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REACTION OF A PYRROLE-CARBENE CHROMIUM COMPLEX WITH ALKYNES: A FACILE HYDROINDOLOQUINONE FORMATION WITH *IN-SITU* PROTECTION.

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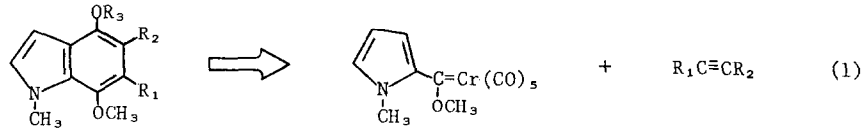
Abstract: Cycloaddition reaction of a pyrrole-carbene chromium complex with alkyne in the presence of acetic anhydride and triethylamine provided the acetylated hydroindoloquinone derivative.

Hydroindoloquinone (**1**, eq 1) is an important structural feature, closely related to a series of indole alkaloids, which may be directly accessible by reaction of an alkyne, CO, and a pyrrole-carbene chromium complex (**2**). Previous synthetic strategies of the hydroindoloquinone derivatives have in common involved addition of a pyrrole ring to a carefully constructed substituted hydroquinone derivative. Since an indole of the type (**1a**) is extensively labile, especially when R_1 and R_2 are the electron rich substituents, protection of the phenolic hydroxy groups is of considerable interest because of their value in multistep alkaloid synthesis. In this paper, we wish to report a facile formation of acetylated hydroindoloquinone (**1b**) by the cycloaddition of the same complex (**2**) with an alkyne in the presence of acetic anhydride and triethylamine. This is the first example of the *in-situ* protection in the alkyne-carbene cycloaddition reaction.[1]

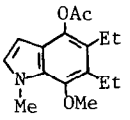
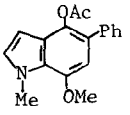
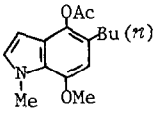
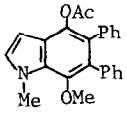
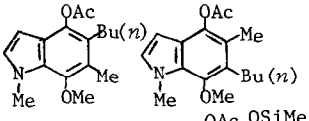
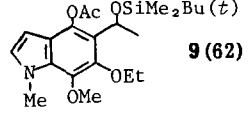
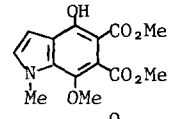
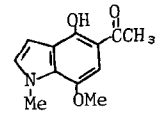


(1)

1; a, R_3=H; b, R_3=Ac 2

The general procedure is as follows: The carbene complex (**2**) was prepared as before from 2-lithio-N-methylpyrrole and chromium hexacarbonyl, followed by methylation with trimethyloxonium tetrafluorobrate (64% yield, orange-yellow crystals).[2] A solution of 2 (3.2 mmole), alkyne (8.7 mmole), acetic anhydride (6.4 mmole) and triethylamine (6.4 mmole) in tetrahydrofuran (THF, 90ml) was heated under argon at 65°C (bath temperature). TLC analysis indicated complete reaction after 3-5 hrs. The mixture was cooled and concentrated by rotary evaporation. The major products were isolated by silica gel flash column chromatography and characterized by ir, mass and ^{1}H NMR spectra analysis. Table-I presents the result of the indole formation by the cycloaddition-protection reaction of **2** with alkynes.[3] Yields varied with the substituents on the alkynes, and sterically hindered diphenylacetylene resulted in inefficient cycloaddition (**6**, entry 4). When pyridine was used in place of triethylamine, no acetylation was observed.[4] Alkynes bearing carbonyl substituents

