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Preparation of organometallic uracil-analogue Fischer carbene complexes: Comparative study of conventional heating vs microwave irradiation

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Abstract

Mono and disubstituted ureas react with alkynyl Fischer carbene complexes to give mono and di *N*,*N*-substituted organometallic uracil analogues. An optimization of the process using different starting metal carbene complexes and variously substituted ureas under conventional heating (with and without solvent) and microwave irradiation techniques is reported. The synthesis of the metal–carbene analog of the commercially available dimethyl uracil is reported.

Keywords: Biorganometallic chemistry; Carbene complex; Uracil analogues; Microwave irradiation; Ureas

1. Introduction

The incorporation of organometallic functional group into a biomolecule in order to modify its properties has been recently developed as main feature of the new area of organometallic chemistry called biorganometallic chemistry. In few decades this topic has attracted an increasing research interest from chemists and several organometallic biomolecules with a variety of activities have been prepared [1]. Recently, the interesting biological properties shown by dihydropyrimidine compounds have stimulated our interest in preparing their organometallic analogues.

The synthesis of compounds with pyrimidine skeleton by reaction of alkynyl alkoxy carbene metal complexes with mono and dimethyl ureas was described some time ago [2]. A suggested mechanism for this conversion involves a nucleophilic attack followed by a cyclization reaction as depicted in Scheme 1. Although the yields in the corresponding metallorganic pyrimidines were generally high, long reaction times were required.

Later on, an improvement of the procedure by means of microwave activation was described allowing a marked reduction of the reaction times [3]. However, only carbene complex **1A** and a limited number of ureas were tested in these studies. In this paper, we describe an optimization and an extension of the precedent procedures using different metal carbene complexes and variously substituted ureas under conventional heating and microwave irradiation techniques in order to have a deeper look at the heating effect. Due to the high stability and the ease of preparation of carbene **1A**, the main part of the work was done with this complex. However, in order to extend the scope of the work we also studied the reactivity of the chromium carbene complex **1B** and the trimethylsilyl alkynyl carbene tungsten complex **1C**. In the later case, we show, also, the preparation of a metallorganic analogue of the bioactive compound dimethyl uracil [4].

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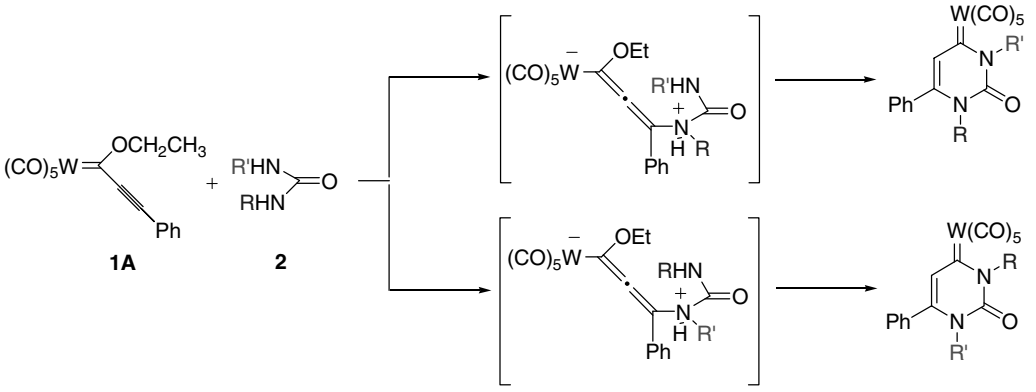


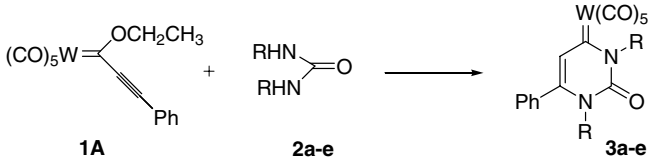
Scheme 1.

