Multicomponent Synthesis of Uracil Analogues Promoted by Pd-Catalyzed Carbonylation of α-Chloroketones in the Presence of Isocyanates and Amines

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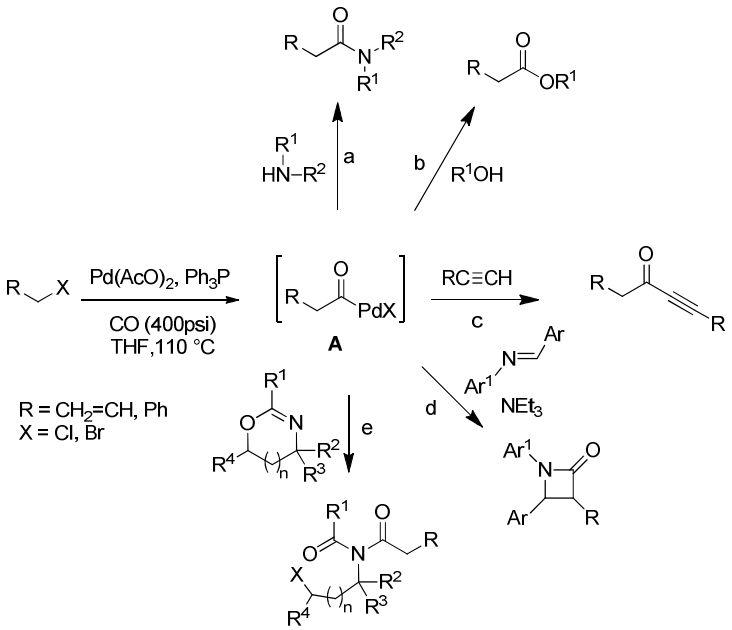
Abstract:

A short and efficient one-pot synthesis of uracil derivatives with a high structural variability is described. The process is a multicomponent reaction based on a palladium-catalyzed carbonylation of α-chloroketones in the presence of primary amines and isocyanates. In most cases, when the formation of unsymmetrical *N*,*N*'-disubstituted uracil derivatives can occur, the methodology demonstrates to be highly regioselective. A mechanistic hypothesis involving β-dicarbonyl palladium intermediates and urea derivatives, generated *in situ*, has been discussed.

Introduction

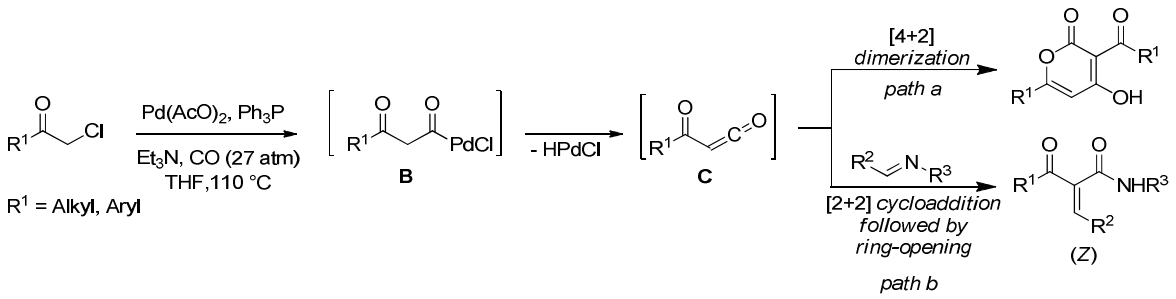
The increasing attention paid by modern organic chemists to economic and ecological issues has oriented their investigations towards the discovery of new sustainable processes.[1] In this context, the multicomponent reactions (MCRs), can be considered as a very powerful synthetic tool that takes into account efficiency, selectivity, molecular diversity and, in particular, atom-economy.[2] Simply by combining at least three starting materials, the MCR produces selectively and in a one-pot process a new product. The latter incorporates, if not all, at least the most part of the atoms of the reagents. All these features probably make the MCR the ideal alternative to sequential multistep synthesis.

In the recent past, our research group was interested in the reactivity of acyl-palladium intermediates (**A**, Scheme 1) generated *in situ* by means of Pd-catalyzed carbonylation of allyl and benzyl halides; such key intermediates were successfully coupled to amines, alcohols and acetylenes to obtain amides (*path a*),[3] esters (*path b*)[4] and acetylenic ketones (*path c*),[5] respectively. Moreover, an interesting reactivity was observed in the coupling reactions of **A** with imines (*path d*) and heterocycles containing a C–N double bond (*path e*) to give *β*-lactams[6] and *N*-(2-chloroethyl)imides,[7] respectively (Scheme 1).



Scheme 1. Synthetic utility of acyl-palladium species **A** in the synthesis of acyclic and cyclic carbonyl compound.

More recently we have also verified that the Pd-catalyzed carbonylation of other unsaturated halides such as *α*-chloroketones constitutes an efficient method to generate valuable *β*-dicarbonyl palladium chloride intermediates (**B**, Scheme 2).[8] We supposed that these palladium species, when generated in the presence of triethylamine, can convert to ketenes (**C**) that are very useful reagents in cycloaddition reactions. In fact, the postulated intermediate **C** was successfully employed for the synthesis of 3-acyl-4-hydroxy-2-pyranones (*path a*)[8a] *via* a dimerizative [4+2] cycloaddition and also coupled with aromatic imines, to yield, *in* a [2+2] cycloaddition, (*Z*)-configured *α*-alkylidene-*β*-oxoamides (*path b*)[8b] with a high stereoselectivity (Scheme 2).



Scheme 2. Synthesis of 3-acyl-4-hydroxy-2-pyranones (*path a*) or α-alkylidene-β-oxoamides *via* Pd-catalyzed carbonylation of α-chloroketones (*path b*).

Results and Discussion

In line with our research work we then investigated the reactivity of β-dicarbonyl palladium species **B** towards isocyanates as a potential partner for the cycloaddition reaction with *in-situ* generated ketenes **C** (Scheme 2).

The first reaction was performed according to the following experimental details: phenylisocyanate (1 mmol), chloroacetone (1 mmol), NEt_3 (3 mmol), $Pd(OAc)_2$ (0.04 mmol) and PPh_3 (0.16 mmol) were dissolved in THF (15 mL); the resulting mixture was placed in an autoclave, under CO pressure (27 atm), and heated at 110 °C for 15 hours. After this time, the TLC analysis of the reaction mixture showed almost complete disappearance of the phenylisocyanate, while a new major product with *m/z* = 278 appeared, as indicated by GC/MS analysis, beside a minor one with a *m/z* = 243. After column chromatography on silica-gel, both products were isolated and the resulting spectroscopic investigation agreed with the heteroaromatic structures **3a**[9] and **4a**[10] showed in Table 1 (entry 1).

