molbank

MDPI

Short Note

3-Cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione

Francesco Messa [1], Serena Perrone [1,*] and Antonio Salomone [2,*]

[1] Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Prov.le Lecce-Monteroni, 73100 Lecce, Italy; francesco.messa@unisalento.it
[2] Dipartimento di Chimica, Consorzio CINMPIS, Università degli Studi di Bari "Aldo Moro", Via E. Orabona 4, 70125 Bari, Italy
* Correspondence: serena.perrone@unisalento.it (S.P.); antonio.salomone@uniba.it (A.S.)

Abstract: The synthesis of a novel uracil derivative, 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**), is reported via a four-component reaction involving an *α*-chloroketone (**1**), an aliphatic isocyanate (**2**), a primary aromatic amine (**3**) and carbon monoxide. The proposed reaction mechanism involves a Pd-catalyzed carbonylation of 2-chloro-1-phenylethan-1-one (**1**), leading to a *β*-ketoacylpalladium key intermediate, and, at the same time, in situ formation of non-symmetrical urea deriving from cyclohexyl isocyanate (**2**) and *p*-toluidine (**3**). After a chemo-selective acylation of the non-symmetrical urea and the subsequent cyclization of the acylated intermediate, 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**) is formed. Uracil derivative **4** was isolated in good yield (73%) and fully characterized by ^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC and 2D ^{1}H-^{13}C HMBC NMR, FT-IR spectroscopy and GC-MS spectrometry.

Keywords: carbonylation; uracil derivatives; palladium catalysis

check for updates

Citation: Messa, F.; Perrone, S.; Salomone, A. 3-Cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione. *Molbank* **2023**, *2023*, M1611. https://doi.org/10.3390/M1611

Academic Editor: Nicola Della Ca

Received: 10 March 2023
Revised: 22 March 2023
Accepted: 23 March 2023
Published: 28 March 2023

1. Introduction

Nitrogen heterocycles and specifically pyrimidines are widespread in many natural biologically active molecules. Uracil represents a valuable six-membered *N*-heterocycle (Figure 1a) that frequently occurs in nature due to one of the four nucleic bases of RNA [1]. In the discovery of new drugs, uracil derivatives are considered very fascinating molecules, both because of their synthetic accessibility and their drug-like properties thanks to the substituents connected at the N^1, N^3, C^5 and C^6 positions of the uracil ring [2].

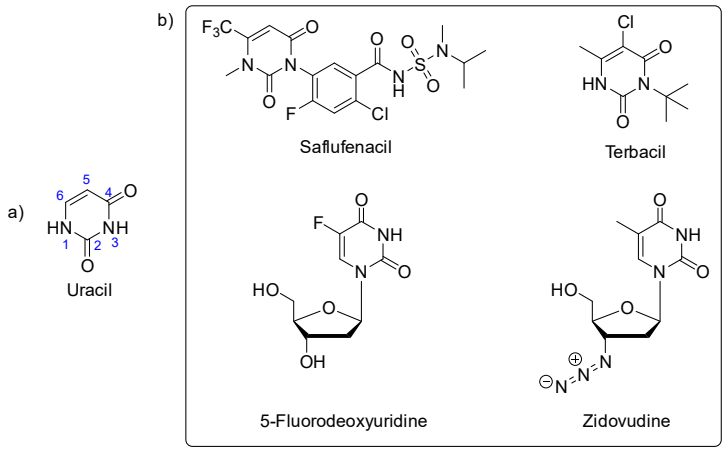
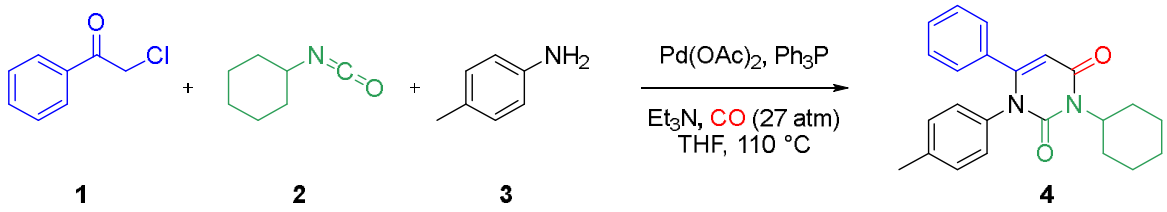


Figure 1. (**a**) Structure of the uracil nucleic base. (**b**) Examples of bio-active uracil derivatives: saflufenacil (herbicide); terbacil (pesticide); 5-fluorodeoxyuridine (anti-cancer agent); zidovudine (anti-HIV drug).