2. Results and discussion

2.1. Reactions in THF under conventional and microwave heating

At room temperature, a variety of ureas reacted with carbene **1A** (0.05 M in THF), but long reaction time were required to get uracil carbene complexes in good yields (see Section 4). In order to evaluate the influence of heating, the reactions were performed smoothly heating at 60 °C a solution of carbene **1A** (0.05 M) in THF obtaining, in shorter times, good tranformations to uracil carbene complexes. Finally, we found that when a more concentrated THF solution of carbene **1A** (0.8 M) was heated at the same temperature even shorter times were needed to afford good results. Disubstituted ureas (Table 1) reacted generally better than monosubstituted ureas (Table 2). However, in both series the yields were decreasing as the substituents were increasing in size. The reactions with monosubstituted ureas showed a moderate regioselectivity. In fact, the nucleophilicity and bulkiness of the substituent of the urea in the addition step were clearly determining the ratio between the expected products **4** and **5**. Product **4**, formed by the first nucleophilic attack due to the unsubtituted nitrogen, was more and more abundant than its isomer **5** as the substituent became bulkier. Interestingly, cyclohexylurea gave conjugate addition but the obtained adduct **9** was not able to cyclize probably due to the steric hindrance. A careful analysis of the reaction mixture allowed the detection of small quantities of a side product, common to all the reactions, characterized as **6** [5], deriving from the nucleophilic addition of ethanol to carbene. In particular, more concentrated solutions, which favoured easier reactivity of ureas, caused also an increasing of **6** formation. This result is probably due to a more efficient interaction between **1A** and the ureas while ethanol, released during the reaction, reacted more easily with carbene **1A** in the concentrated solution. Noteworthy, allyl ureas showed a peculiar behaviour. In fact, diallyl and monoallyl ureas gave both their corresponding adduct, **7** and **8**, due to the interaction of the *N*-allyl moiety closer to the metallic center. The formation of these compounds is due to the

Table 1
Reactions of disubstituted ureas **2a–e** (2 equiv.) and carbene complex **1A** in THF (0.8 M) under conventional (60 °C, CH) and microwave heating (MWH)

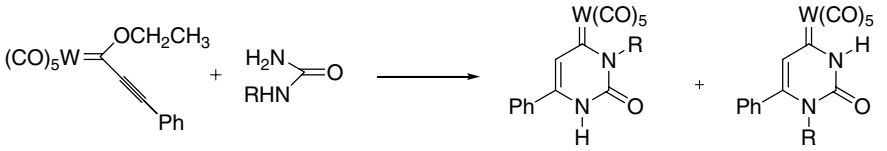


1A **2a-e** **3a-e**

Entry	Ureas		Heating	Time (min)	Total yield (%)	6 (%)	**1A** (%)
	2	R					
1	**a**	Me	CH	30	94	3	–
2	**a**	Me	MWH (400 W)	0.5	97	3	–
3	**b**	Et	CH	75	85	10	–
4	**b**	Et	MWH (400 W)	0.5	90	10	–
5	**c**	Propyl	CH	90	70	16	–
6	**c**	Propyl	MWH (400 W)	5	62	20	–
7	**d**	Butyl	CH	120	77	9	–
8	**d**	Butyl	MWH (400 W)	5	64	13	5
9	**e**	Allyl	CH	420	49 (55)[a]	18	–
10	**e**	Allyl	MWH (100 W)	30	42 (44)[a]	14	34
11	**e**	Allyl	MWH (300 W)	15	19 (44)[a]	18	5

[a] Yield comprehensive of compound **7**.

Table 2
Reactions of monosubstituted ureas **2f–n** (2 equiv.) and carbene **1A** in THF (0.8 M) under conventional (60 °C, CH) and microwave heating (MWH)

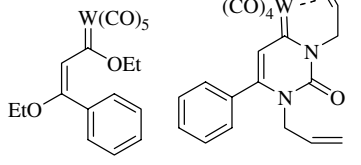


1A **2f-n** **4f-m** **5f-m**

Entry	Ureas		Heating	Time (min)	Total yield (%)	Ratio 4:5	6 (%)	**1A** (%)
	2	R						
1	**f**	Me	CH	60	71	1.3	3	–
2	**f**	Me	MWH (400 W)	2.5	71	1.4	8	17
3	**g**	Et	CH	75	65	2.2	11	–
4	**g**	Et	MWH (400 W)	2.5	63	2.5	11	13
5	**h**	Propyl	CH	90	63	3.2	15	–
6	**h**	Propyl	MWH (100 W)	5	51	3.0	10	13
7	**i**	Butyl	CH	60	59	3.1	13	–
8	**i**	Butyl	MWH (100 W)	5	59	3.0	8	12
9	**l**	Allyl	CH	150	53 (62)[a]	3.2	–	17
10	**l**	Allyl	MWH (400 W)	4	42 (51)[a]	3.8	9	27
11	**m**	Benzyl	CH	150	51	7.4	–	13.5
12	**m**	Benzyl	MWH (600 W)	4	42	5.3	7	19
13	**n**	Cyclohexyl	CH	120	36[b]	–	–	–
14	**n**	Cyclohexyl	MWH (400 W)	5	32[b]	–	–	40

[a] Yield comprehensive of compound **8**.
[b] Yield of open adduct **9**.

replacement of one of the carbonyls by the coordinated double bond. The compounds **7** and **8** were not formed when the reaction was conducted at room temperature. In fact, the conversion to chelated compounds **7** and **8** was enhanced by heating (see for example, entries 9, 10 and 11 in Table 1).



