

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].

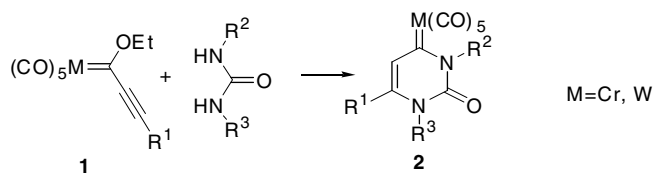
In the present communication, the oxidative process for the release of the organic uracil analogs from the carbene complexes, is studied. Tungsten complexes, rather than chromium complexes, were preferentially considered on account of the better efficiency of their preparation starting from ureas [9]. 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.

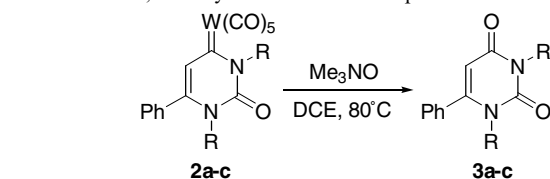
2a. The use of amine oxides was by far the first choice. In our case, trimethyl amine oxide proved to be a better reagent than *N*-methyl morpholine derivative (entries 8 and 9 in Table 1). Raising of the temperature from 40 to 80 °C had a benefic effect. Iodine method (entry 6) gave occasionally a similar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



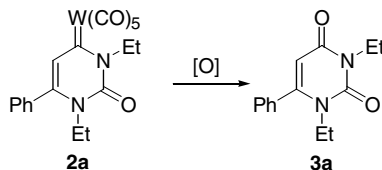
Entry	Substrate	R	Reaction time (h)	Yield (%)
1	2b	Me	5.5	78
2	2a	Et	5	78
3	2c	Allyl	4.5	93

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

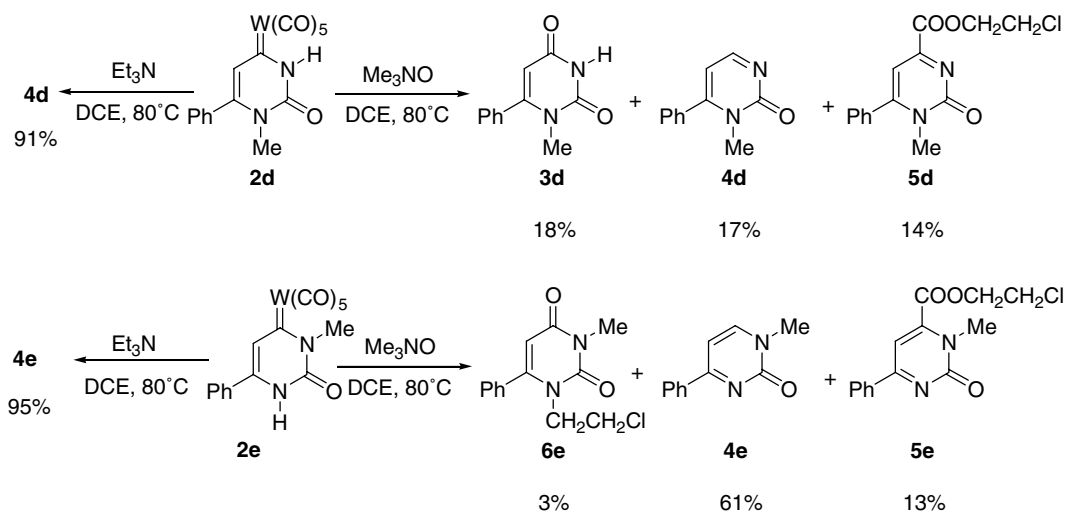
Table 1
Oxidation of carbene complex **2a** with various reagents



