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Short Access to 6-Substituted Pyrimidine Derivatives by the $S_{RN}1$ Mechanism. Synthesis of 6-Substituted Uracils through a One-Pot Procedure

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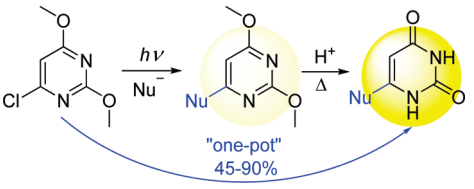

The synthesis of 6-substituted 2,4-dimethoxypyrimidines with different nucleophiles was accomplished with good to excellent yields (50−95%) through $S_{RN}1$ reactions, starting from commercially available 6-chloro-2,4-dimethoxypyrimidine (**1**). Hydrolysis of these derivatives gave access to 6-substituted uracils with good yields and short times by the use of microwave irradiation. The preparation of uracils from **1** without the isolation of 2,4-dimethoxypyrimidine derivatives affords a rapid access to these compounds in good yields and excellent purity by avoiding an unnecessary step of purification.

Introduction

The uracil unit is one of the most important structures in life, being part of the building blocks of RNA and other natural products. Therefore, it is not surprising that uracil derivatives have important biological activity. Actions as antiviral and antitumoral agents are probably among the most widely reported activities;[1] however, uracil derivatives, including herbicides, insecticides, bactericides, and acaricides, among others, have also been synthesized.[2] In addition, uracil units can be found in the chemistry of peptide nucleic acid (PNA) or as part of other fused systems with antiallergic, antihypertensive, cardiotonic, bronchodilator, or antibronchitis activity.[3]

Uracils are considered privileged structures in drug discovery and their functionalization at positions N1, N3, C5, and C6 is of major synthetic importance.[4] In particular, there is a renewed interest in the synthesis of new C6 derivates to be applied to the treatment of cancer or as antiviral compounds.[5]

There are three main synthetic strategies to prepare uracil derivatives: (a) building of the uracil nucleus from acyclic precursors with appropriate substituents; (b) modification of the structure of functionalized uracils or uracil itself by reaction with different reagents; and (c) functionalization of masked uracil moieties with reactions incompatible with the nucleus.[6] The combination of these approaches is often found in the synthesis of target compounds with potential biological activity.[7]

An interesting example has illustrated the first preparation of boron analogues of uracils (borauracils) starting from acyclic precursors.[8] A series of reports have described the synthesis of uracils fused to different heterocycles. Recent examples involve

(1) (a) Parker, W. B. *Chem. Rev.* **2009**, *109*, 2880. (b) Pathak, T. *Chem. Rev.* **2002**, *102*, 1623 and references cited therein.
(2) (a) Saladino, R.; Crestini, C.; Palamara, A. T.; Danti, M. C.; Manetti, F.; Corelli, F.; Garaci, E.; Botta, M. *J. Med. Chem.* **2001**, *44*, 4554. (b) Zhi, C.; Long, Z.; Manikowski, A.; Brown, N. C.; Tarantino, P. M.; Holm, K.; Dix, E. J.; Wright, G. E.; Foster, K. A.; Butler, M. M.; LaMarr, W. A.; Skow, D. J.; Motorina, I.; Lamothe, S.; Storer, R. *J. Med. Chem.* **2005**, *48*, 7063. (c) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Catalán, S.; Ramírez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417. (d) Lagoja, M. *Chem. Biodiversity* **2005**, *2*, 1. (e) Jain, K. S.; Chitre, T. S.; Minutosiyar, P. B.; Kathiravan, M. K.; Bendre, V. S.; Veer, V. S.; Shahane, S. R.; Shishoo, C. J. *Curr. Sci.* **2006**, 793 and references cited therein.
(3) Palasz, A.; *Monatsh. Chem.* **2008**, *139*, 1397 and references cited therein.
(4) Newkome, G. R.; Pandler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, 1982.
(5) Hopkins, A. L.; Ren, J.; Tanaka, H.; Baba, M.; Okamato, M.; Stuart, D. I.; Stammers, D. K. *J. Med. Chem.* **1999**, *42*, 4500.
(6) For one example of each one see: (a) Reference 2c. (b) Uraguchi, D.; Yamamoto, K.; Ohtsuka, Y.; Tokuhisa, K.; Yamakawa, T. *Appl. Catal., A* **2008**, *348*, 137. (c) Reese, C. B.; Wu, Q. *Org. Biomol. Chem.* **2003**, *1*, 3160.
(7) Bardagí, J. I.; Rossi, R. A. *Org. Prep. Proced. Int.* **2009**, *41*, 479–514.
(8) Ruman, T.; Długopolska, K.; Rode, W. *Bioorg. Chem.* **2010**, *38*, 33.