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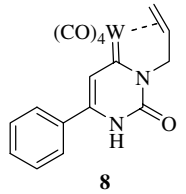
7



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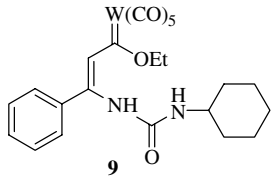

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In order to improve the process we turned to microwave conditions. One of the main advantages of microwave promoted reactions is the flash heating effect, which leads to much reduced reaction times [6]. A preliminary investigation on the application of microwave heating (MWH) was done, during a previous work, using a domestic microwave oven. However, uniform heating in this oven is generally poor due to the inhomogeneous field produced; therefore, we decided to use a laboratory dedicated microwave instrument for this new investigation. To make the most of this feature it is essential the search of the optimal conditions and several reactions were conducted varying power and time of microwave irradiation. Optimal conditions, reported in Tables 1 and 2, allowed significantly to shorten the reaction times with no decrease in yields.

2.2. Reactions in solvent free conditions

Reactions of disubstituted ureas with carbene complex **1A**, using small quantities of reagents, can be conducted successfully without solvents under microwave irradiation [3]. However, the attempt to carry out MW solvent-free reactions using larger quantities of reagents was frustrating, being the results scarcely reproducible so we turned on conventional heating. In this condition *N*,*N*-disubstituted ureas reacted with carbene **1A** in a very simple way. In fact, we obtained excellent conversion into uracil carbene derivatives **3** just putting the reaction vial containing both the reagents in an oil bath (100 °C): few minutes were needed for the process (Table 3). Unfortunately, monosub-

Table 3
Reaction of carbene **1A** and ureas **2** (2 equiv.) in solvent free condition under conventional heating (oil bath 100 °C)

Entry	Ureas	R	Time (min)	Yield (%)	6
1	**2a**	Me	4	81	13%
2	**2b**	Et	5	72	21%
3	**2c**	Propyl	10	59	19
4	**2d**	Butyl	15	66	23
5	**2e**	Allyl	10	37% (42%)[a]	21%

[a] Yield comprehensive of compound **7**.

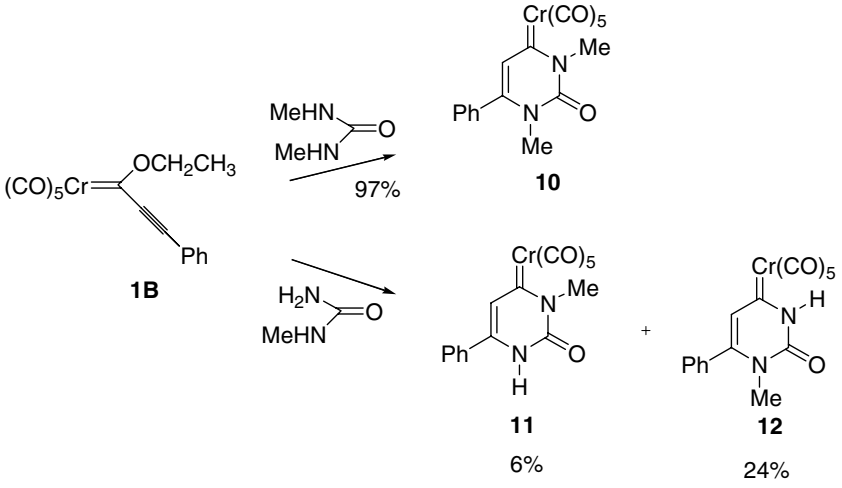
stituted ureas did not give good results in this conditions, probably this is due to their too slow reactivity which determines a degradation of the carbene complex before the expected reaction takes place.

2.3. Metal change

Change of the metal (Cr by W) did not change the overall course of the reaction. The products obtained, when we tried the reaction of carbene **1B** (0.8 M in THF, 60 °C) with mono and disubstituted methyl ureas (**2a** and **2f**, 2 equiv.), were similar in structure to the corresponding tungsten analogs being the yields, in the case of monomethyl urea adducts **11** and **12**, lower than in the case of tungsten (Scheme 2). Furthermore, the major isomer corresponds to the minor one obtained with the tungsten complex. We do not have a clear explanation for this anomalous behaviour, although these results seem to point out not a lowering in the reaction yield, but a decrease in the stability of the chromium complex **11** in the reaction conditions, in comparison with the corresponding tungsten carbene complex **4.**

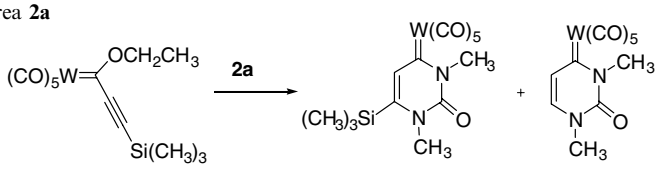
2.4. Alkynyl substituent change

Finally, we studied the influence of changes in the acetylene moiety. In particular, we move to the trimethylsilyl substituted alkynyl carbene complexes. The final objective is to obtain, as we mentioned above, the metallorganic analogue of the commercial 1,3-dimethyl uracil. In fact, the trimethylsilylalkynyl alkoxy metal carbene complex **13**, after reaction with the 1,3-dimethylurea and hydrodesilylation would afford the expected uracil derivative **14**. With this purpose in mind, we studied the reactivity of the alkynyl carbene complex **1C** (Table 4). From Table 4 we observe that long reaction times were required (entries 1and 2) but the yield was improved using catalitic quantities of DBU [7] (compare entries 1 and 2). Then the reac-



Scheme 2. The reaction of pentacarbonylchromium carbene **1B** (0.8 M in THF) with mono and dimethylureas (2 equiv.) under conventional heating conditions (60 °C).

