 8.8 Hz), 6.78 (2H, d, J = 8.8 Hz), 4.50 (2H, q, J = 7.2 Hz, CH$_2$CH$_3$), 2.99 (6H, s, N(CH$_3$)$_2$), 1.40 (3H, t, J = 7.2 Hz, CH$_3$). ^{13}C NMR (100.57 MHz, acetone-d_6) δ: 157.0, 151.7, 147.0, 129.6, 121.0, 120.9, 119.0, 114.6, 111.6, 69.3, 39.4, 14.4. ^{19}F NMR (376.3 MHz, acetone-d_6) δ: −56.64, −56.99. GC-MS: m/z 367(79), 338(100), 310(47), 148(37).
37. Spectroscopic data (**4**): From tricarbonyl[2-ethoxy-3-phenyl-butadiene-1-one] iron (360 mg; 1.10 mmol) and hexafluorobutyne (1.17 g; 7.22 mmol) in THF (6 mL) was obtained 2-ethoxy, 4,5-bis(trifluoromethyl)-biphenylol **4** (yield: 147 mg; 42%) ^{1}H NMR (400 MHz, acetone-d_6) δ 9.56 (1H, s, OH), 7.65 (2H, d, J = 7.2 Hz), 7.49 (2H, t, J = 7.6 Hz), 7.45 (1H, t, J = 7.2 Hz), 7.34 (1H, s) 3.64 (2H, q, J = 7.2 Hz), 1.06 (3H, t, J = 7.2 Hz) ^{13}C NMR (100.57 MHz, acetone-d_6) δ: 152.3, 147.9, 137.5, 136.2, 128.9, 128.7, 124.8, 124.4, 122.6, 122.1, 120.2,113.0, 69.5, 14.4. ^{19}F NMR (376.3 MHz, acetone-d_6) δ: −58.04, −58.85. GC-MS: 350(98), 331(50), 322(70), 301(100), 233(96), 177(45).