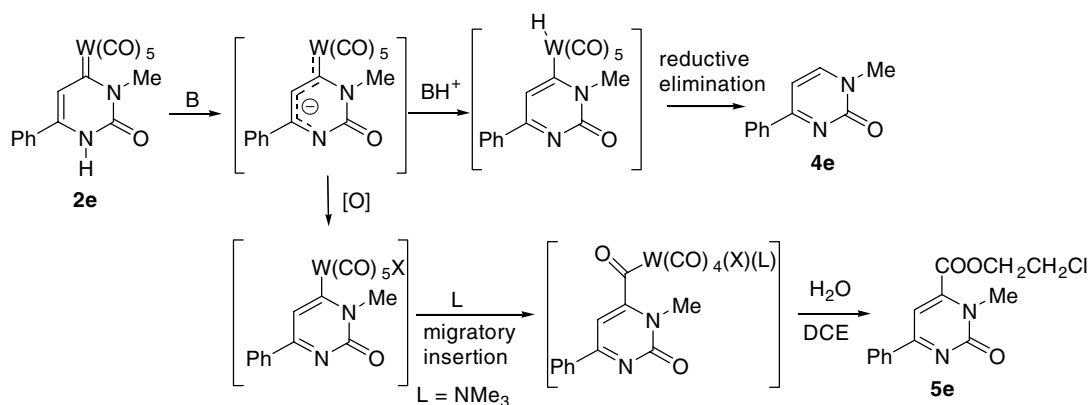
Entry	Reagent	Temperature (°C)	Reaction time (h)	Yield (%)
1	$\text{Ca}(\text{OCl})_2, \text{NaHCO}_3, \text{Bu}_4\text{NHSO}_4$	rt	20	— ^a
2	DMSO	70	72	— ^b
3	DMSO	100	19	28
4	CAN	rt	0.1	28
5	$\text{KI}, \text{NaBO}_3 \cdot \text{H}_2\text{O}, \text{KH}_2\text{PO}_4$	rt	22	26
6	$\text{I}_2, \text{NaHCO}_3$	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.



Scheme 2.



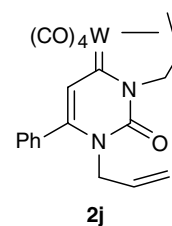
Scheme 3.

of adding TBAF to a substrate containing solution opened to air. Though the mechanism is not suggested, it is clear the catalytic role of fluoride ion, being air the terminal oxidant. As described in Table 3, the efficiency of this system on 1,3-dialkyl as well as 1-alkyl substituted Fischer uracil carbene complexes, was really satisfactory.

The 1,3-dialkyl uracil complexes generally reacted faster (20 min–1 h depending on the steric bulk of 3-alkyl substituent) than unsubstituted analog to **N(3)** (1–3.5 h). As expected, the 6-silylated uracil complex **2i** was simultaneously oxidized and desilylated under TBAF conditions, to afford 1,3-dimethyluracil (entry 9).

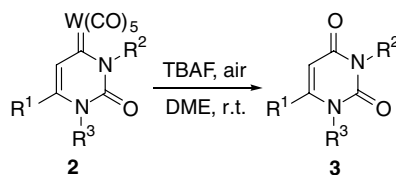
In every case, the addition of TBAF was followed by a fast darkening of mixture. Then a gradual discoloration was observed, indicative for the progressive formation of uracil. The chromatic shift may be due to the displacement of one or more CO ligands in the metal coordination sphere by fluoride. In the intermediate complex generated, the 0 oxidation state of the metal should be destabilized, favouring the oxidation by air [16]. This hypothesis is in agreement with the observation that complex **2j** resulted much less reactive than the π -uncoordinated **2c**. The reac-

tion was not complete even after 15 days. An analysis of the crude mixture displayed only few amounts of oxidation product **3c** together with a complex mixture of undesired products.



As described in Table 3, these oxidation method did not work on N(1)-unsubstituted uracil complexes. Reaction of compound **2e** with TBAF gave only traces of the expected product even after 6 days and bubbling oxygen. When the orange solution of **2e** was treated with TBAF, a change to yellow was observed instead of the usual darkening. The colour turned back to orange on addition of an equal amount of *p*-TsOH, and after work up, the substrate was

Table 3
Oxidation of carbene complexes **2** with TBAF/air



Entry	Substrate	R ¹	R ²	R ³	Reaction time	Yield (%)
1	2b	Ph	Me	Me	20 min	97
2	2d	Ph	H	Me	3.5 h	95
3	2e	Ph	Me	H	6 d	Traces
4	2a	Ph	Et	Et	20 min	90
5	2f	Ph	H	Et	2 h	95
6	2c	Ph	Allyl	Allyl	1 h	84
7	2g	Ph	H	Allyl	15 min	80
8	2h	H	Me	Me	30 min	72
9	2i	Me ₃ Si	Me	Me	20 min	70 ^a

^a The product is 1,3-dimethyluracil (**3h**) owing to concomitant and complete desilylation.

recovered unaltered. We attributed the different behaviour of these substrates to the enhanced acidity of N(1)–H compared to N(3)–H. Of course the acidity may be influenced by the solvent and the large counterion tetrabutylammonium; the proton abstraction at N(3), in fact, could lead to the formation of an hindered ionic pair. The action of basic F[−] should give yellow salt **7**; compound **2e** can be restored by acidification with *p*-TsOH (Scheme 4). The low reactivity is probably caused by the poor reactivity of **7** to the substitution of a CO ligand.