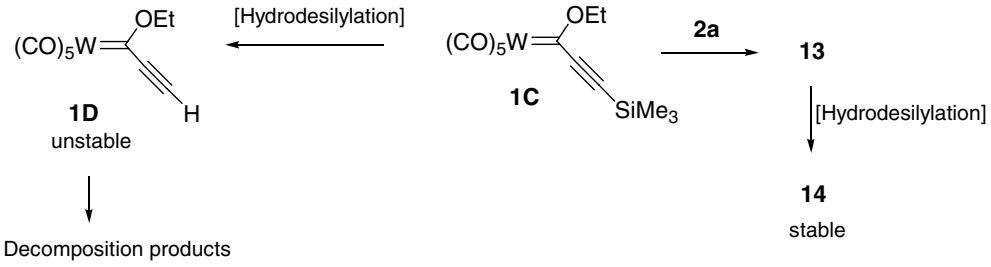
Table 4
Reaction of carbene **1C** and dimethylurea **2a**



1C **13** **14**

Entry	2a (equiv.)	Solvent	Heating	Time	13(%)	14(%)
1	2	THF	CH (r.t.)	10 h	12	–
2[a]	2	THF	CH (r.t.)	10 h	23	–
3	2	THF	CH (60 °C)	12 h	46	11
4	2	–	CH (100 °C)	10 min	21	11
5	5	–	CH (100 °C)	10 min	23	11
6	2	Toluene	CH (100 °C)	10 min	16	9
7	5	Toluene	CH (100 °C)	10 min	20	10
8[a]	5	Toluene	CH (100 °C)	10 min	41	10
9	2	–	MWH (400 W)	5 min	5	2
10	2	THF	MWH (400 W)	10 min	19	7

[a] Reaction performed in the presence of 0.025 mmol of 1,8-diazabicicle[5.4.0]undec-7-ene.



Scheme 3.

tion was conducted in the conditions optimized in the previous part of the work (**1C** 0.8 M in THF) heating at 60 °C. These conditions afforded in good yield the desired compound but still a long reaction time was required. Finally, we conducted the reaction in the solvent free conditions described in the first part of this work obtaining **13** (21%) in shorter time (entry 5). However, in this case also desilylated product **14** was recovered (11%). Better yields were obtained by heating a toluene solution of **1C**, a large excess of 1,3-dimethyl urea and catalytic amount of DBU (entries 6, 7 and 8 Table 4). The use of MWH (entries 9 and 10, Table 4) gave only low yields of the expected products.

The extension of this reaction to other mono and disubstituted ureas afforded only low yields (less than 15%) of the expected uracil analogues. However, even in the best conditions the yields obtained are lower than those observed when the carbene complex **1A** was employed. This could be accounted by the easy desilylation of the starting compound **1C** in the reaction conditions (Scheme 3) which affords a very unstable Fischer carbene such as **1D** [8].

The trimethylsilyl compound **13** was easily desilylated (KF, $BnEt_3NCl$, CH_3CN, r.t.) affording in 80% yield the expected metallorganic analogue of the commercial dimethyl uracil **14**.

3. Conclusions

In conclusion, we have demonstrated that organometallic uracil-analogues of Fischer carbene complexes are readily accessible through reaction of alkynyl alkoxy carbene metal complexes with mono and dimethylureas. The synthetic utility of this methodology was demonstrated by the preparation of a variety of Fischer carbene complexes incorporating the uracil skeleton, and applied to the synthesis of the organometallic dimethyl uracil **14.** Further work related to the reactivity of the organometallic uracil complexes is undertaken in our laboratories.

4. Experimental

4.1. General methods

All reactions were carried out using freshly distilled and dried solvents. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Alkynyl carbenes **1A**, **1B** and **1C** were prepared according to the literature methods [9]. The reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopic (^1H and ^{13}C NMR) pure materials. NMR spectra were recorded on a DRX 400 (400 MHz) and DRX 300 Bruker spectrometers at room temperature. $CDCl_3$ was used as a solvent and residual chloroform ($\delta = 7.26$; ^{13}C, $\delta = 77.0$) was used as an internal standard. Infrared spectra were obtained at a resolution of 2.0 cm^{-1} with a Vector 22 Bruker spectrometer and Perkin–Elmer Spectrum One FT-IR. EI-MS were obtained with a Q-Star Applied Biosystem (70 eV) mass spectrometer. ES-MS was performed using a Quattro micro API mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. Melting points were measured on a digital Electrothermal 9100. Melting points are uncorrected.