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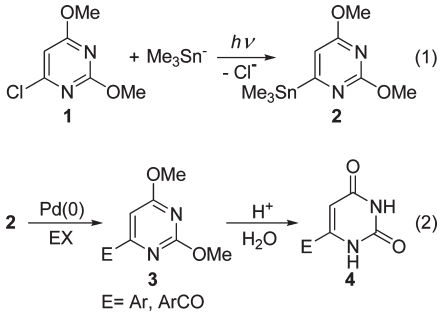
a multicomponent approximation used to prepare pyrido[2,3-*d*:6,5-*d*]dipyrimidines, tetrahydropyrimido[4,5-*b*]quinolines, and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-diones in good yields, starting from barbituric acids, aldehydes, and different amines in water as solvents.[9] The same reactions were performed in short reaction times with ultrasonic irradiations.[10] Likewise, the synthesis of pyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-diones,[11] pyrido[2,3-*d*]pyrimidines,[12] and azocine-pyrimidines[13] has been achieved through condensation, hetero-Diels−Alder, and radical cyclization reactions, respectively.

6-Substituted thymines have been prepared recently via lithiation of a N1-sulfonamide and by reaction with aldehydes.[14] Substitutions at positions five and six by nucleophiles have been accomplished by reaction of tosyl and halouracils (or activated uracils) with different species like amines, alcohols, and anions derived from tiols and selenols.[15] However, as can be inferred, this strategy is limited to nucleophiles with basicity similar to uracil, or in the synthesis of N1-substituted ones.[16]

Recently we studied the reaction of 6-chloro-2,4-dimethoxypyrimidine (**1**) with trimethylstannyl anions by the $S_{RN}1$ mechanism and obtained excellent yields of the corresponding stannane **2** (95%, eq 1). This stannane reacted with electrophiles EX (EX = ArI and ArCOCl) in cross-coupling reactions catalyzed by Pd(0) to obtain 6-aryl and 6-acylpyrimidines **3** that afforded 6-substituted uracil derivatives **4** after hydrolysis with good global yields (eq 2).[17]



The radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which an aromatic nucleophilic substitution is achieved. The scope of this process has increased considerably and it nowadays serves as an important synthetic strategy.[18] The initiation step is an electron transfer (ET) from the nucleophile to the substrate to afford a radical anion. In some systems, the ET step is spontaneous, but in others, light is required to induce the reaction. The propagation steps consist of fragmentation of the radical anion to afford a radical and the leaving group (eq 3), coupling of the radical with the nucleophile to afford a radical anion (eq 4), followed by ET to the substrate (eq 5) forming the intermediate necessary to continue the propagation cycle.

$$(ArX)^{\cdot -} \rightarrow Ar^{\cdot} + X^{-} \quad (3)$$

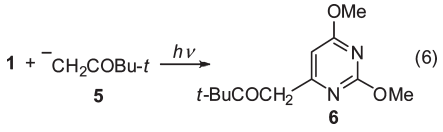
$$Ar^{\cdot} + Nu^{-} \rightarrow (ArNu)^{\cdot -} \quad (4)$$

$$(ArNu)^{\cdot -} + ArX \rightarrow ArNu + (ArX)^{\cdot -} \quad (5)$$

We report now the synthesis of uracil derivatives through a sequence of $S_{RN}1$-hydrolysis reactions from commercially available **1**. We have studied and optimized the two steps separately to obtain the best result. In addition, we examined the possibility of performing the two reactions in a "one-pot" approximation to gain rapid access to the different families of 6-substituted uracils.

Results and Discussion

Some years ago, Wolfe et al. performed the reaction of **1** with pinacolone enolate anion **5** in liquid ammonia and obtained excellent yields of the substitution product after 15 min of irradiation by the $S_{RN}1$ mechanism (eq 6).[19]



We repeated the reaction of **1** and **5** and obtained an excellent yield of the substitution product **6**, in the same experimental conditions (Table 1, expt 1).

TABLE 1. Photostimulated Reactions of Anions from Aliphatic Ketones with 1.[a]

expt	Nu^-	solvent (time)	product (%)[b]	Cl^-,[c] %
1	**5**	NH_3 (15 min)	**6** (95%)	100
2	**5**	DMSO (15 min)	**6** (traces)	<5
3	**7**	NH_3 (30 min)	**8** (69%)[d]	*e*
4	**9**	NH_3 (30 min)	**10** (50%)[d]	77
5	**9**	DMSO (20 min)	**10** (traces)	68
6	**9**	MeCN (15 min)	**10** (traces)	<5

[a]All the photostimulated reactions were performed with 0.25×10^{-3} mol of **1** as substrate and 1.0×10^{-3} mol of nucleophile (Nu^-). Photostimulated reactions were performed with two water-cooled metallic iodure lamps. [b]Yield. [c]Determined potentiometrically. [d]Reduced substrate was detected but not quantified. [e]Not quantified.