Uracil derivatives have a wide spectrum of pharmacological activities and clinical applications. For example, differently substituted uracils containing a benzoyl moiety exhibit herbicidal activity (saflufenacil, Figure 1b) [3] and alkyl-substituted uracils are often employed as pesticides for treatment of citrus and pineapple plantations (terbacil, Figure 1b) [4]. Regarding their pharmacological properties, many uracil-containing drugs have anti-cancer and antiviral activities (fluorodeoxyuridine and zidovudine, respectively, Figure 1b) [5].

There are many synthetic strategies to achieve the uracil heterocycle. Among the reported methods, the simplest one involves the hydrolysis process of cytosine by adding H_2O to produce uracil and ammonia [1]. However, the most widely used methodology to obtain uracil is via a condensation reaction between urea and maleic acid in fuming sulfuric acid [6]. Moreover, many heterocyclic scaffolds can be achieved by employing carbonylative processes, often palladium catalyzed [7–9].

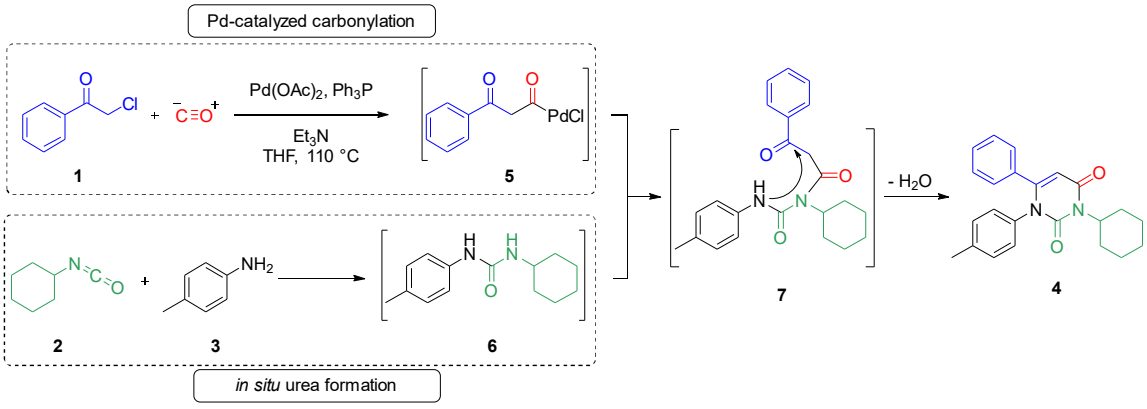
As part of our ongoing interest in the field of metal-catalyzed reactions [10–13] and more specifically of Pd-catalyzed carbonylative syntheses of heterocycles [14–16], herein the multicomponent synthesis of the novel uracil derivative 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**, Scheme 1) is reported. Heterocycle **4** was prepared via a palladium-catalyzed carbonylation reaction of *α*-chloroketone 2-chloro-1-phenylethan-1-one (**1**) in the presence of cyclohexyl isocianate (**2**) and *p*-toluidine (**3**) under a CO atmosphere [17] (Scheme 1).



Scheme 1. Pd-catalyzed multicomponent synthesis of the uracil derivative 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione **4**.

2. Results and Discussion

Regarding the reaction mechanism of the multicomponent synthesis of uracil derivative **4**, we hypothesize the following pathway: a Pd-catalyzed carbonylation of *α*-chloroketone **1** firstly affords the *β*-ketoacylpalladium intermediate **5**, that subsequently acylates the non-symmetrical urea **6** [18]. The latter was generated in situ from the nucleophilic addition of *p*-toluidine **3** to the cyclohexyl isocyanate **2** (Scheme 2).

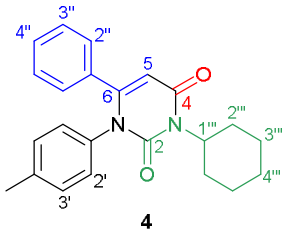


Scheme 2. Proposed mechanism for the four-component synthesis of uracil derivative **4**.

It should be emphasized that the acylation of urea **6** occurred chemoselectively only at the alkyl-substituted nitrogen atom. The observed selectivity was likely due to the higher

nucleophilicity of the alkyl-substituted nitrogen atom compared to the aryl-substituted nitrogen. The subsequent cyclization of intermediate **7**, promoted by an intramolecular nucleophilic attack of the aryl-substituted nitrogen to the carbonyl group, afforded the desired uracil derivative **4** through a condensation process [17] (Scheme 2). The resulting 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione **4** was isolated after column chromatography in 73% yield.