4.2. General experimental representative procedures for the synthesis of uracil-analogues Fischer carbene complexes

4.2.1. Method A (room temperature reactions)

A solution of metallocarbene **1A** (0.4 mmol) and urea **2** (0.8 mmol) in dry THF (8 mL), was stirred, in a round bottomed flask equipped with a condenser, at room temperature until **1A** was completely consumed. Then the solvent was evaporated *in vacuo*. The crude mixture was purified by flash chromatography (gradient eluition with petroleum ether/ethyl acetate mixtures from 9:1 to 1:1) (Table 5).

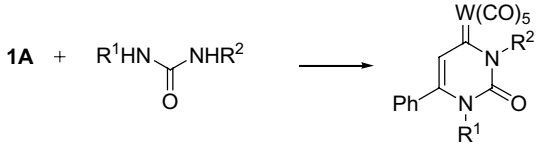
4.2.2. Method B (reactions under thermal conditions)

A screw capped ACE tube containing a solution of metallocarbene **1** (0.4 mmol) and urea **2** (0.8 mmol) in dry THF (0.5 mL), was heated to 60 °C with stirring until **1** was completely consumed. Then the mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The crude mixture was purified by flash chromatography.

4.2.3. Method C (reaction under solvent-free conditions)

Metallocarbene **1** (0.4 mmol) and urea **2** (0.8 mmol) were introduced in an ACE tube that was heated to 100 °C without stirring. Melting of solids occurred. After

Table 5
Reaction of ureas **2** (2 equiv.) and carbene **1A** (0.05 M) in THF at room temperature



2 a-n

3 a-e $R^1 = R^2$
4 f-n R^2 = H
5 f-n R^1 = H

Entry	Ureas			Time (h)	Total yield (%)	Ratio 4:5
	2	R	R′			
1	**a**	Me	Me	48	90	–
2	**b**	Et	Et	144	94	–
3	**e**	Allyl	Allyl	120	58	–
4	**f**	H	Me	48	71	1.3
5	**g**	H	Et	144	68	1.5
6	**h**	H	Allyl	192	70	3.2
7	**l**	H	Butyl	72	88	3.0
8	**m**	H	Benzyl	168	49	3.0
9	**n**	H	Cyclohexyl	168	42[a]	–

[a] Yield of open adduct.

reaction the tube was air-cooled to room temperature. The solid residue was dissolved in the minimal amount of CH_2Cl_2 and purified by flash chromatography.

The reactions under microwave heating were carried out as indicated in Methods B or C by heating in an automatic multimode instruments.

These procedures were followed for all the reactions listed in the tables.

4.3. Compound *3a*

See Ref. [2].

4.4. Compound *3b*

Orange solid; m.p. 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.60$–7.51 (m, 3H overlapped), 7.39 (m, 2H), 7.35 (s, 1H), 4.74 (q, $J = 7.0$ Hz, 2H), 3.84 (q, $J = 7.1$ Hz, 2H), 1.50 (t, $J = 7.0$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 235.9$, 203.6, 198.3, 148.0, 146.8, 131.7, 130.6, 129.0, 127.6, 127.1, 56.1, 43.3, 14.0, 13.8; IR ($CHCl_3$): 2987, 2061, 1904, 1691, 1570, 1062, 758 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 552 (M^+), 524 ($M^+ - CO$), 494, 466, 438, 410.

4.5. Compound *3c*

Yellow solid; m.p. 68–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.60$–7.51 (m, 3H overlapped), 7.38 (bd, $J = 7.8$ Hz, 2H), 7.35 (s, 1H), 4.58 (m, 2H), 3.72 (m, 2H), 1.90 (m, 2H), 1.64 (m, 2H), 1.08 (t,$J = 7.5$ Hz, 3H), 0.76 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 236.5$, 203.3, 198.4, 148.4, 146.7, 131.8, 130.7, 129.1, 127.8, 127.2, 62.5, 49.5, 21.6, 21.5, 11.0, 10.7. IR (KBr):2970, 2059, 1905, 1689, 1566, 1072 cm^{-1}; ES-MS (70 eV) ^{184}W *m/z*: 580 (M^+), 550.

