

Communication

Synthesis of uracil derivatives by oxidation of Fischer tungsten–carbene uracil complexes

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Abstract

A study on the oxidation of Fischer tungsten–carbene uracil complexes has been carried out. Several commonly used oxidants gave results strongly influenced by the presence of substituent on nitrogen atoms. In particular, usual oxidants failed in the oxidation of 3-alkyl uracil carbene complexes. Finally, we showed that *t*-butyl hydroperoxide is able to oxidize successfully also 3-alkyl uracil carbene complexes and can be used as a good alternative to the other methods.

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1. Introduction

Fischer carbene complexes have found numerous applications as intermediates in organic synthesis [1]. Nowadays their use has been extended to other fields like materials chemistry [2] or bioorganometallics [3].

In the course of our studies in the synthesis of bioactive molecules we recently focused our attention in the easy reaction of alkynyl alkoxy metal carbene complexes **1** with ureas [4] in order to obtain metallorganic uracil analogs **2** (Scheme 1).

Although the presence of the organometallic moiety in the uracil structure, represents an interesting case of bioorganometallic system, it could be of interest to have methodologies to release it. Uracils in general and 6-substituted uracils in particular, found important application in medicinal chemistry [6,7] and as building blocks for the construction of nucleotides. In a precedent paper, the recovery of the organic ligand of the organometallic uracil derivatives

by a reductive way was described and the influence of the electronic features of the groups attached to the carbene was pointed out [8].

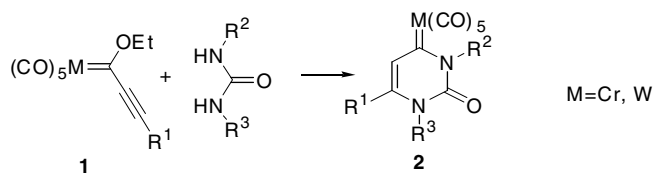
In the present communication, the oxidative process for the release of the organic uracil analogs from the carbene complexes, is studied. Tungsten complexes, rather than chromium complexes, were preferentially considered on account of the better efficiency of their preparation starting from ureas [9]. However, this feature is not advantageous in the oxidation process because it is well known that, in general, chromium complexes are more susceptible of demetallation than tungsten analogs. There are several methods reported to oxidize Fischer carbene complexes, as stated by us and Licandro et al. in precedent studies [10–12]. However, several problems arising from the low yields or byproducts formation, especially in the case of the less reactive nitrogen substituted carbene complexes are observed.

2. Results and discussion

Taking into account these precedents, we tried different common oxidative systems on a model uracil metallocarbene

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Scheme 1.

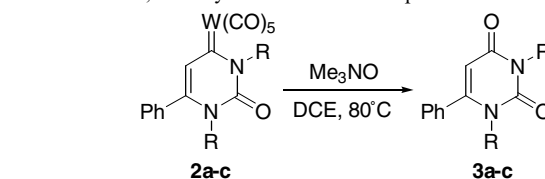
2a. The use of amine oxides was by far the first choice. In our case, trimethyl amine oxide proved to be a better reagent than *N*-methyl morpholine derivative (entries 8 and 9 in Table 1). Raising of the temperature from 40 to 80 °C had a benefic effect. Iodine method (entry 6) gave occasionally a similar yield but suffered of poor reproducibility.

On the ground of these findings we decided to extend the *N*-oxide method to different tungsten Fischer carbene uracil complexes. As is shown in the Table 2, 1,3-dialkyl derivatives **2b** and **2c** responded successfully as well to these oxidative conditions. Reaction times and yields resulted almost independent of the alkyl group bulkiness.

Unfortunately, similar reactions with 1- or 3-monoalkyl derivatives **2d** and **2e**, produced new unwanted products (Scheme 2). Reaction of 1-methyl uracil analog **2d** gave a low yield of oxidation product **3d**, together with pyrimidin-2-ones **4d** and **5d**. An even more disappointing result was observed with 3-methyl complex **2e**. In this case, the expected product was not obtained at all, although traces of its alkylated analog **6e** were isolated. The most abundant product was 6-phenyl-pyrimidin-2-one **4e**, but 4-carboxy derivative **5e** was also obtained.

These anomalous results could be accounted for the basic conditions used. A considerable lowering of the pK_a 's of **2d** and **2e** compared with that of the organic uracils **3d**

Table 2
Oxidation of 1,3-dialkyluracil carbene complex **2c** with Me_3NO



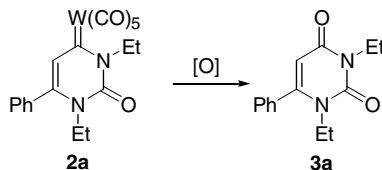
Entry	Substrate	R	Reaction time (h)	Yield (%)
1	2b	Me	5.5	78
2	2a	Et	5	78
3	2c	Allyl	4.5	93

and **3e** (reported pK_a 's were 9.8 and 10.0 respectively in H_2O at 25 °C [13]), seems reasonable due to the withdrawing effect of the $\text{W}(\text{CO})_5$ moiety [14]. Therefore, N(1)-H and N(3)-H might be easily salified by amine *N*-oxide or more probably by amine itself. Moreover, a greater acidity of N(1)-H in comparison with N(3)-H may be hypothesized owing to steric effect of the bulky $\text{W}(\text{CO})_5$. This fact could explain the higher amount of elimination product **4e** and the lack of uracil **3e** in the product mixture. A tentative explaining mechanism for the complex **2e** was reported in Scheme 3. An analogous mechanism is suggested for **2d**.

The formation of **4d** and **4e** in nearly quantitative yields by reaction, respectively, of **2d** and **2e** with triethyl amine (Scheme 2), furnished a proof for the mechanism proposed in Scheme 3. For the 4-carboxy derivative **5** to be obtained, however, the oxidative conditions seem to be determinant.

In a search for to overcome these results the fluoride promoted oxidation system described by Barluenga et al. [15] in the case of alkoxy carbene complexes was attempted. This very useful and simple procedure consists

Table 1
Oxidation of carbene complex **2a** with various reagents



Entry	Reagent	Temperature (°C)	Reaction time (h)	Yield (%)
1	$\text{Ca}(\text{OCl})_2, \text{NaHCO}_3, \text{Bu}_4\text{NHSO}_4$	rt	20	— ^a
2	DMSO	70	72	— ^b
3	DMSO	100	19	28
4	CAN	rt	0.1	28
5	$\text{KI}, \text{NaBO}_3 \cdot \text{H}_2\text{O}, \text{KH}_2\text{PO}_4$	rt	22	26
6	$\text{I}_2, \text{NaHCO}_3$	rt	0.5	66
7	$\text{NMO}, \text{CH}_2\text{Cl}_2$	40	19	60
8	NMO, DCE	80	5	65
9	$\text{Me}_3\text{NO}, \text{DCE}$	80	5	78

^a No reaction.

^b Degradation of the substrate was observed.

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