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Improving methodology for the preparation of uracil derivatives from Fischer carbene complexes. Microwave activation

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Abstract

The effect of the microwave irradiation on the reaction of alkynyl alkoxy carbene complexes with ureas is studied. The results show that the use of microwave activation could represent an alternative to the reaction in conventional conditions for the metal carbene complex chemistry. In particular, is noteworthy that the use of large amounts of solvents could be drastically reduced or even avoided and, in any case, reaction times were dramatically shortened.

Keywords: Carbene complexes; Microwave irradiation; Ureas; Cycloaddition

1. Introduction

The preparation of uracils with N^1 and/or N^3-alkyl substituent has been of considerable interest to synthetic chemists for their biological activities [1] and because they are basic building blocks for the preparation of oligonucleotides, polymeric analogues of nucleic acids and non-nucleoside reverse transcriptase inhibitors [2].

These heterocycles can be assembled using appropriate procedures proposed to this purpose, e.g. the Biginelli reaction [3], among them, a new approach has been developed for their preparation [4]. This methodology relies on the reaction of alkynyl alkoxy Fischer carbene complexes with substituted ureas. The uracil compound was then obtained by oxidation of the metal pentacarbonyl cycloadduct (Scheme 1).

A mechanism suggested for this conversion involves a nucleophilic attack followed by a cyclisation reaction (scheme 2). Of course, if the alkyl groups linked to nitrogen atoms of ureas are different, two isomeric compounds are formed while a single compound is expected when $R = R'$.

In the present communication we have extended this study to different mono and disubstituted ureas with the aim to use them as a starting compounds for the synthesis of uracil derivatives of biological interest.

2. Results and discussion

The results obtained are shown in the Table 1. The yields in the expected products **3** for disubstituted ureas (entries 1 and 3) were good albeit the long reaction time required. However, when we tried to shortened the reaction times by heating (THF or dioxane reflux) yields dropped down considerably (60% in the better case). Finally, some monosubstituted ureas were found as useful starting material for the preparation of uracils (entries 2, 4 and 6, Table 1) but once again long reaction times were required and any improvement were obtained by heating at reflux temperature.

We can conclude from this experiments, that, although this methodology has its own synthetic value, some limitations mainly due to the long reaction times often required could represent a significant drawback for preparative purposes.

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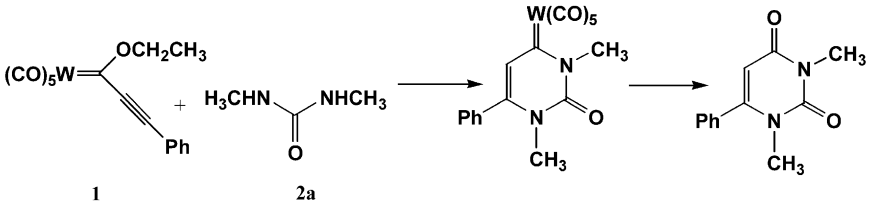


1 2a

Scheme 1.

Table 1
Conventional reaction of ureas and carbene (**1**) at room temperature

Entry	Ureas (**2**)		Time (h)	Product yield [a] (%)
	R	R′		
1	CH_3	CH_3	48	**3a** 90
2	CH_3	H	48	**3b** 71 (1:1.3) [b]
3	CH_2CH_3	CH_2CH_3	144	**3c** 94
4	CH_2CH_3	H	144	**3d** 69 (1:1.5) [b]
5	allyl	allyl	120	**3e** 58
6	allyl	H	192	**3f** 70 (1:3.2) [b]

[a] Reaction conditions: 0.04 mmol of the carbene complex in dry THF (1 ml), two equivalents of the corresponding urea, room temperature.
[b] Ratio of uracils with N^1 or N^3-alkyl substituent.

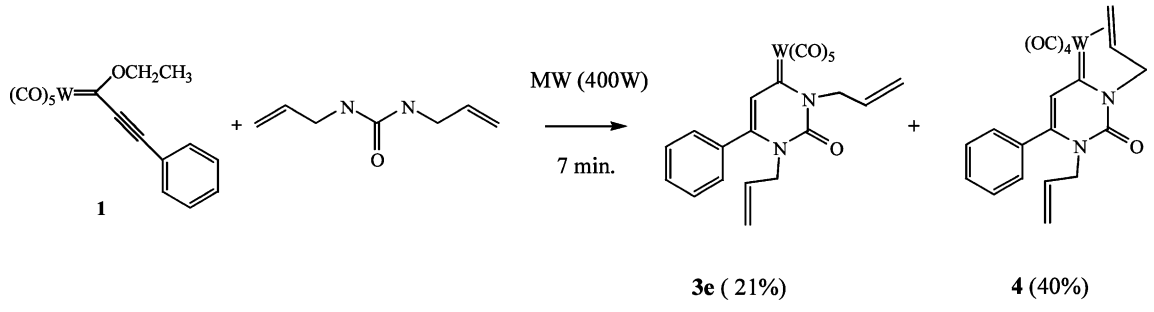
We decided then to investigate the application of microwave irradiation to this process.