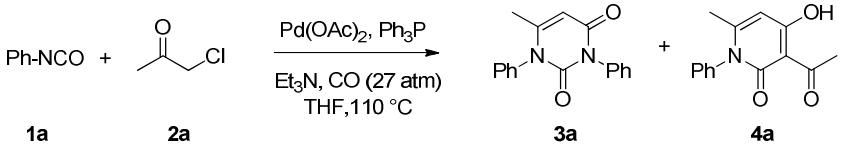
It is noteworthy that the product **3a** is an uracil derivative; uracil analogues are known to exhibit remarkable biological activities such as cytostatic, antiviral, antagonists of GnRH (Gonadotrophin-Releasing Hormone) just to cite few of their most relevant pharmacological roles.[11]

Encouraged by the significant synthetic value of the process and by its complete novelty as a three component reaction (isocyanate, chloroketone, CO), we started a survey of the experimental conditions to clarify

the reaction mechanism and find out the most critical parameters influencing the chemoselectivity of the reaction in favour of the uracil analogues **3a**. For this end a series of experiments were carried out and reported in Table 1.

At first glance it might seem possible to improve the yield of **3a** just by increasing the amount of phenylisocyanate respect to the chloroacetone because of the presence of two phenyl rings in the **3a** structure, but, unfortunately, the experiments described in entries 2-3 (Table 1) clearly demonstrated that the two and three-fold excess of phenylisocyanate scarcely influenced the chemoselectivity of the reaction (ratio **3a**/**4a** = 62/38 and 65/35 respectively); however, we noticed a slight improvement of the total yield (46 and 55% respectively).

Table 1. Examination of the experimental conditions for the carbonylative coupling between chloroacetone and phenylisocyanate.[a]



1a **2a** **3a** **4a**

Entry	Isocyanate **1a** (equiv.)	Chloroacetone **2a** (equiv.)	Total Yield[b] (%)	Ratio **3a**/**4a**
1	1	1	37	60/40
2	2	1	46	62/38
3	3	1	55	65/35
4	1	2	25	55/45
5	1	3	34	47/53
6	1	1	N.R.[c]	–
7	1	Acetone (1)[d]	N.R.	–
8	$PhNH_2$ (1)[e]	1	N.R.	–

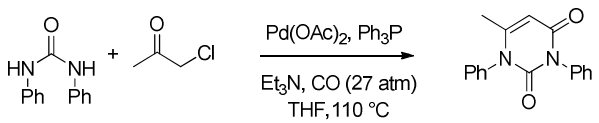
[a]Reagents and conditions on 1 mmole scale: phenylisocyanate (1.0 to 3.0 mmol), chloroacetone (1.0 to 3.0 mmol), NEt_3 (3.0 mmol), $Pd(OAc)_2$ (0.04 mol%), PPh_3 (0.0 to 0.16 mol%), CO (27 atm), THF (15 mL), 110 °C, 15 hours. All reactions were run in duplicate. [b]Calculated by GC analysis of the crude reaction mixture bymeans of internal standard (decane) technique. [c]Reaction performed under N_2 atmoshpere, without CO. [d]Acetone (1 mmol) was used instead of chloroacetone. [e]Aniline (1 mmol) was used instead of phenylisocyanate.

Alternatively, we tried to direct the reaction towards the formation of **4a** by increasing the amount of carbonyl compound (entries 4 and 5, Table 1), since a simple analysis of **4a** structure seems to indicate that two equivalents of chloroketone and only one of phenylisocyanate are necessary to its formation. Also in this case, we found a poor variation of the chemoselectivity of the process being the ratio **3a**/**4a** nearly equimolar (entry 4, Table 1). However, an inversion of the trend was observed by using a three fold excess of chloroacetone (entry 5, Table 1, ratio **3a**/**4a** = 47/53). In both cases, an erosion of the total yield was also observed (25 and 34% respectively).

Subsequently, we examined the hypothesis that the compound **3a** could be formed from 2 equiv. of phenylisocyanate and 1 equiv. of chloroacetone without the participation of carbon monoxide; to this goal, we performed the reaction under a nitrogen atmosphere, as indicated in entry 6 (Table 1). No new product could be detected, suggesting that a Pd-catalyzed carbonylation is essential for the formation of both heterocycles **3a** and **4a**.

Supposing that acetone instead of chloroacetone could participate in the reaction, and having previously found that palladium(0) can promote the dehalogenation of α-chloroketones,[8a,12] in a further experiment acetone was used in place of chloroacetone (entry 7, Table 1). Also in this case no new product was formed. Moreover, it is known that hydrolysis of isocyanates can easily occur[13] leading to carbamic acid derivatives that can smoothly decarboxylate to produce the corresponding amines; for this reason we performed an experiment starting from aniline instead of phenylisocyanate, but no uracil derivative was detected by ^{1}H NMR analysis of the crude reaction mixture (entry 8, Table 1).

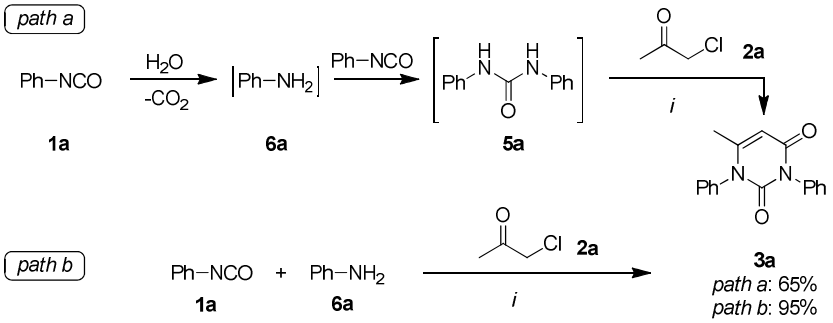
Looking at the molecular structure of **3a** it is possible to recognize an urea motif. For this reason we performed a carbonylation experiment by replacing the phenylisocyanate with the *N*,*N*′-diphenylurea **5a**, in the presence of 1 equivalent of chloroacetone (Scheme 3). To our delight, the product **3a** formed in 65% yield as sole product beside a not negligible amount of unreacted *N*,*N*′-diphenylurea (30%).



5a **2a** **3a** (65%)

Scheme 3. Synthesis of **3a** starting from urea **5a** and chloroacetone **2a**.

On the basis of the collected data (Table 1 and Scheme 3), we hypothesized that the *in situ* formation of the *N,N'*-diphenylurea **5a** from phenylisocyanate is a key step in our multicomponent process; particularly, the partial hydrolysis of the isocyanates **1a** (Scheme 4, *path a*),[13] caused by traces of water in the reaction medium, could form aniline **6a** that performs a nucleophilic attack to the remaining phenylisocyanate affording the urea **5a**.