Table I. The Reactions of a Pyrrole-carbene Complex (2) with Alkynes*a

Entry	Alkynes*b ($R_1C{\equiv}CR_2$)	Ac_2O (mol. eq)	NEt_3 (mol. eq)	Time (hr)	Product (%)*c
1	EtC≡CEt	2.0	2.0	3	 **3 (48)**
2	HC≡CPh	2.0	2.0	4	 **4 (45)**
3	HC≡CBu(*n*)	1.5	1.0	2	 **5 (34)**
4	PhC≡CPh	2.0	2.0	5	 **6 (24)**
5	MeC≡CBu(*n*)	1.5	1.0	5	 **7 & 8 (51)*d**
6	EtOC≡CCHCH$_3$ (OSiMe$_2$Bu(t)) **12**	1.5	1.5	5	 **9 (62)**
7	$MeO_2CC{\equiv}CCO_2Me$	-	-	5	 **10 (36)**
8	HC≡CC(=O)CH$_3$	-	-	4	 **11 (39)**

*aTHF (30ml/mmole) was used as solvent at 65°C (bath temperature).

*bThe 2-4 mol. eq. of an alkyne was applied.

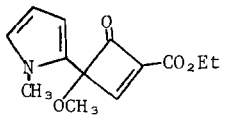
*cIsolated yield.

*dCombined yield, where compounds **7** and **8** were obtained in a ratio of 1.5:1.0 determined by ^{1}H-NMR spectrum and analytical HPLC analysis.

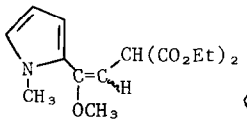
reacted with **2** without acetic anhydride and triethylamine, providing the stable, non-acetylated indole derivatives **10** and **11** (entry 6,7). A solution of 2 (9.5 mmole) and acetylacetylene (38 mmole) in THF (300ml) was heated under argon at 65°C for 4 hrs, and the major product (**11**) was isolated as yellow crystals, mp 154-155°C by silica gel column chromatography (39% yield). An intriguing exception was the reaction of **2** with ethyl propiolate (**13**), which under the similar conditions (THF, 65°C, 4 hrs, argon) provided the cyclobutenone (**14**, 51%) and the vinyl ether (**15**, 5%).[3]

We have reported that the reaction of **2** with the alkoxyalkyne (**12**) (THF, 65°C, 4 hrs, argon) led to the structure (**17**), the dimer of the expected indole (**16**).[5] The presence of acetic anhydride and triethylamine in this reaction condition suppressed the formation of **17**, giving the acetylated monomer (**9**) in a 62% yield (entry 6).

$HC{\equiv}CCO_2Et$ 13



14



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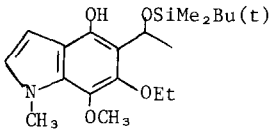

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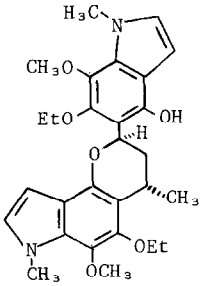
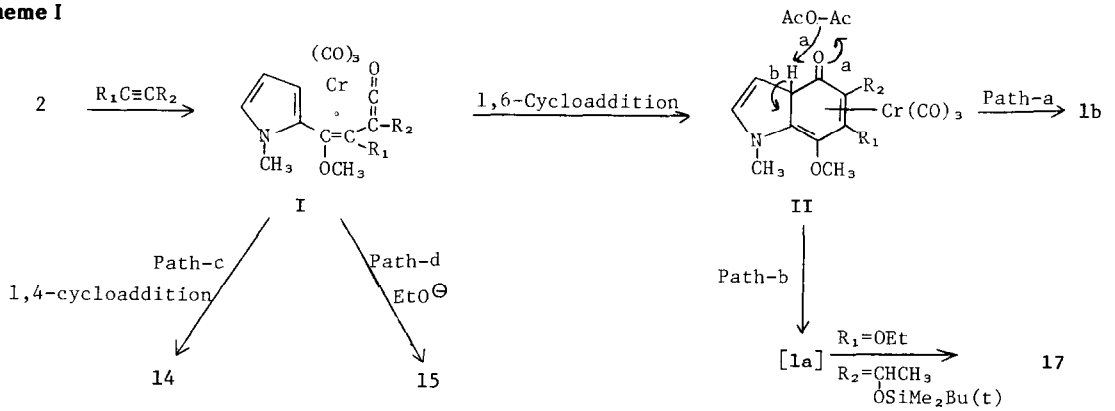


