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SYNTHESIS OF CYCLOPENTANONES VIA REACTION OF FURAN CHROMIUM CARBENE COMPLEXES WITH ALKYNES

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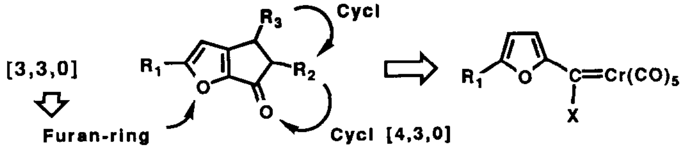
Summary: Reactions of the furan-methoxy chromium carbene complexes with alkynes in DMF at 120 °C provided cyclopentafurans, which served as useful precursors for cyclopentanones and other ring systems.

We have recently reported the conditions for exclusive indene formation from the reactions of the amine substituted-phenyl chromium carbene complex with alkynes.[1] The favorable results prompted us to apply this condition to the synthesis of cyclopenta[b]furans (**3**, **4**) by reactions of furan carbene complexes with alkynes. Cyclopenta[b]furans are valuable as synthetic intermediates since they can be hydrolytically converted to highly substituted cyclopentanones which are useful precursors for the bicyclo[3,3,0] and [4,3,0] systems (scheme 1). In this paper, we report that reactions of the methoxy-furan carbene complexes (**1a**, **1b**) with alkynes predominately produced **3** and **4** as major products, while reactions of the amine-substituted furan carbene complexes (**2a**, **2b**) with alkynes resulted in bisfuran formation. This result is in contrast to our earlier work[1] where intra-molecular carbonylation from the phenyl-morpholino carbene complex was suppressed in the cycloaddition process due to the enamine resonance, and led us to propose an alternative pathway for carbonylation.



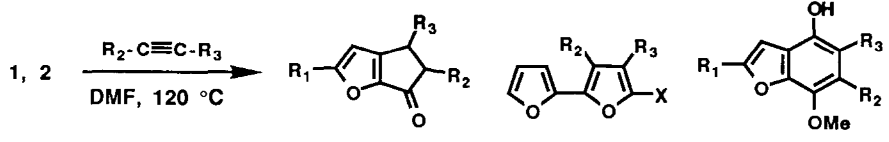
3(trans),4(cis)

1a: X = OMe, R_1 = H
1b: X = OMe, R_1 = Me
2a: X = NMe_2, R_1 = H
2b: X = N-morpholino, R_1 = H

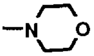
Scheme 1

The methoxy furan complex (**1a**) and its methyl analog (**1b**) were prepared according to the procedure of Fisher.[2] Treatment of **1a** with excess dimethylamine in THF at - 78 °C produced **2a** (85 %).[3] Similarly, **2b** was obtained from **1a** and morpholine (85 %). The complexes were purified by flash column chromatography under argon or direct recrystalization. A solution of **2a** and diphenylacetylene (1.5 mol eq) in DMF was heated at 120 °C (bath temperature) for 5 hrs under argon. The mixture was cooled, diluted with ether, washed (H_2O) and concentrated. The product was purified by flash column chromatography (SiO_2), to provide a crystalline bisfuran (**5a**, 44 %).[4] The reaction of **2b** with diphenylacetylene, under the same conditions which was followed by aqueous acid treatment (1N HCl, MeOH), gave a bisfuran (**5c**, 20 %) and a 1 : 1 mixture of trans and cis diphenylcyclopentafurans (**3a** + **4a**, 27 %). On the other hand, the reaction of **1a** with the same alkyne, under the conditions used for **2b**, provided 3a (24 %), **4a** (37 %) and a benzofuran (**8**, 8 %). Other examples for formation of bisfurans and cyclopentafurans from **2a**, **2b** and **1a**, **1b** are shown on Table I with a series of alkynes.[4] Although benzannulation from **1a** and **1b** cannot be entirely eliminated, diarylalkyne(entry 4,5), aryl-alkyl alkynes (entry 6,8) and dialkylalkynes(entry 7,9) worked well for cyclopentafuran formation.[5] DMF and high reaction temperature were essential for efficient cyclopentafuran formation. For example, the reaction of **1b** with 1-phenyl-1-hexyne in THF at 65 °C provided **6c** as a only product in 51 % yield. The results indicate that the methoxy-furan complex (**1**) is superior for cyclopenta-furan formation to the amino- furan complexes (**2**), and suggest that, in a series of the furan complexes, carbonylation becomes more favored where the electron density is high as in the case for the amine-substituted complexes, in comparison with the methoxy complexes.[6]