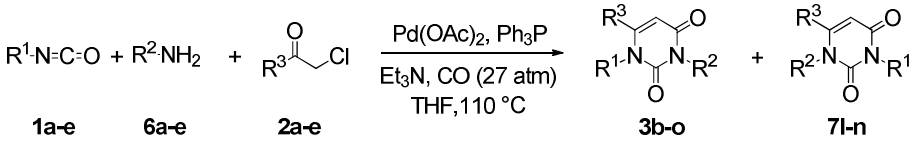
Scheme 4. Synthesis of **3a** starting from either isocyanates **1a** (*path a*) or a mixture of **1a** and **6a** (*path b*). Reaction conditions and reagents (*i*): $Pd(OAc)_2$, Ph_3P, Et_3N, CO (27 atm), THF, 110 °C, 15 hours (*path a*) or 10 hours (*path b*).

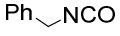
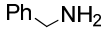
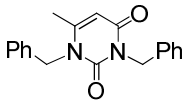
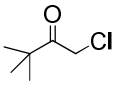
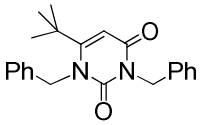
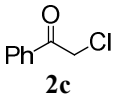
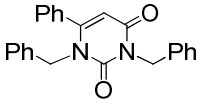
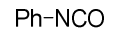
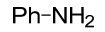
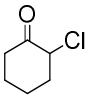
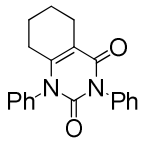
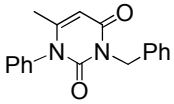
A confirmation of our hypothesis occurred by introducing one equivalent of a primary amine (aniline) in the reaction mixture. Specially, converting the process from three to four components (isocyanate, amine, chloroketone, CO) we found the best experimental conditions. Indeed, a sensible improvement of the reaction yield (95%) and chemoselectivity in favor of **3a** (Scheme 4, *path b*) was achieved in a shorter time (10 hours). The addition of the primary amine as a further reaction component, increased the synthetic potential of our MCR process because a wider molecular diversity can be reached.

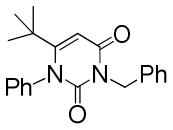
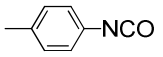
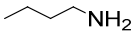
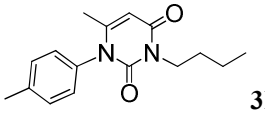
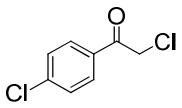
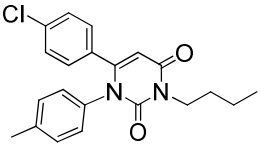
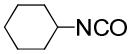
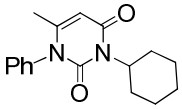
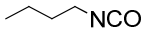
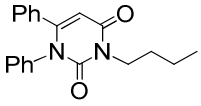
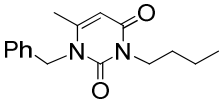
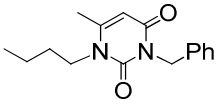
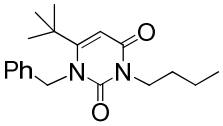
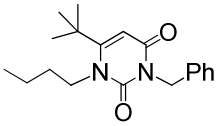
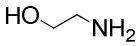
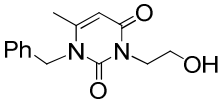
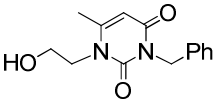
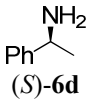
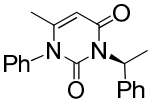
With the aim to investigate the scope and limitations of our Pd-catalyzed MCR, a number of aliphatic and aromatic isocyanates **1a-e**, amines **6a-e** and α-chloroketones **2a-e** were employed (Table 2). The best experimental conditions settled for the synthesis of **3a** (see Scheme 4, *path b*) were applied for the preparation of a large number of variously *N*- and *C*-substituted uracil analogues (**3b-o** and **7l-n**, Table 2).

Our initial goal was to investigate the efficiency of the methodology starting from equally substituted isocyanates and amines to yield symmetrical ureas and then avoiding any problems of regioselectivity. The employment of benzyl isocyanate **1b** and benzyl amine **6b**, in the reactions with the ketones **2a-c**, gave the corresponding desired products **3b-d** in good to excellent yield (70-95%, entries 1-3, Table 2). It is noteworthy that the carbonylative coupling occurred smoothly also in the presence of both a bulky aliphatic group (i.e. R^3 = *t*-Bu, entry 2, Table 2) and an aromatic ring (i.e. R^3 = Ph, entry 3, Table 2) on the α-chloroketone **2**.

Table 2. Multicomponent synthesis of uracil analogues **3b-o**, **7l-n**.[a]



Entry	Isocyanate **1**	Amine **6**	Chloroketone **2**	Product **3** (Yield%)[b]	Product **7** (Yield%)[b]
1	 **1b**	 **6b**	 **2a**	 **3b** (95)	–
2	**1b**	**6b**	 **2b**	 **3c** (70)	–
3	**1b**	**6b**	 **2c**	 **3d** (70)	–
4	 **1a**	 **6a**	 **2d**	 **3e** (90)	–
5	**1a**	**6b**	**2a**	 **3f** (85)	–

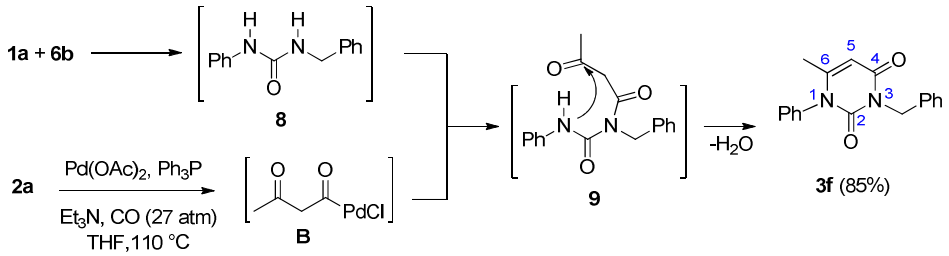
6	**1a**	**6b**	**2b**	 **3g** (60)	
7	 **1c**	 **6c**	**2a**	 **3h** (91)	–
8	**1c**	**6c**	 **2e**	 **3i** (60)	–
9	 **1d**	**6a**	**2a**	 **3j** (85)	–
10	 **1e**	**6a**	**2c**	 **3k** (46)	–
11	**1b**	**6c**	**2a**	 **3l** (38)[c]	 **7l** (57)[c]
12	**1b**	**6c**	**2b**	 **3m** (43)	 **7m** (43)
13	**1b**	 **6e**	**2a**	 **3n** (38)	 **7n** (38)
14	**1a**	 (*S*)-**6d**	**2a**	 **3o** (95), ee (98%)[d]	–

[a]Reagents and conditions: isocyanate **1** (1.0 mmol), chloroketone **2** (3.0 mmol), amine **6** (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol), PPh_3 (0.32 mmol), Et_3N (2 mmol), CO (27 atm), dry THF (15 mL), 110 °C, 10 hours. [b]After isolation by column chromatography on silica gel. [c]Inseparable mixture of isomers. Yield determined by ^1H NMR after column chromatography on silica gel. [d]The optical purity of (–)-**3o** was determined *via* ^1H NMR by means of shift reagent technique (see Experimental Section).