It is proposed that rigid polycyclic moieties like adamantyl or norbornyl could increase the biological activity of compounds; including these moieties in the structure increases the lipophilic properties of drugs. In addition, many compounds containing these polycyclic moieties have biological activity.[20] With the anion derived from 1-adamantylmethyl

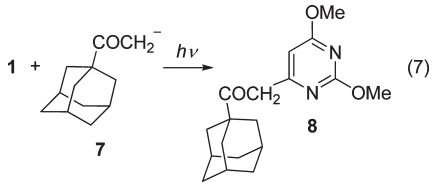
(9) Bazgir, A.; Khanaposhtani, M. M.; Ghahremanzadeh, R.; Soorki, A. A. *C. R. Chim.* **2009**, *12*, 1287.
(10) Mosslemin, M. H.; Nateghi, M. R. *Ultrason. Sonochem.* **2010**, *17*, 162.
(11) Turbiak, A. J.; Kampf, J. W.; Hollis Showalter, H. D. *Tetrahedron Lett.* **2010**, *51*, 1326.
(12) Deb, M. L.; Bhuyan, P. J. *Beil. J. Org. Chem* **2010**, *6*, 11.
(13) Majumdar, K. C.; Mondal, S.; Ghosh, D. *Tetrahedron Lett.* **2010**, *51*, 348.
(14) Loksha, Y. M.; Pedersen, E. B.; Bond, A. D.; La Colla, P.; Secci, B.; Loddo, R. *Synthesis* **2009**, *21*, 3589.
(15) (a) Benhida, R.; Aubertin, A.-M.; Grierson, D. S.; Monneret, C. *Tetrahedron Lett.* **1996**, *37*, 1031. (b) Fang, W.-P.; Cheng, Y. T.; Cheng, Y.-R.; Cherng, Y. J. *Tetrahedron* **2005**, *61*, 3107.
(16) See for example: (a) Saladino, R.; Stasi, L.; Crestini, C.; Nicoletti, R.; Botta, M. *Tetrahedron* **1997**, *53*, 7045. (b) Saladino, R.; Stasi, L.; Nicoletti, R.; Crestini, C.; Botta, M. *Eur. J. Org. Chem.* **1999**, 2751.
(17) Bardagí, J. I.; Rossi, R. A. *J. Org. Chem.* **2008**, *73*, 4491.
(18) For reviews, see: (a) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71–167. (b) Rossi, R. A.; Pierini, A. B.; Santiago, A. N. In *Organic Reactions*; Paquette, L. A., Bittman, R., Eds.; Wiley & Sons: New York, 1999; pp 1−271. (c) Rossi, R. A. In *Synthetic Organic Photochemistry*; Griesberck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2005; Vol. 12, Chapter 15, pp 495−527.
(19) Carver, D. R.; Komin, A. P.; Hubbarda, J. S.; Wolfe, J. F. *J. Org. Chem.* **1981**, *46*, 294.
(20) See for example: (a) Webster, S. P.; Ward, P.; Binnie, M.; Craigie, E.; McConnell, K. M. M.; Sooy, K.; Vinter, A.; Seckl, J. R.; Walker, B. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2838. (b) Rho, H. S.; Baek, H. S.; Lee, B.; Kim, J. H.; Kim, D. H.; Chang, I. S. *Bull. Korean Chem. Soc.* **2006**, *27*, 115.

TABLE 2. Hydrolysis of 6-Substituted-2,4-dimethoxypyrimidines

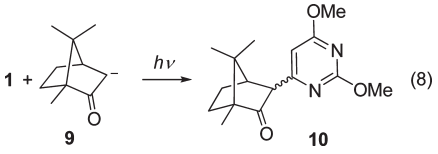
expt	substrate, 10^{-3} M	conditions	product (%)	heating[a]
1	**6**, 16.7	0.2 M HCl, reflux 48 h	**19** (85)[b]	CH
2	**6**, 6.0 (17%)[c,d]	0.2 M HCl, 120 °C, 80 min, sealed tube	**19** (37)[d]	CH
3	**8**, 12.0	0.2 M HCl, reflux 48 h	**20** (75)[b]	CH
4	**18**, 10.7	0.2 M HCl, reflux 48 h	**21** (69)[b]	CH
5	**6**, 16.7	0.1 M HCl, 120 °C, 40 min, sealed tube	**19** (78)[e]	MW
6	**6**, 16.7	0.1 M HCl, 120 °C, 10 min, sealed tube	**19** (81)[e]	MW
7	**6**, 16.7	0.01 MHCl, 120 °C, 1 h, sealed tube	**19** (85)[e]	MW
8	**6**, 6.0 (85%)[c,d]	water, 120 °C, 80 min, sealed tube	-[f]	MW
9	**6**, 16.7	0.1 M HCl, constant power 70 W (100−103 °C), 20 min, open tube	**19** (∼12)[e]	MW

[a]CH: conventional heating. MW: microwave irradiation. [b]Yield. [c]Remaining substrate. [d]Quantified by ^{1}H NMR. [e]Quantified by HPLC. [f]No product detected.

ketone (**7**), we obtained the corresponding pyrimidine 1-adamantyl-2-(2,6-dimethoxypyrimidin-4-yl)-1-oxoethane (**8**) with good yields after 30 min of irradiation (eq 7, Table 1, expt 3); reduced substrate 2,4-dimethoxypyrimidine was detected but not quantified. The low solubility of this anion in liquid ammonia might be responsible for the lower yield found.

