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Synthesis of hydrophenanthrenes through a 'green' Fischer carbene–alkyne coupling process

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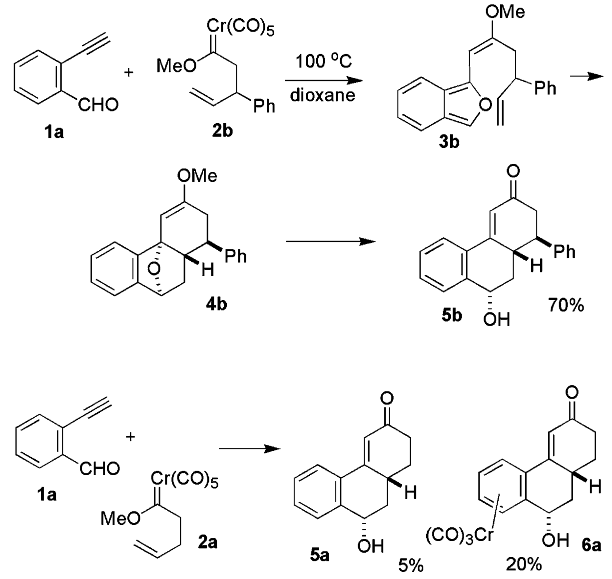
Abstract—Coupling of alkynylbenzoyl systems with γ,δ-unsaturated Fischer carbene complexes leads to the formation of hydrophenanthrene derivatives. This reaction is not affected by aqueous systems, which offer a further advantage such that chromium hexacarbonyl sublimes during the reaction process. Chromium carbene–alkyne coupling processes can thus be performed in environmentally friendly solvents with substoichiometric net consumption of chromium hexacarbonyl.

A novel two-component stitching of the hydrophenanthrene ring system via the reaction of alkynylbenzaldehyde derivatives with γ,δ-unsaturated carbene complexes has recently been developed in this laboratory (e.g., conversion of **1a**+**2b** to **5b** in Scheme 1).[1] The reaction proceeds with a high degree of diastereo-selectivity when chiral γ,δ-unsaturated carbene complexes (e.g., **2b**) were employed to afford a single compound (e.g., **5b**) in good yield. The analogous reaction using simple butenylcarbene complex **2a** is considerably less efficient than the more highly substituted examples presented in Refs. 1a–c,[2] and afforded a low yield of a mixture of complexed and uncomplexed derivatives after silica gel chromatography. As part of a general effort to prepare hydrophenanthrene natural products (including morphine alkaloids and abietanes) using the reaction in Scheme 1, the coupling of highly oxygenated alkynylbenzoyl derivatives (e.g., **1c**, Scheme 2) with simple γ,δ-unsaturated carbene complexes was tested. The most satisfactory yield optimization experiment involved the deliberate addition of water to the reaction mixture.[3] When the coupling of alkynylbenzaldehyde **1c** and carbene complex **2a** was conducted in 19:1 dioxane–water, the yield of hydrophenanthrene **5c** was higher than in any other experiment and chromium hexacarbonyl was deposited onto the condenser.



Scheme 1.

Since carbene complex **2a** was originally prepared from chromium hexacarbonyl (see Scheme 3), the net effect is that the overall transformation is substoichiometric in chromium. In this letter, these two effects will be explored in more depth. The ultimate goal is to devise a system where chromium carbene complexes couple with an alkyne in a process that employs cheap and environmentally friendly solvents with minimal net consumption of chromium.[4] Although alkylation of chromium carbene complex stabilized anions,[5] synthesis

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Keywords: Carbene complexes; Alkynes; Isobenzofurans; Diels–Alder reaction; Aqueous reactions.

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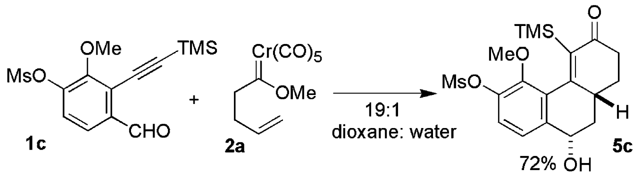
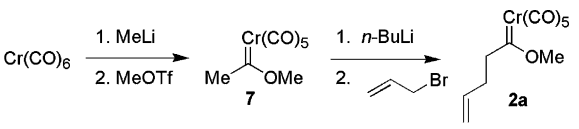


Scheme 2.