The use of 2-chlorocyclohexanone **2d**, as a model cyclic chloroketone, proved to be equally viable providing the bicyclic uracil analogue **3e** in a very good yield (90%, entry 4, Table 2).

Our attention was then turned towards the investigation of the carbonylative coupling in the presence of differently substituted isocyanates and amines to produce, *in situ*, unsymmetrical ureas. These last ones, reacting with chloroketones and CO, under Pd-catalysis, could provide two isomeric uracils. Conversely, we were pleased to find that the Pd(0)-catalyzed MCR of chloroacetone **2a** with phenylisocyanate **1a,** benzylamine **6b** and CO led to the product **3f** in 85% yield (entry 5, Table 2) as a sole isomer.[14] Its structure was established both by ^{1}H, ^{13}C, GC-MS and ^{1}H-^{1}H 2D NOESY experiments.

On the basis of the last experiment (entry 5, Table 2), we hypothesize that the unsymmetrical urea **8**, formed *in situ* from **1a** and **6b** (Scheme 5), was acylated only at the alkyl-substituted nitrogen because of its better nucleophilicity, to produce the intermediate **9** in a selective manner. The subsequent intramolecular nucleophilic attack of the aryl-substituted nitrogen produces, after elimination of the water, the product **3f** (Scheme 5).



Scheme 5. Mechanistic hypothesis for the observed regioselective formation of 1-aryl 3-alkyl substituted uracil **3f**.

In order to assay our hypothesis, a number of experiments was performed by using aromatic isocyanates and aliphatic amines (entries 6-8) or, complementarily, aliphatic isocyanates with aniline (entries 9-10, Table 2). In all cases, the formation of the predicted 1-aryl 3-alkyl uracil derivative **3g-k**, as the only regioisomer, in moderate to good yields (46-91%) was observed.

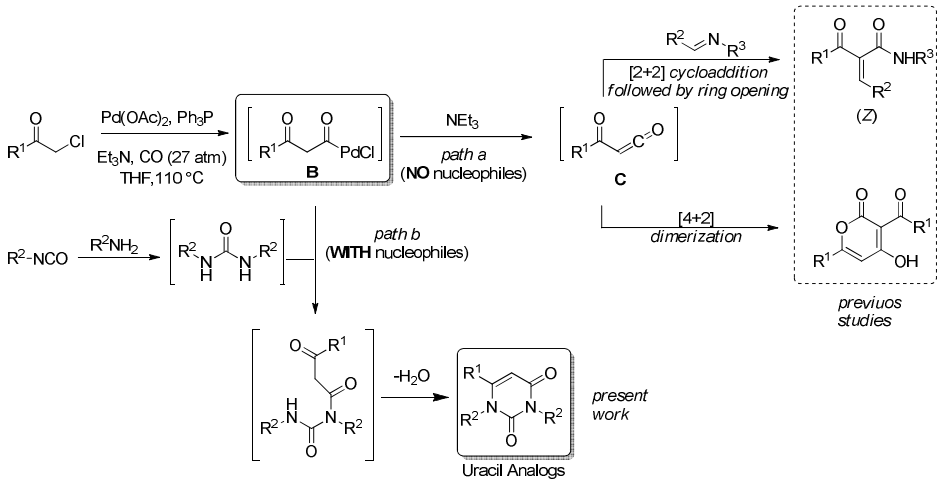
Encouraged by the above mentioned results, we probed the scope of the reaction with regard to the presence of a non-symmetrical *N*,*N*′-dialkyl substituted urea generated *in situ*. Two experiments were performed by employing the aliphatic isocyanate **1b** and the alkylamine **6c**, in the presence of the ketones **2a-b** (entries 11-12, Table 2). Although these reactions provided the uracil analogues in good overall yields (86-95%), no

regioselectivity was observed. Indeed, a nearly equimolar mixture of the regioisomers **3l-m** and **7l-m** was isolated after column chromatography.

We then wondered if our methodology would be effective in the preparation of uracil analogues bearing an hydroxyl group; this could be an important aspect for the synthesis of uracil nucleoside derivatives. We were pleased to find that a couple of *N*-(2-hydroxyethyl) substituted uracil analogues **3n** (yield: 38%) and **7n** (yield: 38%), were formed by our Pd-carbonylation reaction, starting from ethanolamine **6e**, benzylisocyanate **1b** and chloroacetone **2a** (entry 13, Table 2).

Finally, a simple experiment was carried out to check if an enantiopure uracil derivative could be also synthesized. As shown in entry 14 (Table 2), the carbonylative coupling of chloroacetone **2a** with enantiomerically pure (*S*)-1-phenylethylamine **6d** and benzyl isocyanate **1b**, gave straightforwardly the product (−)-**3o** as the sole regioisomer in very good yield (95%) and with the same optical purity of the starting amine (*S*)-**6d**.

On the basis of our previous results and the experiments presented herein, some considerations about the reactivity of the *β*-oxoacyl-palladium intermediate **B** (Scheme 6) can be carried out. In a recent study, we have found that the Pd-catalyzed carbonylation of *α*-cloroketones in the presence of imines gave *α*-alkylidene *β*-oxoamides,[8b] whereas the simple carbonylation of *α*-chloroketones with CO and a Pd(0) source gave 3-acyl-4-hydroxy-2-pyranones[8a] (Scheme 6). We hypothesize that, in the absence of a nucleophile, the dicarbonyl palladium intermediate **B** is involved in a *β*-elimination reaction promoted by NEt_3 to afford the ketene **C**, a key intermediate for the subsequent [2+2] and [4+2] cycloaddition reactions (*path a*, Scheme 6).

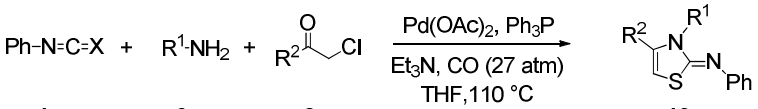


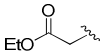
Scheme 6. Reactivity of the dicarbonyl palladium species **B** in the absence of nucleophiles (*path a*) or in the presence of *N*,*N*′-disubstituted urea derivatives as nucleophilic reagents (*path b*).

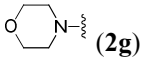
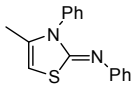
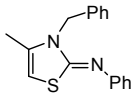
On the contrary, the acylpalladium **B** behaves differently when it is formed in the presence of nucleophiles,[3a,b] such as the *in situ* generated ureas derived from amines and isocyanates (*path b*, Scheme 6). Specifically, the strong electrophilic character of the carbonyl group bound to palladium, in structure **B**, should promote the acylation of the nucleophile providing, after a condensation reaction, the uracil analogues described in the present work (Scheme 6).[15]

In a further expansion of the applicability of our MCR, we employed functionalized chlorinated carbonyl compounds as substrates for the carbonylation process or isothiocyanates as precursors of thiourea derivatives (Table 3).