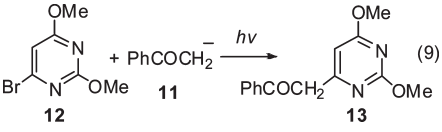


The anion of camphor (**9**) allows us to prepare the interesting substituted compound **10** in 50% yield (eq 8). Again, the low solubility and the greater steric demand of the anion may be the cause of the lower yields obtained.



We tried the synthesis in other solvents. However, it was not possible to obtain the products with all anions studied (Table 1, expts 2, 5, and 6). On the basis of GC and CG/MS analysis we estimated that polar addition reactions with the activated nucleus of pyrimidine are faster than electron transfer reactions at room temperature because of the appearance of products of pyrimidine decomposition.

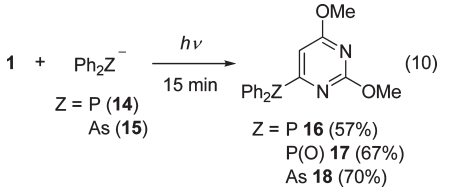
The photostimulated reaction of **1** with acetophenone enolate anion (**11**), a nucleophile representative of aromatic ketones, gave only ca. 9% of chloride anion in liquid ammonia. We changed the leaving group chlorine to bromine (**12**) since, in the photostimulated reaction, it is more reactive. However, in liquid ammonia and after 3 h of irradiation, only 15% of the substitution product **13** was obtained (eq 9).



It was not possible to obtain a good yield of **13** in DMSO or in any other solvent.[21] Probably in the case of **13**, competitive polar reactions are responsible for the high number of unidentified byproduct.

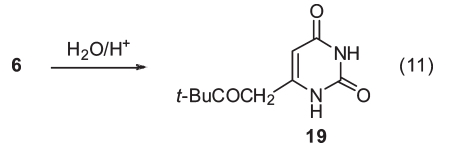
(21) See Table S1 in the Supporting Information for details.

With nucleophiles derived from arsenic and phosphorus it has been possible to prepare arsanes and phosphanes with good yields. We performed the reactions of **1** and diphenylphosphanide (**14**) or diphenylarsenide (**15**) anions, as representative of this type of nucleophiles, and prepared the corresponding pyrimidines with good yields (eq 10). With **14** as a nucleophile, it was possible to obtain phosphane **16**[22] and phosphane oxide **17**.

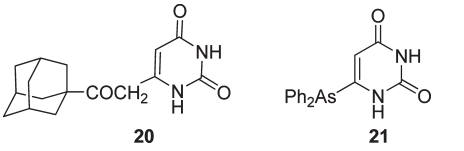


Hydrolysis of 2,4-Dimethoxypyrimidines. Uracils can be obtained by treating dialkoxypyrimidines with concentrated acids at reflux; good yields have been obtained.[23] However, reaction times are generally high and the conditions are very drastic. Some caution is also needed concerning the concentration of pyrimidine to avoid undesirable isomerization reactions.[24]

Seeking better conditions to obtain uracils from 6-substituted-2,4-dimethoxypyrimidines synthesized, we studied this reaction in different conditions, using compound **6** as a model substrate to afford uracil **19** (eq 11, Table 2).[25]



We found that the best choice was to perform the hydrolysis in a solution of HCl without cosolvent, synthesizing 85% yield of **19** after 48 h at reflux (Table 2, expt 1). This condition worked well even for other substrates, in which we obtained good yields of 6-(2-oxo-2-(1-adamantyl)ethyl)-uracil (**20**) and 6-(diphenylarsanyl)uracil (**21**) starting from **8** and **18** (Table 2, expts 3 and 4).



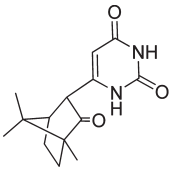
(22) This product was identified only by GC/MS. The purity was determined by GC.

(23) See for example: (a) Reference 8. (b) Boudet, N.; Knochel, P. *Org. Lett*. **2006**, *8*, 3737. (c) Ismail, M. A.; Zoorob, H. H.; Strekowski, L. *Arkivoc*; ARKAT Foundation, 2002; Part x, p 1.