4.6. Compound *3d*

Deep orange solid; m.p. 67–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.55$ (m, 3H), 7.38 (m, 3H), 4.64 (m, 2H), 3.79 (m, 2H), 1.88 (m, 2H), 1.58 (4H), 1.18 (m, 2H), 1.04 (t, 7.3 Hz, 3H), 0.79 (t, 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 236.4$, 203.3, 198.4, 148.4, 146.6, 131.8, 130.7, 129.1, 127.8, 127.2, 61.0, 47.8, 30.1, 19.9, 19.7, 13.8, 13.3. IR (KBr): 2955, 2059, 1913, 1566, 1465 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 608 (M^+), 580 ($M^+ - CO$), 520, 496 ($M^+ - 4CO$), 494, 466.

4.7. Compound *3e*

Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.58$ (m, 1H), 7.52 (m, 2H), 7.45–7.39 (m, 3H overlapped), 6.04 (ddt, $J = 17.1$, 10.3, 5.3 Hz, 1H), 5.82 (ddt, $J = 17.2$, 10.4, 5.5 Hz, 1H), 5.39–5.29 (m, 4H overlapped), 5.25 (bd, $J = 10.4$ Hz, 1H), 4.99 (bd, $J = 17.2$ Hz, 1H), 4.38 (bd, $J = 5.6$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 239.2$, 203.3, 198.2, 148.2, 146.7, 131.6, 131.5, 131.0, 130.6, 129.1, 128.0, 127.3, 119.1, 118.1, 62.4, 50.2; IR ($CHCl_3$): 3024, 2062, 1889, 1696, 1566, 769 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 548 ($M^+ - CO$), 520 ($M^+ - 2CO$), 464 ($M^+ - 4CO$), 436, 434.

4.8. Compound *4f*

Red brown solid; m.p. 145 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.19$ (bs, 1H, NH), 7.86 (bs, 1H), 7.79 (m, 2H), 7.66 (m, 1H), 7.60 (m, 2H), 4.15 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 243.0$, 203.6, 198.5, 150.3, 141.8, 132.8, 129.7, 127.3, 124.2, 46.4; IR ($CHCl_3$): 3019, 2061, 1929, 1685, 1594, 1216, 757 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 510 (M^+), 482 ($M^+ - CO$), 454 ($M^+ - 2CO$), 426 ($M^+ - 3CO$).

4.9. Compound *4g*

Orange solid; m.p. 155 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.34$ (bs, 1H, NH), 7.89 (s, 1H), 7.80 (m, 2H), 7.66 (m, 1H), 7.58 (m, 2H), 4.73 (q, $J = 7.0$ Hz, 2H), 1.47 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 241.6$, 203.3, 198.3, 149.7, 141.8, 132.8, 129.8, 127.3, 124.6, 55.1, 13.8; IR ($CHCl_3$): 3019, 2061, 1928, 1681, 1515, 1215, 758 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 524 (M^+), 496 ($M^+ - CO$), 466, 438, 414, 412.

4.10. Compound *4h*

Red solid; m.p. 150 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.72$ (bs, 1H, NH), 7.83 (bs, 1H), 7.72–7.63 (m, 3H overlapped), 7.60 (m, 2H), 4.57 (m, 2H), 1.88 (m, 2H), 1.08 (t, $J = 7.1$ Hz, 3H). ^{1}H NMR (400 MHz,

DMSO-d_6) $\delta = 7.81$ (m, 2H), 7.67–7.57 (m, 4H overlapped), 4.41 (m, 2H), 1.79 (m, 2H), 1.00 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.5 MHz, DMSO) $\delta = 232.2$, 203.5, 198.6, 148.2, 145.6, 132.3, 129.8, 129.2, 128.2, 122.4, 60.6, 21.1, 10.5; IR (KBr): 2962, 2361, 1898, 1689, 1573, 1026, 802 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 538 (M^+), 510, 480, 452, 424.

4.11. Compound **4i**

Dark red solid; m.p. 140 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 12.07$ (bs, 1H, NH), 7.92 (bs, 1H), 7.84 (m, 2H), 7.67 (m, 1H), 7.59 (2H), 4.61 (2H), 1.82 (m, 2H), 1.50 (m, 1H), 0.99 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 241.2$, 203.2, 198.4, 150.1, 141.9, 132.7, 129.6, 127.5, 124.8, 59.8, 30.3, 20.0, 13.8. IR (KBr, $CHCl_3$): 2962, 2060, 1897, 1666, 1512, 1072 cm^{-1}; ES-MS ^{184}W *m/z*: 497 [$(M + H)^+ - 2CO$], 469 [$(M + H)^+ - 3CO$], 441 [$(M + H)^+ - 4CO$], 413 [$(M + H)^+ - 5CO$].