Table 3. Pd-catalyzed carbonylation attempts on functionalized carbonyl compounds **2f,g** or isothiocyanate **1f**: synthesis of thiazol-2-imine derivatives **10**.[a]



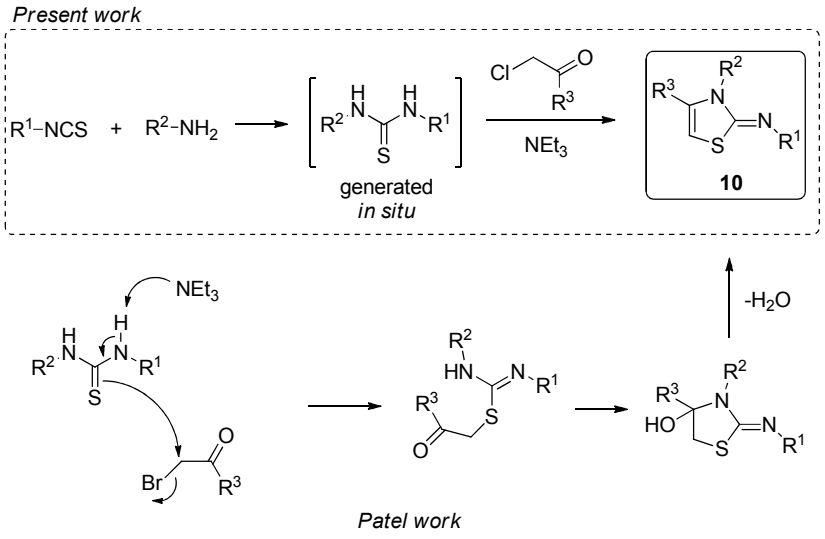
Entry	Iso(thio)cyanate**1**	Amine **6** R^1	Carbonyl compound **2** R^2	Product**10** (Yield %)[b]
1	**1a** (X = O)	Ph (**6a**)	 (**2f**)	–

2	**1a** (X = O)	$PhCH_2$(**6b**)	 (**2g**)	–
3	**1f** (X = S)	Ph (**6a**)	CH_3(**2a**)	 **10a**(95)
4	**1f** (X = S)	$PhCH_2$(**6b**)	CH_3(**2a**)	 **10b**(97)

[a]Reagents and conditions: iso(thio)cyanate **1** (1.0 mmol), chloroketone **2** (3.0 mmol), amine **6** (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol), PPh_3 (0.32 mmol), Et_3N (2.0 mmol), CO (27 atm), dry THF (15 mL), 110 °C, 10 hours. [b]After isolation by column chromatography on silica gel.

Unfortunately, in both cases no uracil analogues were detected. Particularly, in the reactions performed with ethyl 4-chloro-3-oxobutanoate **2f** (entry 1) or 2-chloro-1-morpholinoethanone **2g** (entry 2), as chlorinated carbonyl compounds, the starting reagents were quantitatively recovered (Table 3).

In the experiments with the isothiocyanate **1f**, chloroacetone **2a**, and amines **6a** or **6b**, two sulfur containing heterocyclic products **10a** or **10b** were formed in a very high yield (95-97%, entries 3-4, Table 3). Such thiazol-2-imine derivatives are obtained, presumably, by a simple nucleophilic attack of the *in situ* generated thiourea to the chloroacetone, without any participation of palladium and carbon monoxide (Scheme 7). This hypothesis has been formulated in analogy to the work reported by Patel *et al.* in which the thiazol-2-imine derivatives **10a,b** were formed starting from thiourea derivatives and α-bromoketones (Scheme 7).[16]



Scheme 7. Synthesis of thiazol-2-imine derivatives **10**.

Conclusions

In conclusion, this paper reports a new method for the synthesis of uracil analogues, which are valuable products showing a wide range of biological activities. The reaction is based on the Pd-catalyzed carbonylation of α-chloroketones in the presence of primary amines and isocyanates; in some cases, when *N*-aryl, *N*'-alkyl disubstituted ureas could be formed, the reaction showed a complete regioselectivity leading to only one uracil isomer.

Moreover, enantiopure amines can also be employed for this reaction to provide the desired optically active uracil analogue without the loss of any chiral purity from the starting amines.

We believe that the methodology described herein represents a good example of modern organic synthesis being a catalytic multicomponent reaction that allows the preparation of uracil derivatives with high structure variability, in a single synthetic step, starting from easily available substrates and with high atom economy.

Experimental Section

General methods

Isocyanates **1a-e,** α-chloroketones **2a-e**, primary amines **6a-e**, triethylamine (NEt_3), $Pd(AcO)_2$, PPh_3, were of commercial grade and used without further purification. THF was purified by distillation from sodium before use. Petroleum ether refers to the 40−60 °C boiling fraction. The ^1H and the ^{13}C NMR spectra were recorded at 400.13 MHz for ^1H and 100.62 MHz for ^{13}C, with $CDCl_3$ as the solvent and TMS as an internal standard (δ = 7.26 ppm for ^1H spectra; δ = 77.0 ppm for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer. Gas chromatography (GC) was conducted on an Rt_x-5 30-m fused silica capillary column (split ratio 100:1). The following program was used: method A = initial temperature of 100 °C for 0.0 min, ramp 10 °C/min to 280 °C, and hold for 15 min; the standard operating conditions were 300 °C injector temperature and 290 °C detector temperature. GC-MS analyses, conducted using method A, were performed with a gas chromatograph equipped with a 5% phenylpolymethylsiloxane capillary column, 30 m, 0.25 mm i.d., and a mass-selective detector operating at 70 eV. The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid Q-TOF mass spectrometer equipped with an ion-spray ionization source. MS (+) spectra were acquired by direct infusion

(5 mL min^{-1}) of a solution containing the appropriate sample (10 pmol mL^{-1}) dissolved in a solution 0.1% acetic acid, methanol/water (50:50) at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. TLC was performed on silica gel plates with F-254 indicator; viewing was by UV light (254 nm) or *p*-anisaldehyde and phosphomolybdic acid staining solution. Chromatographic separations were performed on silica gel (63−200 mesh) using petroleum ether/ethyl acetate (AcOEt) mixture as eluent. All reactions involving air-sensitive reagents were performed under an atmosphere of nitrogen in oven-dried glassware by using syringe/septum cap techniques.

The structure of unsymmetrical uracils **3f-o** and **7l-n** was established both by ^{1}H, ^{13}C, GC-MS and ^{1}H-^{1}H 2D NOESY experiments.