(24) Wong, J. L.; Fuchs, D. S. *J. Org. Chem*. **1970**, *35*, 3786.

(25) A list of all conditions examined can be seen in the Supporting Information (Table S2).

TABLE 3. "One-Pot" Synthesis of 6-Substituted Uracils[a]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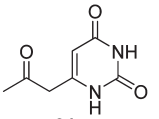
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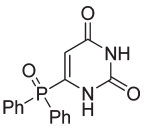

25

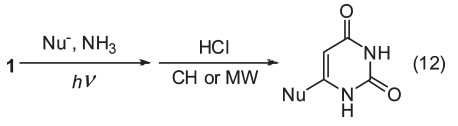
					yield (%)			
					"one-pot"[b]		step-by-step	
expt	nucleophile, 10^{-3} mol	1st step conditions (*hv*)	2nd step conditions	product	CH	MW	CH	MW
1	**5**, 1.0	15 min	48 h (CH); 10 min (MW)	**19**	84	82	80	76
2	**8**, 1.0	20 min	56 h (CH); 10 min (MW)	**20**	45	42	52	
3	**18**, 0.26	5 min	48 h (CH); 40 min (MW)	**21**	69	56	48	
4	**9**, 1.0	30 min	48 h (CH); 40 min (MW)	**22**			25	
5	$CH_3COCH_2^-$ (**23**), 1.0	15 min	48 h (CH); 10 min (MW)	**24**	90			
6	**14**, 0.27	10 min	48 h (CH); 20 min (MW)	**25**	55	44		

[a]All reactions were performed with 0.25×10^{-3} mol of substrate **1**. CH: conventional heating. MW: microwave irradiation. [b]The purity of products was determined by HPLC and was >96% in all cases.

In view of the long reaction times required, we decided to perform the reaction under microwave irradiation (MW) instead of conventional heating (CH). We studied the reaction in solutions of chlorohydric acid under different conditions, using **6** as a model substrate (Table 2, expts 5−9 and Table S2, expts 8−17 in the Supporting Information). The results show some advantage of MW in comparison with CH, allowing us to prepare good yields of **19** after having worked 10−60 min in sealed tubes at 120 °C. As seen, temperature and type of heating are responsible for the short reaction times, because changing only one variable, such as temperature (Table 2, expt 1 vs 2) or type of heating (expt 1 vs 9), has not produced better results.

Synthesis of 6-Substituted Uracils. In our synthetic strategy we studied the two steps and synthesized uracils **19**−**21** in good yields. We then decided to explore the possibility of synthesizing the target compounds without the isolation of 2,4-dimethoxypyrimidines, to avoid an instance of purification and a possible loss of yield.[17,26]

SCHEME 1. Synthesis of 6-Substituted Uracils through a One-Pot Procedure



(12)

We performed the reaction of **1** and pinacolone enolate ion **5** in liquid ammonia under photostimulation for 15 min. We allowed the ammonia to evaporate and added a solution of HCl. Finally, we heated the mixture at reflux and obtained **19** in an excellent yield (Scheme 1, Table 3, expt 1).[27] CH and MW irradiation was used, obtaining with the latter short reaction times in less severe conditions. If we compare the step-by-step synthesis with the "one-pot" procedure in the synthesis of **19**−**21** the results are satisfactory: similar yields could be obtained in less time through a simplified "one-pot" procedure.

To explore the scope of the present "one-pot" approach, we performed the reactions with different nucleophiles and **1** in the conditions described above (Scheme 1, Table 3). It was possible to obtain, excepting one case, the pure isolated product through the "one-pot" approach. Even when the yields of product were less satisfactory with MW, it should be noted that the experimental conditions were not optimized.

The only case where the product could not be obtained was when anion **9** was used, due to the large quantity of by-product which made impossible the purification through a simple procedure. However, working with the step-by-step approximation we could prepare compound **22** in 25% global yield, which is acceptable if we consider the interesting structure of this uracil.

Conclusions

The preparation of 6-substituted pyrimidines by reaction with nuclephiles by $S_{RN}1$ reactions was possible in good to excellent yields and short reaction times. In addition, the syntheses of 6-substituted uracils were successful through a "one-pot" $S_{RN}1$-hydrolysis sequence, obtaining good yields and purity of products in a simplified procedure. The use of MW also allowed us to prepare the same product in shorter times but with fewer yields in some cases.

These results together with those obtained in the three-step "one-pot" synthesis of substituted uracils with different electrophiles[17] highlight the fact that the $S_{RN}1$ reactions could be useful to prepare different pyrimidines in good yields.