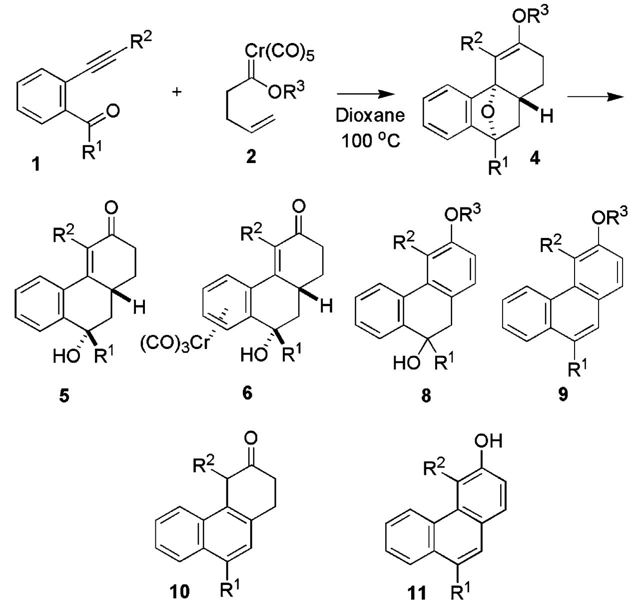


Scheme 3.

of carbene complexes,[6] and pK_a measurements[7] can be conducted in water at or below room temperature, studies of aqueous thermally induced chromium carbene–alkyne couplings are extremely limited.[8]

Prior to evaluation of the aqueous phenanthrene synthesis, the reaction of complex **2a** with various 2-alkynylbenzoyl systems in conventional ethereal solvents was tested (Table 1). As noted in Table 1, the reaction afforded a diverse array of different products related to oxanorbornene derivative **4**, and to some extent the distribution of these products could be controlled through the work-up procedure. These substrates will be the focus of aqueous-phase investigations in anticipation that a viable high-yielding and convenient procedure can be developed for the isolation of the desired products **5**. For the convenience of evaluating the overall efficiency

Table 1. Reaction of butenylcarbene complexes **2a**/**2c** with alkynylbenzoyl systems



1: **a** R^1,R^2 = H; **d** R^1 = H, R^2 = n-Bu; **e** R^1 = H, R^2 = TMS; **f** R^1 = Ph, R^2 = n-Bu

2: **a** R^3 = Me, **b** R^3 = Bn

5,6, 8-14: **a** R^1,R^2 = H, R^3 = Me; **d** R^1 = H, R^2 = n-Bu, R^3 = Me; **e** R^1 = H, R^2 = TMS, R^3 = Me; **f** R^1 = Ph, R^2 = n-Bu, R^3 = Bn

Entry	R^1	R^2	R^3	Conditions[a]	Products
1 (**1a**+**2a**)	H	H	Me	SiO_2	**5a** (5%) **6a** (20%)
2 (**1a**+**2a**)	H	H	Me	HCl	**10a** (20%)
3 (**1d**+**2a**)	H	*n*-Bu	Me	HCl	**10d** (56%)
4 (**1e**+**2a**)	H	TMS	Me	SiO_2	**5e** (15%) **6e** (trace)
5 (**1e**+**2a**)	H	TMS	Me	HCl	**9e** (4%)[b] **10e** (51%)[b] **11e** (3%)[b]
6 (**1f**+**2c**)	Ph	*n*-Bu	Bn	SiO_2	**5f** (9%) **8f** (67%)
7 (**1f**+**2c**)	Ph	*n*-Bu	Bn	HCl	**8f** (11%) **10f** (61%)

[a] SiO_2—the product after extractive work-up was purified by Flash chromatography; HCl—After the reaction mixture cooled to room temperature, 1 M aqueous HCl was added.

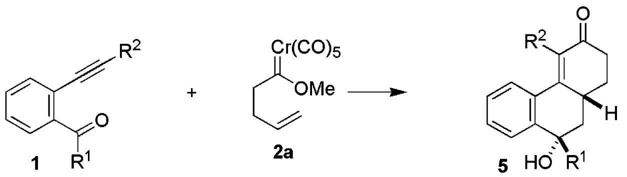
[b] R^2 = H in the products **9**–**11**.

of the process, in some cases the crude reaction mixture was treated with aqueous HCl, which afforded predominantly dehydration products. The results in Table 1 reveal that: (1) the yield of adducts are generally higher using phenyl ketones instead of aldehydes (compare entries 6 and 7 with all others),[9] (2) the yields of adducts with internal alkynes are generally higher than those with terminal alkynes (note the unusually low yields in entries 1 and 2), and (3) the yields of the desired adducts **5** are highest when the crude reaction is subjected to chromatography on silica gel, however even under these optimal conditions there are often significant amounts of dehydration/oxidation byproducts (entry 6) and chromium is not efficiently decomplexed from the arene (entries 1 and 4). The reaction is of similar efficiency with both methoxycarbene complexes and benzyloxycarbenes (entries 6 and 7), despite the known thermal chemistry of benzyloxycarbene complexes.[10]