Enantiomeric purity assay for compound (−)-**3o** was carried out with both racemic and optically active substrates using ^{1}H NMR (400 MHz) in the presence of the chiral shift reagent Europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate], $Eu(hfc)_3$. The chromatographed product (10 mg) was dissolved in $CDCl_3$ (0.5 mL) and a solution of the shift reagent $Eu(hfc)_3$ (50 mg in 1 mL of $CDCl_3$) was sequentially added in small portions (50 μL) until the singlet at 5.70 ppm was split on two separated singlets. The enantiomeric excess was calculated from the integral values of two separated singlets.

General Procedure for the multicomponent synthesis of the uracil analogues 3a-o and 7l-n

A solution containing the isocyanate **1** (1.0 mmol), α-chloroketone **2** (3.0 mmol), primary amine **6** (1.5 mmol), $Pd(AcO)_2$ (9 mg, 0.04 mmol), PPh_3 (85 mg, 0.32 mmol) and NEt_3 (0.28 mL, 2.0 mmol) in anhydrous THF (15 mL) was placed in a 45 mL autoclave. The autoclave was purged, pressurized with CO (27 atm) and then heated at 110 °C under magnetic stirring, for 10 hours. After this time, the solution was cooled to room temperature and the solvent was removed under reduced pressure to give a crude material. The crude mixture was then purified by chromatography on silica gel [petroleum ether/AcOEt (90:10 to 50:50)] to obtain the corresponding uracil derivatives **3a-o** and **7l-n** as pure compounds.

1,3-Dibenzyl-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione **3d** is known and its characterization data resulted in agreement with those reported in the literature.[17]

Spectroscopic data for the uracil analogues **3a-c,e-o** and **7l-n** are reported below.

6-Methyl-1,3-diphenylpyrimidine-2,4(1H,3H)-dione (***3a***). Purification was carried out by column chromatography (petroleum ether/AcOEt 90:10 → 50:50) to afford the uracil analogue **3a** as a pure white solid (264 mg, 95%); mp 182–183 °C; R_f = 0.47 (petroleum ether/AcOEt 70:30); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.91 (s, 3H), 5.84 (s, 1H), 7.27–7.50 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 20.9,101,6, 128.2, 128.3, 128.4, 128.5, 129.1, 129.6, 132.7, 136.6, 152.0, 152.3, 162.3 ppm; FT-IR ($CHCl_3$): ν 3012, 2966, 2927, 2857, 1712, 1669, 1488, 1411, 1376 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 278 (80) $[M]^+$, 159 (100), 144 (50), 131 (45), 130 (60), 118 (40); 77 (75); HRMS (ESI): calcd. for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ 279.1134; found 279.1132.

*1,3-Dibenzyl-6-methylpyrimidine-2,4(1H,3H)-dione (**3b**)*. Purification was carried out by column chromatography (petroleum ether/AcOEt 80:20→60:40). This gave the uracil analogue **3b** as a pale yellow solid (291 mg, 95%); mp 72–73 °C; R_f = 0.55 (petroleum ether/AcOEt 80:20); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 2.30 (s, 3H), 5.07 (s, 2H), 5.16 (s, 2H), 5.64 (s, 1H); 7.11–7.48 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 19.3, 44.7, 48.0, 102.0, 126.4, 127.5, 127.8, 128.4, 128.9, 129.0, 136.1, 137.0, 151.9, 152.6, 162.1 ppm; FT-IR ($CHCl_3$): ν 3011, 2959, 2929, 2870, 1705, 1663, 1465, 1432 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 306 (95) $[M]^+$, 215 (16), 172 (75), 132 (18), 91 (100); HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_2$ $[M+H]^+$ 307.1447; found 307.1449.

1,3-Dibenzyl-6-tert-butylpyrimidine-2,4(1H,3H)-dione (***3c***). Purification was carried out by column chromatography (petroleum ether/AcOEt 70:30→80:20). This gave the uracil analogue **3c** as a pale yellow oil (244 mg, 70%); R_f = 0.65 (petroleum ether/AcOEt 70:30);^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.34 (s, 9H), 5.09 (s, 2H), 5.31 (s, 2H), 5.92 (s, 1H), 7.21–7.36 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 30.2, 36.1, 44.6, 50.0, 100.2, 127.2, 127.3, 128.3, 128.6, 128.7, 129.0, 138.1, 156.5, 161.9, 162.7 ppm; FT-IR ($CHCl_3$): ν 3030, 2971,

2936, 2876, 1698, 1654, 1440 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 348 (72) $[M]^+$, 257 (33), 214 (34), 152 (40), 91 (100); HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1917; found 349.1916.

*1,3-Diphenyl-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione (**3e**)*. Purification was carried out by column chromatography (petroleumether/AcOEt90:10 → 70:30) to give the uracil analogue **3e** as a yellow solid (286 mg, 90%); mp 190–171 °C; R_f = 0.52 (petroleum ether/AcOEt 70:30); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.68–1.72 (m, 4H), 2.03–2.11 (m, 2H), 2.48–2.56 (m, 2H), 7.26–7.52 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 21.1, 22.0, 22.1, 28.1, 109.6, 128.3*, 128.8, 129.1, 129.4, 129.5, 135.2, 136.5, 148.7, 151.6, 163.1 ppm, *two carbon atoms with identical chemical shift; FT-IR ($CHCl_3$): ν3012, 2946, 2934, 2863, 1704, 1652, 1490, 1438 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 318 (100) $[M]^+$, 240 (17), 199 (27), 198 (30), 143 (50), 77 (30); HRMS (ESI): calcd. for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1447; found319.1448.

*3-Benzyl-6-methyl-1-phenylpyrimidine-2,4(1H,3H)-dione (**3f**)*. Purification was performed by column chromatography (petroleum ether/AcOEt 80:20 → 60:40) to give the uracil analogue **3f** as a pale yellow solid (248 mg, 85%); mp 227–228 °C; R_f = 0.44 (petroleum ether/AcOEt 80:20); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.84 (s, 3H), 5.12 (s, 2H), 5.74 (s, 1H), 7.20–7.32 (m, 5H), 7.44–7.53 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 20.8, 44.4, 101.5, 127.6, 128.3, 128.5, 129.4, 129.5, 129.8, 136.9*, 151.6, 152.2, 162.3 ppm, *two carbon atoms with identical chemical shift; FT-IR ($CHCl_3$): ν 3009, 2956, 2930, 2855, 1707, 1663, 1447, 1416 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 292 (100) $[M]^+$, 160 (38), 159 (51), 130 (28), 77 (32); HRMS (ESI): calcd. for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1291; found 293.1293.