Experimental Section

General Methods. High Pressure Liquid Chromatographic (HPLC) analyses were performed on an instrument with a UV detector (diode array) equipped with a C18 column. Gas Chromatographic (GC) analyses were performed on an instrument with a flame ionization detector equipped with a VF-5 ms column (15 m × 0.25 mm × 0.25 μm). Gas Chromatographic−Mass Spectrometer analyses were carried out on an instrument equipped with a quadrupole detector and a VF-5 ms column (30 m × 0.25 mm × 0.25 μm). High Resolution Mass Spectra were done in a MS/MS instrument over the pure products.

(26) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737.
(27) See the Experimental Section for details.

^{1}H NMR (400.16 MHz), ^{31}P NMR (162 MHz), and ^{13}C NMR (100.62 MHz) data are shown in ppm. Irradiation was conducted in a reactor equipped with two 400-W lamps of metal iodide[28] refrigerated with air and water. MW reactions were performed in a single mode instrument equipped with a noncontact infrared sensor to measure the temperature. Potentiometric titrations of halide ions were performed in a pH meter with an Ag/Ag^+ electrode. Melting points were performed with an electronic air-heating instrument and are uncorrected. Quantification by GC was performed by the Internal Standard Method with a standard deviation ≤5%. Quantification by HPLC was performed by the External Standard Method with a standard deviation ≤7%. Quantification by ^{1}H NMR was performed by adding a Standard to the crude in D_2O as solvent.

Materials. 6-Chloro-2,4-dimethoxypyrimidine, potassium *tert*-butoxide, pinacolone, 1-adamantyl methyl ketone, camphor, acetophenone, triphenylphosphane, triphenylarsane, trifluoroacetic acid, tetrachloromethane, and hydrochloric acid were commercially available and used as received from the supplier. DMSO was dried with molecular sieves. All solvents were analytical grade and used as received from the supplier. Silica gel (0.063−0.200 mm) was used in column chromatography. Silica gel (60 PF254) plates (1 mm and 2 mm) were employed in radial thin-layer chromatography purification. 6-Bromo-2,4-dimethoxypyrimidine was prepared has previously indicated.[29]

1-(2,6-Dimethoxypyrimidin-4-yl)-3,3-dimethylbutan-2-one (6): Reactions of 1 with Enolate Anions in Liquid Ammonia (Typical Procedure). Ammonia (150 mL), previously dried with Na metal under nitrogen, was condensed into a three-necked, 250-mL round-bottomed flask equipped with a coldfinger condenser charged with ethanol, a nitrogen inlet, and a magnetic stirrer. Potassium *tert*-butoxide (117.0 mg, 1.04 mmol) was then added and stirred for 5 min. Pinacolone was later added (125 μL, 1.00 mmol) and the mixture was stirred for 15 min. The irradiation was started and then 6-chloro-2,4-dimethoxypyrimidine (43.6 mg, 0.25 mmol) was added to the solution dissolved in 1 mL of dried ethyl ether and the reaction mixture was irradiated for 15 min with two metal iodide lamps of 400 W. Ammonium nitrate was added in excess to eliminate any remaining anions; the ammonia was allowed to evaporate. Water (50 mL) was added and the aqueous phase was extracted with ethyl acetate. The organic phase was dried (magnesium sulfate) and filtered, and the solvent was evaporated under vacuum. The product was isolated as a brown oil in 95% yield (59.4 mg, >97% purity). The product was extra purified by column chromatography on silica gel eluting with dichloromethane/methanol (100:0 to 96:4), yielding a colorless oil (54.0 mg, 86%). The spectroscopic data (^{1}H and ^{13}C NMR) are in agreement with those previously reported.[19] ^{1}H NMR (400 MHz, CCl_3D): δ 13.91 (s, 1H, enol), 6.30 (s, 1H, keto), 5.95 (s, 1H, enol), 5.29 (s, 1H, enol), 4.00 (s, 3H, enol), 3.96 (s, 6H, keto), 3.94 (s, 3H, enol), 3.81 (s, 2H, keto), 1.22−1.20 (s superimposed, 9H, keto−enol). ^{13}C NMR (100.62 MHz, CCl_3D) keto−enol: δ 211.0, 178.7, 171.9, 171.6, 166.7, 166.0, 165.2, 101.7, 95.0, 91.4, 54.7, 54.6, 53.8, 45.1, 44.9, 36.7, 27.9, 26.2. GC/MS (*m*/*z*): 238 (M^+; 4), 181 (52), 155 (15), 154 (60), 153 (28), 96 (13), 72 (25), 58 (13), 57 (100), 55 (13), 41 (37).