In order to avoid the employment of basic reagent, the catalytic action of different halide salts such I[−], Br[−] and Cl[−] is investigated under analogous conditions. However, introduction of TBAI, TBABr or TBACl in place of TBAF gave no transformation of **2e** even after several days and bubbling oxygen. Moreover no darkening of the orange solution was observed. Apparently catalytic properties of fluoride ion are unique in this process.

So we decided to design a wholly different oxidative system, presumably compatible with the high acidity of N(1) unsubstituted Fischer carbene uracil complexes. Our attention moved to peroxide reagents. Though it is well known the ability of these compounds to decompose transition metal salts and complexes in low oxidation state [17], they were poorly investigated as reagents for oxidative demetalation of Fischer-type carbene complexes. Only the very reactive dimethyldioxirane has been extensively used to this purpose [10,18]. To our knowledge MCPBA was sometime

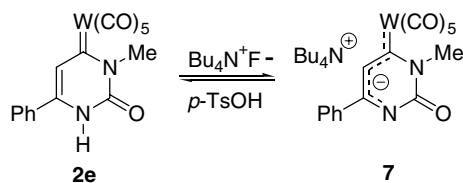
employed only with the more reactive dialkyl Fischer carbenes [19], and hydrogen peroxide [20] was scarcely introduced as reagent in this kind of process until now.

In a first experiment MCPBA oxidated metalcarbene **2e** at room temperature in moderate yield (59%). Traces of the elimination product **4e** were isolated (<5%). So we next examined *t*-butyl hydroperoxide, a less reactive, more stable and selective reagent. Hydroperoxides, in fact, are known to oxidatively decompose metalcarbonyl complexes and other transition metal compounds in low oxidation state, with a single electron transfer mechanism [16,21]. A similar behaviour should therefore be expected with the isoelectronic Fischer-type carbene complexes. To our great satisfaction this was just the case. In fact, not only **2b** and **2d** but also **2e**, reacted with TBHP at 70 °C in DCE furnishing the desired carbonyl product in good yield (Table 4, entry 3) [22].

The use of different solvents, as refluxing toluene, gave lower yields. The method was extended successfully to other N(1) unsubstituted uracil complexes whose oxidation gave unsatisfactory results using other reagents (entries 4, 5 and 8). Furthermore, the effectiveness of the hydroperoxide method was demonstrated in the oxidations of coordinated carbene **2j** and 6-silyl-uracil carbene **2i**. In the first case uracil **3c** was obtained easily (entry 6). 6-Silyl-uracil **3i**, a potential building block for the preparation of different 6-substituted uracils, was cleanly obtained by oxidation of **2i**, without concomitant desilylation (entry 7).

3. Conclusions

In conclusion, herein is described the oxidation of Fischer-type carbene uracil complexes which allowed to set up a convenient two-steps method for the preparation of 6-substituted uracils starting from alkynyl alkoxy tungsten carbene complexes and ureas. Barluenga's protocol based on the use of fluoride ion, was successfully applied



Scheme 4.

Table 4
Oxidation of carbene complexes **2** with TBHP (DCE, 70 °C)

Entry	2	R ¹	R ²	R ³	Reaction time (h)	Yield of 3 (%)	Yield of 4 (%)
1	b	Ph	Me	Me	1.5	72	–
2	d	Ph	H	Me	2	60	–
3	e	Ph	Me	H	3	77	14
4	k	Ph	Et	H	1.25	70	14
5	l	Ph	Allyl	H	4	57	4
6	j	Ph	η^2 -Allyl	Allyl	0.5	75	–
7	i	Me ₃ Si	Me	Me	5	65	–
8	m	H	Me	H	8	80	n.d.

with 1,3-dialkyl and 1-alkyl uracil complexes while failed with 3-alkyl analogs and η^2 -allyl derivatives. On the other hand these uracil carbene complexes were satisfactorily oxidated by *t*-butyl hydroperoxide. Noteworthy, the latter reagent, employed for the first time in the oxidation of Fischer-type carbene complexes, can be used in general as a good alternative to the other already available methods. New synthetic applications of Fischer carbene uracil complexes, as the preparation of pyrimidine-2-ones, will be the subject of future works.

Acknowledgements

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- [22] *Typical procedure of oxidation of carbene complexes 2 with TBHP*: In a screw capped ACE tube containing a solution of metallocarbene **2** (0.1 mmol) in 1,2-dichloroethane, a solution of TBHP (5.5 M in *n*-decane, 1 mmol) was added. The mixture was warmed at 70 °C until completion of oxidation. Decoloration of solution and formation of a white precipitate was indicative of transformation. Sodium sulfite (10%) aqueous solution (6 ml) was added and the resulting mixture was stirred for 3 h then extracted with dichloromethane. The organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography using chloroform–methanol mixtures as eluant afforded uracil **3**.