4.12. Compound **4l**

Red solid; m.p. 176 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.05$ (bs, 1H, NH), 7.91 (bs, 1H), 7.77 (m, 2H), 7.65 (m, 1H), 7.59 (m, 2H), 6.02 (m, 1H), 5.31 (m, 3H overlapped), 5.20 (d, $J = 17.0$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 243.3$, 203.2, 198.2, 149.3, 141.7, 132.9, 131.5, 129.8, 129.6, 127.3, 124.4, 118.0, 61.2; IR (KBr): 2978, 2060, 1905, 1690, 1574, 1512 cm^{-1}; ES-MS ^{184}W *m/z*: 559 [$(M + Na)^+$], 508 [$(M^+ - CO$], 531 [$(M + Na)^+ - CO$], 447 [$(M + Na)^+ - 4CO$].

4.13. Compound **4m**

Red solid; m.p. 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.70$ (bs, 1H, NH), 7.96 (s, 1H), 7.67 (m, 3H overlapped), 7.49 (2H), 7.30 (m, 3H overlapped), 7.16 (bd, $J = 7.2$ Hz, 2H), 5.89 (bs, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 243.4$, 202.9, 197.9, 149.8, 142.1, 135.3, 132.6, 129.6, 129.3, 128.5, 127.6, 127.3, 126.0, 124.3, 62.5; IR (KBr): 2924, 2060, 1921, 1682, 1512 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 586 (M^+), 558, 502, 474.

4.14. Compound **5f**

Red orange solid; m.p. 180 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.46$ (bs, 1H, NH), 7.65–7.53 (m, 3H overlapped), 7.42 (m, 2H), 7.14 (d, $J = 1.4$ Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 234.4$, 203.5, 198.1, 149.4, 149.2, 131.6, 131.2, 129.3, 127.8, 126.1, 34.8; IR ($CHCl_3$): 2926, 2063, 1930, 1692, 1560, 1206, 772 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 510 (M^+), 482 ($M^+ - CO$), 426 ($M^+ - 3CO$).

4.15. Compound **5g**

Yellow solid; m.p. 185 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.30$ (bs, 1H, NH), 7.62–7.52 (m, 3H overlapped), 7.40 (m, 2H), 7.08 (d, $J = 1.5$ Hz, 1H), 3.84 (q, $J = 7.1$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 234.2$, 203.6, 198.1, 149.3, 148.9, 131.7, 130.9, 129.2, 127.6, 126.6, 42.7, 13.6; IR ($CHCl_3$): 3019, 2061, 1929, 1685, 1560, 1216, 770 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 524 (M^+), 496 ($M^+ - CO$), 440 ($M^+ - 3CO$), 412 ($M^+ - 4CO$).

4.16. Compound **5h**

Orange solid; m.p. 158–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.09$ (bs, 1H, NH), 7.63–7.52 (m, 3H overlapped), 7.39 (m, 2H), 7.07 (bs, 1H), 3.73 (m, 2H), 1.64 (m, 2H), 0.78 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 229.0$, 198.1, 192.9, 144.2, 143.3, 126.5, 125.6, 123.9, 122.4, 121.0, 43.4, 24.5, 16.5. IR (KBr): 3433, 2923, 2060, 1905, 1704, 1566, 1458, 1064, 586 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 538 (M^+), 509, 454, 426.

4.17. Compound **5i**

Orange solid; m.p. 178 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.2$ (bs, 1H, NH), 7.62–7.53 (m, 3H overlapped), 7.40 (m, 2H), 7.07 (d, $J = 1.4$ Hz, 1H), 3.77 (m, 2H), 1.60 (m, 2H), 1.16 (m, 2H), 0.78 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 234.1$, 203.4, 198.1, 149.4, 148.7, 131.7, 130.8, 129.1, 127.7, 126.3, 47.0, 30.2, 19.7, 13.2; IR (KBr): 2962, 2360, 1905, 1697, 1566, 1458, 1072 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 552 (M^+), 524 ($M^+ - CO$), 468 ($M^+ - 3CO$), 440 ($M^+ - 4CO$), 412 ($M^+ - 5CO$).

4.18. Compound **5l**

Orange solid; m.p. 179 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.50$ (bs, 1H, NH), 7.59 (m, 1H), 7.53 (m, 2H), 7.41 (m, 2H), 7.10 (bd, $J = 1.4$ Hz, 1H), 5.82 (1H, ddt, $J = 17.0$, 10.2, 5.6 Hz), 5.26 (1H, bd, $J = 10.2$ Hz), 5.01 (bd, $J = 17.0$ Hz, 1H), 4.37 (bd, $J = 5.6$ Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 235.2$, 203.5, 198.0, 149.1, 148.8, 131.3, 130.9, 130.4, 128.9, 127.8, 126.5, 119.4, 49.3; IR (KBr): 2924, 2060, 1905, 1705, 1566, 1458 cm^{-1}; ES-MS ^{184}W *m/z*: 537 [$(M + H)^+$], 509 [$(M + H)^+ - CO$], 481 [$(M + H)^+ - 2CO$], 453 [$(M + H)^+ - 3CO$], 425 [$(M + H)^+ - 4CO$].