Next, the reaction of carbene complex **2a** with alkynylbenzoyl systems was tested in the presence of water and various water-like solvent systems (Table 2). As noted in entries 1–9 of Table 2, the reaction of the silylated alkyne was highly tolerant of an aqueous environment. Furthermore, the reaction was free of dehydration products and arene–chromium complexes, and only the desired product **5e** was obtained. Chromium hexacarbonyl can be recovered from the system in a moderate-excellent yield by merely scraping the condenser after the reaction is over. The yield of hydrophenanthrene **5e** was not affected by the amount of water or ethanol in the reaction mixture. The reaction could even be performed successfully in pure water if surfactants were added to the reaction mixture (entries 7–9) and was equally successful using pure sodium dodecyl sulfate (SDS) and hand soap. The major complication in the experiments using anionic surfactants (entries 7 and 9) is that the extractive work-up that is typically employed is difficult in the presence of the surfactant and required the use of dichloromethane instead of ether.[11] These conditions were also effective for reactions using the butylacetylene analog (entries 10 and 11) and the phenyl ketone analog (entries 15 and 16), in all cases leading exclusively to the desired adduct **5**.

These reaction conditions were not effective in promoting the coupling of the terminal alkyne (entries 12–14). The reaction in entry 12 of Table 2 afforded only the dienol ether **14** (Scheme 4). The reaction in entry 13 led to the alkylidenephthalan **13**. Formation of this product suggests that either: (1) the rate of the Diels–Alder step of the tandem reaction process is lower in this system, (2) that the presence of water has an activating effect on a 1,7-hydrogen shift process,[12] or (3) that the isobenzofuran intermediate **3a** can directly hydrolyze to afford the alkylidenephthalan.

Table 2. Reaction of γ,δ-unsaturated carbene complex **2a** with alkynylbenzaldehydes



1 and 5: **a** R^1, R^2 = H; **d** R^1 = H, R^2 = *n*-Bu; **e** R^1 = H, R^2 = TMS; **f** R^1 = Ph, R^2 = *n*-Bu

Entry	R^1	R^2	Solvent[a]	Cr(CO)$_6$[b] (%)	**5** (%)
1	H	TMS	95:5 d:w	75	61
2	H	TMS	90:10 d:w	89	71
3	H	TMS	80:20 d:w	90	74
4	H	TMS	70:30 d:w	89	74
5	H	TMS	50:50 d:w	89	74
6	H	TMS	95:5 e:w	59	76
7	H	TMS	w+10% SDS[c]	81	76
8	H	TMS	w+5% Bu_4NBr	70	84[d]
9	H	TMS	w+hand soap[e]	80	74
10	H	*n*-Bu	95:5 d:w	63	56
11	H	*n*-Bu	w+5% Bu_4NBr	77	58
12	H	H	95:5 d:w	60	0[f]
13	H	H	70:30 d:w	67	0[f]
14	H	H	w+5% Bu_4NBr	71	0
15	Ph	*n*-Bu	w+10% SDS	85	80
16	Ph	*n*-Bu	w+5% Bu_4NBr	35	75

[a] d = dioxane, w = water, e = ethanol.

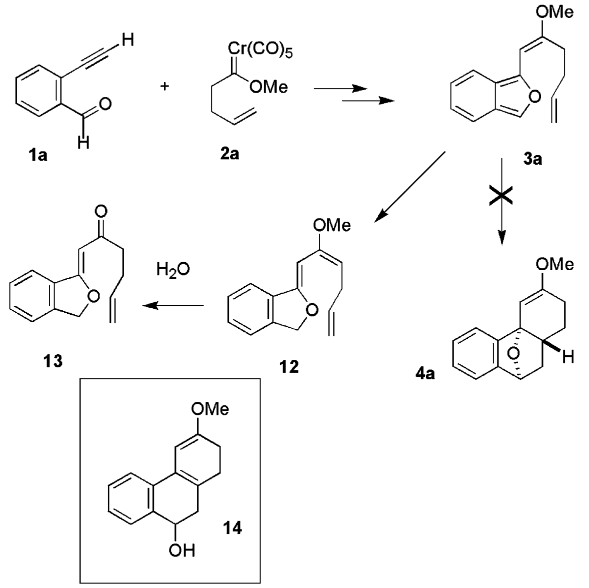
[b] The theoretical yield of Cr(CO)$_6$ is 0.83 mol/mol of carbene complex used.

[c] SDS = sodium dodecylsulfate.

[d] For an experimental procedure, see Ref. 13.

[e] The major ingredients listed are water, sodium dodecylbenzenesulfonate, and SDS.

[f] See Scheme 4.



Scheme 4.

In summary, we have shown that carbene–alkyne coupling can be performed in an aqueous solvent system. About 60–90% of the chromium can be recovered. Unlike most systems that are not catalytic but allow metal recovery, this one is practical. The metal comes out of the reaction in the same form in which it was purchased commercially, and the recovery process amounts to a simple scraping of the condenser.

Acknowledgements

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