The uracil derivative 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione **4** was fully characterized by ^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC and 2D ^{1}H-^{13}C HMBC NMR, FT-IR spectroscopy and GC-MS spectrometry (see Supplementary Materials for copies of spectra). The ^{1}H NMR spectrum of uracil derivative **4**, recorded at 25 °C in $CDCl_3$ solution, shows the presence of a distinctive singlet proton at 5.81 ppm due to the vinylic proton, H-5, (Figure 2) of the uracil moiety, in analogy with the chemical shift of similar uracil derivatives reported in a previous work [17]. The signal at 4.87 ppm, a multiplet similar to a triplet of triplets, was attributed to the axial H1′″ bonded to the tertiary C-1′″ of the cyclohexyl substituent. This peak has multiplicity due to a vicinal axial–axial (ax–ax) coupling, ^{3}J = 12.2 Hz, and a vicinal axial–equatorial (ax–eq) coupling, ^{3}J = 3.8 Hz. Other protons belonging to the cyclohexyl ring appear in the spectrum as follows. (a) The two equivalents axial protons H-2′″ resonate at 2.46 ppm, the signal is a multiplet resembling a quartet of doublets. The multiplicity (qd) comes from three couplings of similar magnitude (12.2 Hz, one geminal (^{2}J), two vicinal (axial–axial) with H-3′″ and H-1′″) and a smaller coupling (^{3}J = 3.8 Hz) corresponding to a vicinal axial–equatorial interaction with H-3′″. (b) Four multiplets are observed in the range from 1.84 to 1.16 ppm relative to the remaining 8H of the cyclohexyl ring. (c) Finally, the singlet at 2.25 ppm was clearly assigned to the methylic protons of the *p*-tolyl moiety (see Supplementary Material for a copy of the ^{1}H NMR spectrum).



4

Figure 2. Structure of uracil derivative **4** with carbon atoms numbered.

The ^{13}C NMR spectrum shows the presence of four characteristic signals belonging to the carbons of the uracil ring: (1) The carbonyl carbon C4 resonates at 162.9, as confirmed by the coupling with protons H-5 and H-1′″ observed in the HMBC spectrum. (2) The carbonyl carbon C-2 resonates at 152.0 ppm and appears as a broad signal, likely because of the bonds with quadrupolar nuclei N-1 and N-2. Its proximity to the cyclohexyl ring was proven by an intense cross peak with the proton H-1′″ (HMBC). (3) The peak at 103.3 ppm was assigned to the C-5 of the uracil nucleus based on its coupling with H-5 observed in the HSQC spectrum. (4) The resonance of carbon C-6 was assigned to the peak at 153.9 ppm and confirmed by a cross peak with protons H-5 and H-2′′ (HMBC). (See Supplementary Materials for copies of the ^{13}C NMR, 2D HSQC and 2D HMBC spectra.)

3. Materials and Methods

3.1. General Methods

NMR spectra were recorded on a Bruker 500 MHz spectrometer and chemical shifts were reported in parts per million (δ). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet and br = broad. The FT-IR spectrum was recorded on a Perkin-Elmer 681 spectrometer. GC-MS analyses were performed on a HP 5995C model. Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F254, and visualization was accomplished by UV light

(254 nm) or by spraying a solution of 5% (*w*/*v*) ammonium molybdate and 0.2% (*w*/*v*) cerium(III) sulfate in 100 mL 17.6% (*w*/*v*) aq. sulfuric acid and heating to 473 K until blue spots appeared. Chromatography was conducted using silica gel 60 with a particle size distribution of 40–63 μm and 230–400 ASTM. Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and TCI (Tokyo Chemical Industry, Europe, N. V., Eschborn, Germany) and used without any further purification. Petroleum ether refers to the 40–60 °C boiling fraction.