17

A plausible pathway for acetylation and formation of **14**, **15**, and **17** is outlined in Scheme I. The well established cycloaddition pathway produces the vinyl ketene chromium intermediate (**I**).[1e] The 1,6-cyclization of **I** forms the cyclohexadienone intermediate (**II**), which then aromatizes to the indole (**1a**) by a proton shift (path-b). In the presence of acetic anhydride and triethylamine, intermediate (**II**) aromatizes and rapidly acetylates to 1b (path-a). Thus, path-b can be blocked. The vinyl ketene intermediate (**I**), produced in the ethyl propiolate reaction, can undergo 1,4-cycloaddition to the

Scheme I



cyclobutenone **14** (path-c). This reaction has been suggested to be aided by coordination to the metal which favors the 5-cis-diene conformation required in this reaction.[6] Alternatively, the vinyl ketene (I) can react with ethoxide (generated from ethyl propiolate) to produce **15** (path-d).

This alkyne-carbene cycloaddition with *in situ* protection can be an important addition to heterocyclic methodology and the application of this method to the synthesis of complex alkaloid is currently under study.

References:

1. The basic alkyne cycloaddition process has been extensively studied with aryl- and vinyl-carbene complexes, and has begun to be applied in natural product synthesis.
   a) K.H.Dötz, *Angew. Chem. Int. Ed.*, 14 644 (1975).
   b) K.H. Dötz. B. Fügen-Köster, *Chem. Ber.*, 113 1449 (1980).
   c) W.D. Wulff, P.C. Tang, J.S. McCallum, *J. Amer. Chem. Soc.*,103 7677 (1981).
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   f) M.A. McCuire, L.S. Hegedus, *J. Amer. Chem. Soc.*, 104 5538 (1982).
   g) W.D. Wulff, P.C. Tang, *J. Amer. Chem. Soc.*, 106 434 (1984).
2. A. Yamashita, T.A. Scahill, *Tet. Lett.*, 23 3765 (1982).
3. All indole derivatives (**3, 4, 5, 6, 7, 8, 9, 10,** and **11**) and the compound **14** gave satisfactory ir, mass, ^{1}H-NMR spectra and combustion analysis. The vinyl ether **15** and its corresponding ketone obtained by acid hydrolysis showed the same physical behaviors as those of the authentic samples (see ref 2). The stereochemistry of compounds **7** and **8** was determined by measurement of nuclear Overhauser effects at 500MHz on a Brüker wm-500 spectrometer. These experiments involved n.O.e. difference spectroscopy.
4. The reaction under these conditions could have produced the corresponding indoles (**1a**) bearing the free hydroxy groups which had difficulties for purification.
5. The dimer was understood in terms of formation of **16**, followed by the side chain elimination (orthoquinonemethide formation), isomerization to the styryl derivative, then subsequent Diels-Alder cycloaddition between the orthoquinonemethide and the styryl derivative. A. Yamashita, T.A. Scahill, C.G. Chidester, *Tet. Lett.*, in press.
6. The 1,4 cycloaddition process has been observed when diphenylacetylene was reacted with a phenyl chromium carbene complex (n-Bu_2O, 70°C, 1 hr), providing the chromium tricarbonyl complex of the diphenyl cyclobutenone derivative in a 27% yield.
   a) K.H. Dötz, R. Dietz, *J. Organometal. Chem.*, 157 C55-C57 (1978).
   b) K.H. Dötz, *Pure & Appl. Chem.*, 55 (11) 1689 (1983).

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