1-(1-Adamantyl)-2-(2,6-dimethoxypyrimidin-4-yl)ethanone (8). 1-Adamantylmethyl ketone (178.0 mg, 1.0 mmol) instead of pinacolone was added dissolved in 1 mL of diethyl ether and the mixture was stirred for 30 min; some precipitate of the enolate anion appeared. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (99:1) yielding a white solid (51.4 mg, 69%) with mp 97−100 C. In the NMR data the keto and enol tautomers are observed. ^{1}H NMR (400 MHz, CCl_3D): δ 13.88 (s, 1H, enol), 6.28 (s, 1H, keto), 5.94 (s, 1H, enol), 5.22 (s, 1H, enol), 4.00−3.94 (s, 6H, keto−enol mixture), 3.78 (s, 2H, keto), 2.08 (br s, 3H, keto−enol mixture), 1.88 (m, 6H, keto−enol mixture), 1.79−1.69 (m, 6H, keto−enol mixture). ^{13}C NMR (400 MHz, CCl_3D) keto−enol: δ 210.7, 178.4, 171.8, 171.6, 166.8, 166.1, 165.2, 163.3, 101.7, 95.0, 91.4, 54.7, 53.8, 47.2, 44.6, 39.6, 38.0, 36.8, 36.5, 28.2, 27.9. ^{1}H−^{1}H COSY NMR (CCl_3D): δ_H/δ_H 13.88/13.88, 6.28/6.28, 5.94/5.94, 5.22/5.22, 4.00/4.01, 3.96/3.97, 3.78/3.78, 2.08/1.78, 2.08/2.08, 2.08/1.89, 1.88/1.72, 1.88/2.08, 1.88/1.89, 1.76/2.10, 1.76/1.77, 1.72/1.74, 1.71/1.89. ^{1}H−^{13}C HSQC NMR (CCl_3D): δ_H/δ_C 6.28/101.7, 5.94/95.0, 5.22/91.4, 4.00/54.7, 3.96/54.7, 3.95/53.8, 3.78/44.6, 2.12/27.9, 2.04/27.9, 1.88/38.0, 1.87/39.6, 1.75/36.5, 1.73/36.8. GC/MS (*m*/*z*): 317 ($M^+ + 1$; 3), 316 (M^+; 16), 181 (59), 154 (17), 136 (12), 135 (100), 107 (10), 93 (18), 79 (22). ESI/APCI-HRMS Anal. Calcd for $C_{18}H_{25}N_2O_3$ ($M + H^+$) 317.1860, found 317.1872.

3-(2,6-Dimethoxypyrimidin-4-yl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (10). Camphor (152.2 mg, 1.0 mmol) was added dissolved in 1 mL of diethyl ether and the mixture was stirred for 30 min; some precipitate of the enolate anion appeared. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (99:1) yielding a yellow oil (36.0 mg, 50%). In the NMR data the keto and enol tautomers are observed. ^{1}H NMR (400 MHz, CCl_3D): δ 6.84 (d, J = 1.15, 1H, enol), 6.37 (s, 1H, keto), 5.29 (s, 1H, enol), 4.00−3.96 (m, 6H, keto−enol mixture), 3.68 (d, J = 4.74, 1H, keto), 2.57−2.55 (m, 1H, keto−enol mixture), 1.74−1.72 (m, 2H, keto−enol mixture), 1.51−1.43 (m, 1H, keto−enol mixture), 1.31−1.26 (m, 1H, keto−enol mixture), 1.05 (s, 3H, keto−enol mixture), 0.99 (s, 6H, keto−enol mixture). GC/MS (*m*/*z*): 291 ($M^+ + 1$, 2), 290 (M^+, 11), 275 (10), 247 (37), 182 (10), 181 (76), 180 (17), 179 (11), 167 (47), 155 (14), 154 (100), 72 (12), 55 (16), 41 (21). ESI/APCI-HRMS Anal. Calcd for $C_{16}H_{23}N_2O_3$ ($M + H^+$) 291.1703, found 291.1699.

2-(2,6-Dimethoxypyrimidin-4-yl)-1-phenylethanone (13). Acetophenone (117 μL, 1.0 mmol) and pinacolone (32 μL,, 0.25 mmol) were added. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (100:0 to 96:4) yielding a brown oil. In the NMR data the keto and enol tautomers are observed. ^{1}H NMR (400 MHz, CCl_3D): δ 14.23 (s, 1H enol), 8.07−8.05 (m, 2H), 7.84−7.82 (m, 2H), 7.61−7.57 (m, 1H), 7.50−7.43 (m, 5H), 6.38 (s, 1H keto), 6.10 (s, 1H enol), 5.97 (s, 1H, enol), 4.29 (s, 2H, keto), 4.07 (s, 3H), 3.99 (s, 3H), 3.96 (s superimposed, 6H). GC/MS (*m*/*z*): 259 (M^++1, 2), 258 (M^+,15), 230 (34), 229 (44), 105 (100), 77 (54), 51 (11). ESI/APCI-HRMS Anal. Calcd for $C_{14}H_{15}N_2O_3$ ($M + H^+$) 259.1077, found 259.1080.