*3.2. Synthesis of 3-Cyclohexyl-6-phenyl-1-(p-tolyl)pyrimidine-2,4(1H,3H)-dione (**4**)*

A solution containing cyclohexyl isocyanate **2** (125.2 mg, 128 μL, 1.0 mmol), 2-chloro-1-phenylethan-1-one **1** (463.8 mg, 3.0 mmol), *p*-toluidine **3** (160.7 mg, 1.5 mmol), $Pd(AcO)_2$ (trimeric, FW = 673.46, 4 mol%, 27.0 mg, 0.04 mmol), PPh_3 (83.9 mg,0.32 mmol) and NEt_3 (202.4 mg, 278 μL, 2.0 mmol) in anhydrous THF (15 mL) was placed in a 45 mL autoclave. The autoclave was purged three times and pressurized with CO at 27 atm. Then, the reactor was heated at 110 °C under magnetic stirring for 10 h. After this time, the reaction system was cooled to room temperature, carefully depressurized and the solvent was evaporated under reduced pressure to give a crude material. The crude mixture was purified by column chromatography on silica gel using petroleum ether/AcOEt 80:20 as the eluent, affording 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**) as a clear yellow oil (263.2 mg, 73% yield).

^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.24–7.22 (m, 1H), 7.19–7.16 (m, 2H), 7.11–7.10 (m, 2H), 7.04–7.03 (m, 2H), 6.95–6.93 (m, 2H), 5.81 (s, 1H), 4.87 (tt, *J* = 12.2, 3.8 Hz, 1H), 2.46 (qd, *J* = 12.2, 3.8 Hz, 2H), 2.25 (s, 3H), 1.84–1.82 (m, 2H), 1.73–1.63 (m, 3H), 1.39–1.37 (m, 2H), 1.21–1.16 (m, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 162.9, 153.9, 152.0, 138.2, 134.8, 133.5, 129.4, 129.3, 128.9, 128.3, 128.1, 103.3, 54.2, 28.4, 26.3, 25.3, 21.0; FT-IR (film, cm^{-1}): 2931, 2856, 1703, 1657, 1623, 1512, 1447, 1417, 1406, 1360, 1344, 815, 764, 728, 716, 697, 532; GC-MS (70 eV) *m*/*z*: 360 (M^+, 1), 279 (100), 235 (16), 207 (31), 194 (17), 91 (13), 77 (4), 65 (6), 55 (4).

4. Conclusions

The novel uracil derivative 3-cyclohexyl-6-phenyl-1-(*p*-tolyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4**) was synthetized through a four-component Pd-catalyzed reaction and isolated by column chromatography in good yield (73%). The uracil derivative **4** was fully characterized by ^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC and 2D ^{1}H-^{13}C HMBC NMR, FT-IR spectroscopy and GC-MS spectrometry.

Supplementary Materials: The following spectra are available online: ^{1}H NMR ($CDCl_3$, 500 MHz); ^{13}C NMR ($CDCl_3$, 125 MHz); 2D ^{1}H-^{13}C HSQC NMR ($CDCl_3$)—Aromatic portion; 2D ^{1}H-^{13}C HSQC NMR ($CDCl_3$)—Uracil portion; 2D ^{1}H-^{13}C HSQC NMR ($CDCl_3$)—Aliphatic portion; 2D ^{1}H-^{13}C HMBC NMR ($CDCl_3$)—Aromatic/Uracil portion; 2D ^{1}H-^{13}C HMBC NMR (CDCl3)—Aliphatic portion (selected); FT-IR (film); GC-MS (70 eV).

Author Contributions: A.S. and S.P. designed chemical synthesis, analyzed results, and wrote the manuscript. F.M. performed the experiments, analyzed results, and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data presented in this study are available in this article and Supplementary File.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Garrett, H.R.; Grisham, C.M. *Principles of Biochemistry with a Human Focus*; Brooks/Cole: Pacific Grove, CA, USA, 2001; ISBN 0-03-097369-4.
2. Newkome, G.R.; Paudler, W.W. *Contemporary Heterocyclic Chemistry: Syntheses, Reactions, and Applications*; Wiley: New York, NY, USA, 1982; ISBN 978-0-471-06279-0.