4.19. Compound **5m**

Solid; m.p. 160–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 10.8$ (bs, 1H, NH), 7.55 (m, 1H), 7.45 (m, 2H), 7.29–7.21 (m, 6H overlapped), 7.10 (m, 1H), 6.92 (m, 2H), 5.04 (bs, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 243.6$, 203.2, 198.0, 149.2, 148.8, 134.7, 131.5, 130.9, 129.0, 128.8, 128.2, 127.9, 127.3, 126.5, 49.9; IR (KBr): 3464, 2924, 2060, 1929, 1689, 1458 cm^{-1}; EI-MS (70 eV) ^{184}W *m/z*: 586 (M^+), 558 ($M^+ - CO$), 502 ($M^+ - 3CO$), 474 ($M^+ - 4CO$), 446 ($M^+ - 5CO$).

4.20. Compound 7

Deep red oil; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.55$ (m, 1H), 7.50 (m, 2H), 7.39 (m, 2H), 7.09 (s, 1H), 5.80 (ddt, $J = 17.2$, 10.4, 5.5 Hz, 1H), 5.29 (dd, $J = 15.0$, 4.9 Hz, 1H), 5.22 (bd, $J = 10.4$ Hz, 1H), 4.98 (bd, $J = 17.2$ Hz, 1H), 4.65 (m, 1H), 4.35–4.27 (m, 3H overlapped), 3.48 (d, $J = 13.2$ Hz, 1H), 3.43 (d, $J = 8.8$ Hz 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 240.5$, 212.1, 209.4, 202.7, 202.4, 148.3, 147.7, 131.9, 130.9, 130.7, 128.9, 127.9, 123.2, 119.1, 70.7, 59.9, 58.5, 49.8; IR ($CHCl_3$): 2924, 2060, 2021, 1910, 1692, 1565, 768 cm^{-1}; EI-MS (70 eV) ^{184}W m/z: 548 (M^+), 532, 507, 503.

4.21. Compound 8

Solid; m.p. 104 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 10.55$ (bs, 1H, NH), 7.76–7.54(m, 6H overlapped), 5.25 (m, 1H), 4.64 (m, 1H), 4.26 (m, 1H), 3.48–3.43 (m, 2H overlapped); ES-MS ^{184}W m/z: 509 [$(M + H)^+$], 487, 480, 457.

4.22. Compound 9

Red solid; m.p. 140–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.37$ (bs, 1H), 7.57–7.45 (m, 5H overlapped), 6.80 (s, 1H), 4.92 (q, $J = 7.3$ Hz, 2H), 4.32 (bd, $J = 6.8$ Hz, 1H), 3.49 (m, 1H), 1.73 (t, $J = 7.3$ Hz, 3H), 1.66 (m, 2H), 1.47 (m, 2H), 1.30–1.18 (m, 4H overlapped), 0.90 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 293.5$, 203.6, 198.1, 151.8, 142.4, 135.3, 131.2, 129.1, 128.4, 128.3, 78.7, 49.4, 32.6, 25.2, 24.2, 15.3; IR (KBr): 2931, 2060, 1913, 1535, 1211 cm^{-1}; ES-MS ^{184}W m/z : 647 [$(M + Na)^+$], 619 [$(M + Na)^+ - CO$], 591 [$(M + Na)^+ - 2CO$].

4.23. Compound 10

See Ref. [2].

4.24. Compound 11

Deep red solid; m.p. 130 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.78$ (m, 2H), 7.63 (m, 3H), 7.28 (bs, 1H), 4.24 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 262.8$, 223.8, 217.5, 149.3, 139.3, 132.2, 130.4.

4.25. Compound 12

Red solid; m.p. 158 °C dec.; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 11.42$ (bs, 1H), 7.59 (m, 3H overlapped), 7.44 (m, 2H), 7.11 (bs, 1H), 3.37 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 259.1$, 223.6, 217.3, 148.6, 145.9, 131.6, 131.1, 129.3, 128.1, 124.2, 34.7; IR (KBr, $CHCl_3$): 3107, 2956, 2057, 1989, 1926, 1903, 1686, 1562, 665 cm^{-1}.

4.26. Compound 13

Orange solid; m.p. 164–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.58$ (s, 1H), 4.14 (s, 3H), 3.56 (s, 3H), 0.48 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 238.3$, 203.8, 199.3, 149.7, 132.6, 47.8, 37.7, −1.0; IR (CH_2Cl_2): 2960, 2059, 1967, 1930, 1693, 1542 cm^{-1}.

4.27. Compound 14

Brown solid; m.p. 131–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.45$ (d, $J = 6.9$ Hz, 1H), 6.87 (d, $J = 6.9$ Hz, 1H), 4.16 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 243.2$, 203.7, 198.3, 134.4, 125.1, 47.8, 38.8; IR (CH_2Cl_2): 2063, 1970, 1929, 1701, 1611 cm^{-1}.

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