3-*Benzyl-6-tert-butyl-1-phenylpyrimidine-2,4(1H,3H)-dione* (***3g***). Purification was carried out by column chromatography (petroleum ether/AcOEt80:20→70:30). This gave the uracil analogue **3g** as a yellow oil (200 mg, 60%);R_f = 0.62 (petroleum ether/AcOEt 80:20);^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.34 (s, 9H), 5.10 (s, 2H), 5.99 (s, 1H), 6.96–7.56 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 30.2, 36.1, 44.7, 100.7, 127.5, 128.3, 128.6, 129.5, 129.7, 130.3, 136.7, 136.8, 153.2, 153.5, 162.7 ppm; FT-IR ($CHCl_3$): ν3030, 2966, 2936, 2875, 1701, 1654, 1447, 1444 cm^{-1};GC/MS (70 eV): *m/z* (%) = 334 (100) $[M]^+$, 186 (48), 167 (40), 144 (91), 77 (38);HRMS (ESI): calcd. for $C_{21}H_{23}N_2O_2$ $[M+H]^+$ 335.1760; found 335.1759.

*3-Butyl-6-methyl-1-p-tolylpyrimidine-2,4(1H,3H)-dione(**3h**)*. Purification was performed by column chromatography (petroleum ether/AcOEt70:30→60:40) to give the uracil analogue **3h** as a pale yellow solid (247 mg, 91%); mp 95–96 °C; R_f = 0.43 (petroleum ether/AcOEt 70:30);^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.92 (t, J = 7.4 Hz, 3H), 1.37 (sextet, J = 7.4 Hz, 2H), 1.60–1.68 (m, 2H), 1.85 (s, 3H), 2.40 (s, 3H), 3.94 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H), 5.70 (s, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.6, 20.1, 20.5, 21.0, 29.5, 41.1, 101.2, 127.9, 130.3, 134.1, 139.3, 151.8, 152.2, 162.5 ppm; FT-IR ($CHCl_3$): ν3010, 2962, 2932, 2874, 1701, 1623, 1513, 1450, 1433, 1420 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 272 (9) $[M]^+$, 255

(80), 216 (51), 173 (100), 144 (39), 91 (35);HRMS (ESI): calcd. for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ 273.1604; found 273.1605.

3-Butyl-6-(4-chlorophenyl)-1-p-tolylpyrimidine-2,4(1H,3H)-dione ***(3i)***. Purification was performed by column chromatography (petroleum ether/AcOEt 85:15→70:30) to give the uracil analogue **3i** as a pale yellow solid (221 mg, 60%); mp 110–111 °C; R_f = 0.47 (petroleum ether/AcOEt 85:15);^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.93 (t, J = 7.4 Hz, 3H), 1.39 (sextet, J = 7.4 Hz, 2H), 1.66–1.71 (m, 2H), 2.29 (s, 3H), 3.98–4.02 (m, 2H), 5.83 (s, 1H), 6.94 (d, J = 8.3 Hz, 2H), 7.04–7.08 (m, 4H), 7.17 (d, J = 8.5 Hz, 2H) ppm;^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.7, 20.3, 21.1, 29.6, 41.5, 103.3, 128.5, 128.8, 129.7*,131.9, 134.5, 135.6, 138.6, 152.0, 152.8, 162.2 ppm,*two carbon atoms with identical chemical shift; FT-IR ($CHCl_3$): ν3002, 2962, 2933, 2874, 1706, 1666, 1492, 1438 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 368 (12) $[M]^+$, 351 (100), 312 (75), 369 (81), 241 (96), 91 (51);HRMS (ESI): calcd. for $C_{21}H_{22}ClN_2O_2$ $[M+H]^+$ 369.1371; found 369.1373.

3-Cyclohexyl-6-methyl-1-phenylpyrimidine-2,4(1H,3H)-dione ***(3j)***. Purification was performed by column chromatography (petroleum ether/AcOEt 70:30→50:50) to give the uracil derivative **3j** as a white solid (241 mg, 85%); mp 122–123 °C; R_f = 0.45 (petroleum ether/AcOEt 70:30);^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 1.21–1.40 (m, 4H), 1.60–1.78 (m, 4H), 1,82 (s, 3H), 2.35–2.45 (m, 2H), 4.78–4.84 (m, 1H), 5.67 (s, 1H), 7.18–7.27 (m, 2H), 7.45–7.55 (m, 3H) ppm;^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 20.6, 25.2, 26.3, 28.4, 53.8, 101.7, 128.1, 128.5, 129.1, 129.7, 137.1, 151.1, 162.8 ppm; FT-IR ($CHCl_3$): ν3010, 2934, 2857, 1701, 1664, 1447, 1419 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 284 (3) $[M]^+$, 203 (100), 160 (13), 130 (13), 77 (15);HRMS (ESI): calcd. for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1604; found 285.1602.

3-Butyl-1,6-diphenylpyrimidine-2,4(1H,3H)-dione ***(3k)***. Purification was carried by column chromatography (petroleum ether/AcOEt 80:20 → 70:30) to give the uracil derivative **3k** as a yellow oil (147 mg, 46%); R_f = 0.58 (petroleum ether/AcOEt 80:20); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.82 (t, J = 7.4 Hz, 3H), 1.23–1.29 (m, 2H), 1.55–1.63 (m, 2H), 3.90–3.95 (m, 2H), 5.74 (s, 1H), 6.93–7.45 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.6, 20.1, 29.5, 41.4, 89.5, 128.0, 128.2, 128.4, 128.7, 129.0, 135.8, 137.1, 151.9, 154.0, 162.4 ppm; FT-IR ($CHCl_3$): ν 3013, 2962, 2930, 1687, 1661, 1598, 1446, 1416 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 320 (8) $[M]^+$, 264 (38), 221 (36), 193 (100), 77 (48); HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ 321.1604; found 321.1606.

1-Benzyl-3-butyl-6-methylpyrimidine-2,4(1H,3H)-dione ***(3l)*** and *3-benzyl-1-butyl-6-methylpyrimidine-2,4(1H,3H)-dione* ***(7l)***. Purification was carried by column chromatography (petroleum ether/AcOEt 70:30 →50:50) to give the uracil derivatives **3l** and **7l** as an inseparable mixture of isomers, yellow oil (258 mg, 95%); ratio **3l**/**7l** = 40/60 calculated by ^{1}H NMR; R_f = 0.41 (petroleum ether/AcOEt 70:30); ^{1}H NMR ($CDCl_3$, 400.13

MHz): δ 0.93–0.97 (m, 6H), 1.32–1.43 (m, 4H), 1.57–1.68 (m, 4H), 2.15 (s, 3H), 2.22 (s, 3H), 3.75–3.79 (m, 2H), 3.95–3.99 (m, 2H), 5.10 (s, 4H), 5.60 (s, 1H), 5.61 (s, 1H), 7.15–7.46 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.6, 13.7, 19.6, 19.8, 19.9, 20.1, 29.5, 30.8, 41.2, 44.2, 45.0, 47.7, 101.5, 101.9, 126.0, 127.3, 127.6, 128.2, 128.7, 128.9, 136.1, 136.9, 151.2, 151.4, 151.9, 152.4, 162.1 ppm; FT-IR ($CHCl_3$): ν 3010, 2964, 2935, 2876, 1699, 1659, 1466, 1445, 1430 cm^{-1}; *Minor isomer*, GC/MS (70 eV): *m/z* (%) = 272 (9) $[M]^+$, 255 (43), 216 (38), 215 (35), 91 (100); *Major isomer*, GC/MS (70 eV): *m/z* (%) = 272 (100) $[M]^+$, 257 (23), 216 (49), 199 (15), 91 (63); HRMS (ESI): calcd. for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ 273.1604; found 273.1607.