3. Yang, J.; Guan, A.; Wu, Q.; Cui, D.; Liu, C. Design, Synthesis and Herbicidal Evaluation of Novel Uracil Derivatives Containing an Isoxazoline Moiety. *Pest Manag. Sci.* **2020**, *76*, 3395–3402. [CrossRef] [PubMed]
4. Ivanova, B.; Spiteller, M. UV-MALDI Mass Spectrometric Quantitation of Uracil Based Pesticides in Fruit Soft Drinks along with Matrix Effects Evaluation. *Ecotoxicol. Environ. Saf.* **2014**, *100*, 233–241. [CrossRef] [PubMed]
5. Parker, W.B. Enzymology of Purine and Pyrimidine Antimetabolites Used in the Treatment of Cancer. *Chem. Rev.* **2009**, *109*, 2880–2893. [CrossRef] [PubMed]
6. Brown, D.J. *The Chemistry of Heterocyclic Compounds*; Wiley: Hoboken, NJ, USA, 1994; Volume 52, ISBN 978-0-471-50656-0.
7. Gabriele, B.; Mancuso, R.; Salerno, G. Oxidative Carbonylation as a Powerful Tool for the Direct Synthesis of Carbonylated Heterocycles. *Eur. J. Org. Chem.* **2012**, *2012*, 6825–6839. [CrossRef]
8. Wu, X.F.; Neumann, H.; Beller, M. Synthesis of Heterocycles via Palladium-Catalyzed Carbonylations. *Chem. Rev.* **2013**, *113*, 1–35. [CrossRef] [PubMed]
9. Gabriele, B.; Della Ca, N.; Mancuso, R.; Veltri, L.; Ziccarelli, I. Palladium(II)-Catalyzed Carbonylations. In *Carbon Monoxide in Organic Synthesis*; Gabriele, B., Ed.; Wiley: Hoboken, NJ, USA, 2021; pp. 235–294. ISBN 9783527829354.
10. Perrone, S.; Cannazza, G.; Caroli, A.; Salomone, A.; Troisi, L. Ring Opening of Heterocycles Containing a C–N Double Bond: A Simple Synthesis of Imides Promoted by Acyl Palladium Species. *Tetrahedron* **2014**, *70*, 6938–6943. [CrossRef]
11. Messa, F.; Perrone, S.; Capua, M.; Tolomeo, F.; Troisi, L.; Capriati, V.; Salomone, A. Towards a Sustainable Synthesis of Amides: Chemoselective Palladium-Catalysed Aminocarbonylation of Aryl Iodides in Deep Eutectic Solvents. *Chem. Commun.* **2018**, *54*, 8100–8103. [CrossRef] [PubMed]
12. Messa, F.; Dilauro, G.; Paparella, A.N.; Silvestri, L.; Furlotti, G.; Iacoangeli, T.; Perrone, S.; Salomone, A. Deep Eutectic Solvents Meet Safe, Scalable and Sustainable Hydrogenations Enabled by Aluminum Powder and Pd/C. *Green Chem.* **2022**, *24*, 4388–4394. [CrossRef]
13. Paparella, A.N.; Messa, F.; Dilauro, G.; Troisi, L.; Perrone, S.; Salomone, A. A Glycerol-Based Deep Eutectic Solvent as Natural Medium and Organic Reductant for Homocoupling of (Hetero)Aryl Chlorides: A Green Route to 2,2′-Bipyridine and Biaryl Scaffolds. *ChemistrySelect* **2022**, *7*, e202203438. [CrossRef]
14. Perrone, S.; Capua, M.; Cannazza, G.; Salomone, A.; Troisi, L. Synthesis of β-Enamino Acid and Heteroaryl Acetic Acid Derivatives by Pd-Catalyzed Carbonylation of α-Chloroimines and 2-Chloromethyl Aza-Heterocycles. *Tetrahedron Lett.* **2016**, *57*, 1421–1424. [CrossRef]
15. Capua, M.; Perrone, S.; Bona, F.; Salomone, A.; Troisi, L. A Direct Synthesis of Isocytosine Analogues by Carbonylative Coupling of α-Chloro Ketones and Guanidines. *Eur. J. Org. Chem.* **2017**, *2017*, 1780–1787. [CrossRef]
16. Capua, M.; Granito, C.; Perrone, S.; Salomone, A.; Troisi, L. Palladium-Catalyzed Carbonylative Coupling of α-Chloroketones with Hydrazines: A Simple Route to Pyrazolone Derivatives. *Tetrahedron Lett.* **2016**, *57*, 3363–3367. [CrossRef]
17. Perrone, S.; Capua, M.; Salomone, A.; Troisi, L. Multicomponent Synthesis of Uracil Analogues Promoted by Pd-Catalyzed Carbonylation of α-Chloroketones in the Presence of Isocyanates and Amines. *J. Org. Chem.* **2015**, *80*, 8189–8197. [CrossRef] [PubMed]
18. Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. Efficient Synthesis of Ureas by Direct Palladium-Catalyzed Oxidative Carbonylation of Amines. *J. Org. Chem.* **2004**, *69*, 4741–4750. [CrossRef] [PubMed]