Microwave heating is one of the most promising non conventional methodology nowadays used in organic synthesis [5,6]. One of the first applications of microwave to induce organic chemical reaction dates back 1969 when Vanderhoff described a successful emulsion polimerization of butylacrylate, acrylic acid and methacrylic acid under microwave irradiation [7]. However, only after the pioneering works of Geyde et al. [8] and Giguere et al. [9] in 1986 really started the wide application of this technology to organic synthesis and microwave heating (MWH) has been successfully applied in recent years to a large number of chemical reactions [10]. Use of microwave generally allows to conduct organic reactions in a easy way and also dramatically decrease reaction time. In fact, we expected that the use of carbene **1** and substituted ureas under microwave irradiation should be effective for the rapid preparation of uracils.

We decided to start considering microwave processes without solvents and, during our investigation, several experiments were performed under solvent-free conditions using various irradiation powers for different times. The best result (92% yield) was obtained just irradiating a mixture of carbene **1** and dimethylurea for only 5 min at 300 W of irradiation power. In a similar way, we studied also the reaction of diethyl urea with carbene **1**. Under solvent free conditions 84% yield of the expected product **3c** was obtained in only 10 min (Table 2).

Reactions with monosubstituted ureas proved to be very difficult in solvent free conditions under microwave irradiation. In fact, unsatisfactory transformations were obtained in these conditions (entries 2 and 5, Table 2). However, when a small quantity of solvent (THF) was added it was possible to obtain the expected products in very short times and excellent yields (entries 3 and 6, Table 2).

The case of diallylurea deserves a special comment. Diallylurea reacted very slowly in fact, and compound **3e** [11] was obtained in 58% yield after 5 days in conventional conditions. When we tried to apply microwave irradiation to this reaction in solvent free conditions an unexpected result was obtained. The derivative **3e** was obtained together with another compound **4** which after chromatographic separation showed to be the main product of the reaction.



1 **3e** (21%) **4** (40%)

Table 2
Reaction of ureas and carbene (**1**) under microwave irradiation

Entry	R	R′	Solvent	Microwave power [a] (W)	Irradiation time (min)	Yield [b] (%)
1	CH_3	CH_3	–	300	5	**3a** 92
2	CH_3	H	–	300	5	**3b** 20 (1:1.5)
3	CH_3	H	THF	400	5	**3b** 69 (1:1.5)
4	CH_2CH_3	CH_2CH_3	–	250	10	**3c** 84
5	CH_2CH_3	H	–	300	10	**3d** 38 (1:1.5)
6	CH_2CH_3	H	THF	400	5	**3d** 63 (1:1.5)
7	Allyl	H	THF	350	5	**3f** 54 (1:3)

[a] The microwave powers and the irradiation times selected are those which allow a full conversion. (stated by the disappearance of the starting carbene complex).
[b] Reaction conditions: all the reactions were conducted in a sealed pressure tube using a domestic microwave oven (0.04 mmol carbene complex, 0.08 mmol urea; THF 50 L, when indicated).

In order to understand the nature of this compound several NMR experiments were performed and a careful examination of the obtained data allowed to suggest for this new compound a tetracarbonylic structure. The new compound was clearly formed by **3e** and, we found that it is possible to obtain **4** [12] exposing **3e** to microwave or conventional heating.

We assumed that, in the microwave conditions, one of the carbonyls was lost and replaced by the coordinated double bond. As expected from this assumption longer reaction times enhanced the yield on product **4**.

3. Conclusions

In conclusion, we shown here that the use of a microwave irradiation could represent an alternative to the reaction in conventional conditions for the metal carbene complexes chemistry. In particular, is noteworthy that the use of large amounts of solvents could be drastically reduced or even avoided and, in any case, reaction times were dramatically shortened.

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[11] Compound **3e**: ^{1}H-NMR δ ($CDCl_3$): 7.52 (3H, m), 7.40 (3H, m), 6.02 (1H, m), 5.81 (1H, m), 5.36–5.23 (5H, m), 5.00 (1H, d, J = 17.2 Hz), 4.37 (2H, bd, J = 5.3 Hz).^{13}C NMR δ ($CDCl_3$): 50.2 (t), 62.4 (t), 118.2 (t), 119.1 (t), 127.3 (d), 128.0 (d), 129.0 (2C, d), 130.6 (2C, d), 131.0 (d), 131.5 (s), 131.6 (s), 146.7 (s), 147.0 (s), 198.2 (4C, s), 203.3 (s), 239.3 (s).
[12] Compound **4**: ^{1}H-NMR δ ($CDCl_3$): 7.55 (1H, m), 7.51 (2H, m), 7.38 (2H, d, J = 7.3 Hz), 7.08(1H, s), 5.80 (1H, m), 5.26 (1H, dd, J = 14.4, 4.8 Hz), 5.23 (1H, d, J = 10.3 Hz), 4.98 (1H, d, J = 17.8 Hz), 4.64 (1H, m), 4.33 (2H, d, J = 6.3 Hz), 4.32 (1H, m), 3.46 (1H, d, J = 11.5 Hz), 3.44 (1H, d, J = 16.2 Hz). ^{13}C-NMR δ ($CDCl_3$): 49.8 (t), 58.5 (t), 59.9 (t), 70.7 (d), 119.0 (t), 123.1 (d), 127.9 (2C, d), 128.8 (2C, d), 130.7 (d), 130.9 (d), 131.9 (s), 147.8 (s), 148.3 (s), 202.4 (s), 202.7 (s), 209.5 (s), 212.1 (s), 240.6 (s).