*1-Benzyl-6-tert-butyl-3-butylpyrimidine-2,4(1H,3H)-dione (**3m**)* and *3-benzyl-6-tert-butyl-1-butylpyrimidine-2,4(1H,3H)-dione (**7m**)*. Purification was carried out by column chromatography (petroleum ether/AcOEt 80:20 → 70:30) to afford the uracil analogue **3m** and **7m** as a pure compound. **3m**: pale yellow oil (135 mg, 43%); R_f = 0.52 (petroleum ether/AcOEt 80:20); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.93 (t, J = 7.4 Hz, 3H), 1.33–1.37 (m, 11H), 1.52–1.58 (m, 2H), 3.87–3.91 (m, 2H), 5.32 (s, 2H), 5.89 (s, 1H), 7.01–7.02 (m, 2H) 7.29–7.34 (m, 3H) ppm;^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.7,20.1, 30.3, 31.2, 36.0, 41.2, 50.0, 100.2, 124.9, 127.1, 128.7, 137.3, 152.7, 161.7, 162.8 ppm; FT-IR ($CHCl_3$): ν 3026, 2963, 2933, 2874, 1698, 1652, 1446cm^{-1}; GC/MS (70 eV): *m/z* (%) = 314 (20) $[M]^+$, 297 (33), 243 (25), 91 (100); HRMS (ESI): calcd. for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2073; found 315.2072. **7m**: pale yellow oil (135 mg, 43%); R_f = 0.59 (petroleum ether/AcOEt 80:20); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.95 (t, J = 7.5 Hz, 3H), 1.35–1.39 (m, 11H), 1.59–1.68 (m, 2H), 3.92–3.97 (m, 2H), 5.12 (s, 2H), 5.82 (s, 1H), 7.23–7.32 (m, 3H), 7.47–7.49 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 13.6,19.9, 30.0, 30.4, 36.1, 44.3, 47.1, 104.1, 127.4, 128.3, 129.0, 136.8, 152.8, 161.6, 162.9 ppm; FT-IR ($CHCl_3$): ν 3026, 2964, 2934, 2875, 1695, 1649, 1442 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 314 (100) $[M]^+$, 258 (65), 257 (55), 138 (67), 91 (90); HRMS (ESI): calcd. for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2073; found 315.2071.

*1-Benzyl-3-(2-hydroxyethyl)-6-methylpyrimidine-2,4(1H,3H)-dione (**3n**) and 3-benzyl-1-(2-hydroxyethyl)-6-methylpyrimidine-2,4(1H,3H)-dione (**7n**)*. Purification was carried out by column chromatography (petroleum ether/AcOEt 20:80) to afford the uracil analogue **3n** and **7n** as a pure compound. **3n**: yellow oil (99 mg, 38%); R_f = 0.50 (petroleum ether/AcOEt 20:80); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 2.16 (s, 3H), 2.85 (broad s, 1H, OH, exchange with D_2O), 3.85 (t, J = 5.1 Hz, 2H), 4.23 (t, J = 5.1 Hz, 2H), 5.10 (s, 2H), 5.64 (s, 1H), 7.20–7.38 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 19.9, 44.0, 48.1, 61.6, 102.0, 126.1, 127.5, 129.0, 135.7, 152.6, 153.3, 163.0 ppm; FT-IR ($CHCl_3$): ν 3015, 2963, 2927, 2856, 1697, 1657, 1465, 1431, 1355 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 260 (8) $[M]^+$, 217 (65), 91 (100); HRMS (ESI): calcd. for $C_{14}H_{17}N_2O_3$ $[M+H]^+$ 261.1240; found 261.1243. **7n**: yellow oil (99 mg, 38%); R_f = 0.58 (petroleum ether/AcOEt 20:80); ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 2.26 (s,

3H), 2.82 (broad s, 1H, OH, exchange with D_2O), 3.83 (t, J = 5.1 Hz, 2H), 3.95 (t, J = 5.1 Hz, 2H), 5.07 (s, 2H), 5.59 (s, 1H), 7.14–7.41 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 20.4, 44.3, 47.3, 60.6, 101.7, 127.8, 128.3, 128.8, 136.8, 152.3, 152.4, 162.2 ppm; FT-IR ($CHCl_3$): ν 3012, 2960, 2927, 2855, 1699, 1659, 1465, 1430, 1350 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 260 (100) $[M]^+$, 216 (38), 132 (15), 96 (81); HRMS (ESI): calcd. for $C_{14}H_{17}N_2O_3$ $[M+H]^+$ 261.1240; found 261.1242.

*(–)-(S)-6-Methyl-1-phenyl-3-(1-phenylethyl)pyrimidine-2,4(1H,3H)-dione (**3o**)*. Purification was carried by column chromatography (petroleum ether/AcOEt70:30 → 50:50) to give the uracil derivative (–)-**3o** as a yellow solid (291 mg, 95%); R_f = 0.43 (petroleum ether/AcOEt 70:30); $[\alpha]_D^{24}$ = −125.5 (c = 0.1, $CHCl_3$), ee = 98%; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.80 (s, 3H), 1.87 (d, J = 7.2Hz, 3H), 5.70 (s, 1H), 6.31 (q, J = 7.2Hz, 1H), 7.08–7.11 (m, 1H), 7.19–7.25 (m, 2H), 7.26–7.30 (m, 2H), 7.40–7.49 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 15.8,20.6, 50.4, 101.4, 126.9, 127.4, 127.9, 128.3, 128.5, 129.1, 129.6, 136.8, 140.2, 151.5, 162.6 ppm; FT-IR ($CHCl_3$): ν 3013, 1706, 1665, 1490, 1418 cm^{-1}; GC/MS (70 eV): *m/z* (%) = 306 (100) $[M]^+$, 202 (41), 160 (55), 159 (60), 105 (85), 77 (70); HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_2$ $[M+H]^+$ 307.1447; found 307.1445.

Supporting Information

Copies of NMR spectra for compounds **3a-o** and **7l-n** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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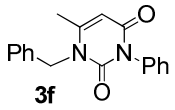
(14) No trace of the isomeric product **3f** was detected by ^{1}H-NMR analysis on the crude reaction mixture.



3f

(15) In principle, also the ketene **C** can act as an acylating agent to produce the *N*-acylated urea and then the corresponding uracil derivative after water elimination. Although this possibility, we believe that in the reaction conditions here described, the formation of the highly reactive ketene **C** is not favored. In fact, we have never found the product of ketene dimerization (2-pyranones derivatives) previously described (see reference 8a) probably because the intermediate **B** reacts very rapidly with the urea derivative.

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