Table I: Reactions of 1a, 1b, 2a and 2b with alkynes



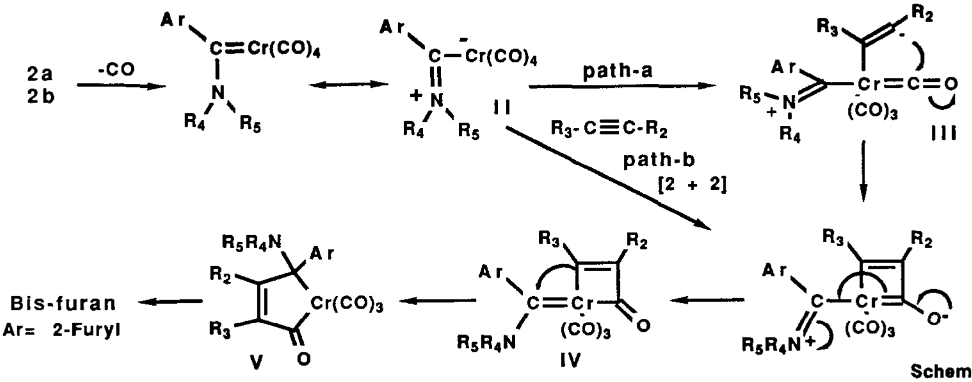
3(trans);4(cis) 5 6

Entry	Complex	X	R_1	R_2	R_3	Products (%, Yield)[*a]
1	2a	NMe_2	H	Ph	Ph	5a(44)
2	2a	NMe_2	H	n-Bu	Ph	5b(21)
3	2b		H	Ph	Ph	5c(20) + 3a + 4a(1 : 1;27)[*b]
4	1a	OMe	H	Ph	Ph	3a(24) + 4a(37) + 6a(8)[*b]
5	1b	OMe	Me	Ph	Ph	3b(24) + 4b(32) + 6b(9)[*b]
6	1b	OMe	Me	n-Bu	Ph	3c(14) + 4c(37) + 6c(15)[*b]
7	1b	OMe	Me	n-Bu	n-Bu	3d(34) + 6d(37)[*b]
8	1b	OMe	Me	$CH_2CH=CH_2$	Ph	3e(26) + 4e(10) + 6e(14)[*b]
9	1b	OMe	Me	$(CH_2)_2CH=CH_2$	t-Bu	3f(72)[*b]

*a: Isolated yield after flash chromatography
*b: Followed by aqueous work up procedure (1N HCl, MeOH, 25 °C).

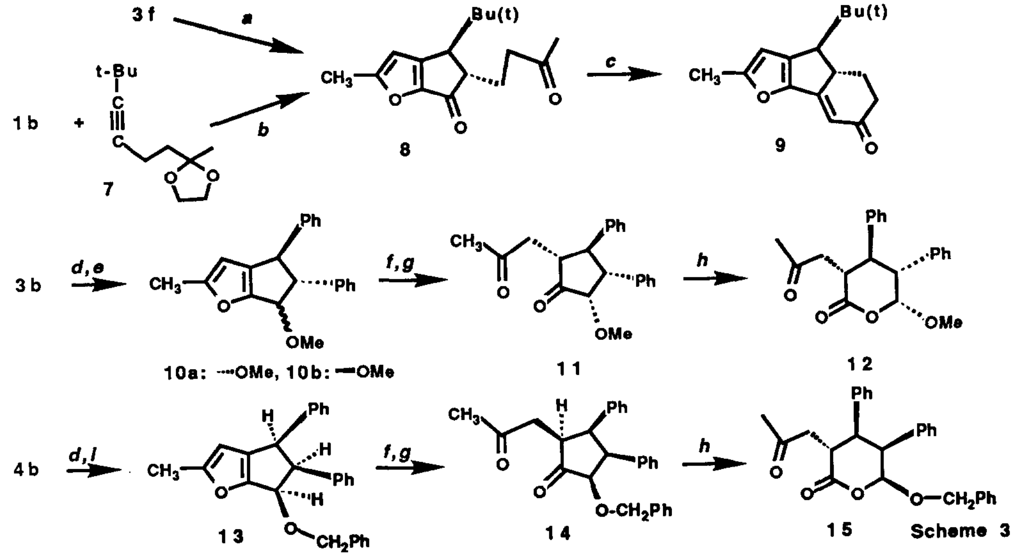
The plausible pathway, which can rationalize these observations, is outlined in Scheme 2. Instead of the previously proposed mechanism[7] where the initial carbon carbon bond formation between the alkyne carbons and the metal-ligand produces metallocyclobutene, the acetylene carbon might occupy the ligand position to the metal, which is negatively charged by the enamine resonance from the amine attached to the carbene carbon, generating the zwitter-ionic intermediate (**III**, path-a). Carbon monoxide insertion at the negatively charged acetylenic carbon of **III** would lead to the metallocyclobutenone intermediate (**IV**). Alternatively, direct [2 + 2] cycloaddition between the alkyne and the metal-ligand (path-b) could generate

IV. Then, carbon-carbon bond formation between the carbene carbon and the ligand carbon could produce the metallocyclopentanone (V). Then, α-elimination and migration of the amine unit would lead to the observed bisfuran.[8]



Scheme 2

Further transformation of cyclopentafurans is illustrated in scheme 3 for formation of various cyclopentanones and other derivatives. The olefin (**3f**) was converted to the ketone (**8**) under the Wacker's procedure [(*a*) O_2 gas, $PdCl_2$, CuCl, DMF, H_2O, 80 %].[9] Alternatively, **8** was directly obtained by reaction of **1b** with the alkyne (7)[10] [(*b*) DMF, 125 °C, 5 hr, acid work up, 60 %]. Treatment of **8** with base [(*c*) t-BuOK, t-BuOH, 25 °C, 18-crown-6][11] produced the tricyclic ring system (**9**; mp 123-124 °C) in 62 % yield. For conversion of **3** to the cyclopentanone, reduction of **3b** [(*d*) LAH, THF], followed by methylation [(*e*) NaH, MeI, THF, 90 %], gave a 10 : 1 inseparatable mixture of the methyl ethers (**10a** + **10b**). Oxidative furan ring opening of **10a** + **10b** [(*f*) mCPBA, CH_2Cl_2, 25 °C],[12] followed by hydrogenation [(*g*) 10 % Pd on carbon, MeOH] provided a cyclopentanone (**11**, 76 %) as a major component with three minor isomers. Baeyer-Villiger oxidation of **11** [(*h*) mCPBA, CH_2Cl_2, 25 °C] occurred between the cyclic ketone and the carbon bearing the ether, forming the γ-lactone (**12**, 90 %).



Scheme 3

In a parallel process[(*d*), (*i*) NaH, $PhCH_2Br$, THF, (*f*), (*g*), (*h*)], **4b** was converted to the cyclopentanone (**14**, 65 % overall) then the γ-lactone (**15**, 90 %)[13] as a single isomer.

In summary, we demonstrated the synthetic utility of the reaction of a furan chromium carbene complex with alkynes for formation of highly functionalized cyclopentanones as a useful addition to organic synthesis. We are currently studying the application of this method for synthesis of complex molecules, as well as further supports for the carbonylation process.

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(4) The structure of **4a** and **5a** were verified by X-ray crystallographic analyses. The stereochemistry of **3a** was determined based upon spectral data (high and low resolution mass, IR and ^1H- and ^{13}C-NMR), in comparison with those of **4a**. Also, **4a** is epimerized to the thermodynamically more stable **3a** upon treatment with base. Satisfactory spectral data (high resolution mass, IR and ^1H-NMR) were obtained for all new compounds; **1b**, **2a,b**, **3a-f**, **4a-e**, **5a-c**, **6a-e**, **7**, **8**, **9**, **10a** + **10b**, **11**, **12**, **13**, **14** and **15**. Combustion analyses were obtained for **3a-f**, **4a-e**,, **5a-c**, **6a-e**, **7**, **8**, **9**, **10a** + **10b**, **11**, **12**, **13**, **14** and **15**. The crystallographic data of **4a** and **5a** have been deposited for publication in *Acta Crystallographica C*.

(5) However, the reactions of **1a** or **1b** with terminal alkynes, such as 1-hexyne, phenylacetylene and ethyl propiolate, resulted in predominate formation of the corresponding benzofurans.

(6) We suggested that carbon monoxide insertion is intercepted in the reaction of morpholino-phenyl carbene complex with alkynes since chromium metal is negatively charged by back donation of the electron density from the electron rich substituents on the carbene carbon (enamine resonance for example), predominating a Nazarov cyclization, generating cyclopentanones.

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(13) It is presumed that, becuase of highly hindered all cis configuration, mild aqueous base work-up procedure caused the rapid epimerization to **15**.

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