Diphenyl(2,4-dimethoxy-6-pyrimidyl)phosphane Oxide (17): Reactions of $Ph_2P^-Na^+$ (or $Ph_2As^-Na^+$) in Liquid Ammonia (Typical Procedure). Ammonia (150 mL), previously dried with Na metal under nitrogen, was condensed into a three-necked, 250-mL round-bottomed flask equipped with a coldfinger condenser charged with ethanol, a nitrogen inlet, and a magnetic stirrer. PPh_3 (68.8 mg, 0.26 mmol) was then added, and Na metal was introduced in small pieces; total discoloration between each addition was expected. Addition was continued until the solution maintained its dark brown for at least 5 min. After the color became red, *tert*-butanol was added to eliminate the NH_2^- anions formed. An orange solution of Ph_2P^- ions is obtained. The irradiation was started and then 6-chloro-2,4-dimethoxypyrimidine **1** (43.6 mg, 0.25 mmol) was added to the solution dissolved in 1 mL of dried ethyl ether. The reaction mixture was irradiated for 10 min. Ammonium nitrate was added in excess to eliminate any remaining anions; the ammonia was allowed to evaporate. Hydrogen peroxide 20 vol (2 mL) and water (50 mL) were added and the mixture was stirred for 30 min. The aqueous phase was extracted with ethyl acetate, the organic phase was dried (magnesium sulfate), and the solvent was

(28) A spectrum of the lamp can be seen in www.luz.philips.com.ar/archives/lamps_hid_hpiplus.pdf.

(29) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *66*, 1963.

evaporated under vacuum. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (100:0 to 96:4) yielding a white solid (57.2 mg, 67%) with mp 143.5−146 C. ^{1}H NMR (400 MHz, CCl3D): δ 7.95−7.9 (m, 4H), 7.57−7.54 (m, 2H), 7.5−7.46 (m, 4H), 7.39 (d, ^{H-P}J = 7.28 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (400 MHz, CCl_3D): δ 172.1 (d, ^{C-P}J = 13.22 Hz), 166.1 (d, ^{C-P}J = 124.74 Hz), 165.1 (d, ^{C-P}J = 22.08 Hz), 132.3 (d, ^{C-P}J = 2.83 Hz), 132.1 (d, ^{C-P}J = 9.56 Hz), 130.9 (d, ^{C-P}J = 105.44 Hz), 128.4 (d, ^{C-P}J = 12.33 Hz), 107.7 (d, ^{C-P}J = 18.61 Hz), 55.2, 54.3. ^{1}H−^{13}C HSQC NMR (CCl_3D): δ_H/δ_C 132.3/7.54, 132.3/7.52, 132.2/7.93, 132.2/7.88, 132.2/7.91, 128.5/7.44, 128.5/7.48, 128.5/7.46, 107.8/7.37, 107.6/7.35, 55.0/3.94, 54.1/3.99. ^{1}H−^{13}C HMBC NMR (CCl_3D): δ_H/δ_C 172.0/4.01, 172.2/4.01, 165.0/7.40, 165.3/7.38, 165.5/3.96, 166.8/3.96, 132.0/7.95−7.9, 132.1/7.95−7.9 132.2/7.95−7.9, 132.3/7.95−7.9, 132.0/7.57−7.54, 132.1/7.57−7.54, 132.2/7.57−7.54, 132.3/7.57−7.54, 132.0/7.5−7.46, 132.1/7.5−7.46, 132.2/7.5−7.46, 132.3/7.5−7.46, 130.4/7.95−7.9, 131.5/7.95−7.9, 130.4/7.5−7.46, 131.5/7.5−7.46, 128.3/7.5−7.46, 128.5/7.5−7.46. GC/MS (m/z): 341 ($M^+ + 1$, 8), 340 (M^+, 37), 339 (100), 325 (19), 263 (40), 201 (20), 199 (14), 183 (15), 77 (33), 51 (14). ESI/APCI-HRMS Anal. Calcd for $C_{18}H_{18}N_2O_3P$ ($M + H^+$) 341.1045, found 341.1061.

Diphenyl(2,4-dimethoxy-6-pyrimidyl)phosphane (16). After the irradiation time, ammonium nitrate was added in excess to eliminate any remaining anions; the ammonia was allowed to evaporate under nitrogen. Deoxygenated water (50 mL) was added and the aqueous phase was extracted with ethyl acetate, the organic phase was dried (magnesium sulfate), and the solvent was evaporated under vacuum. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (98:2 to 96:4) yielding a white solid (46.1 mg, 57%). GC/MS (m/z): 325 ($M^+ + 1$, 14), 324 (M^+, 73), 323 (100), 247 (11), 183 (46), 107 (15).

Diphenyl(2,4-dimethoxy-6-pyrimidyl)arsane (18). $AsPh_3$ (80.4 mg, 0.26 mmol) was added instead of Ph_3P. The ammonia was allowed to evaporate. Water (50 mL) was added, the aqueous phase was extracted with ethyl acetate, the organic phase was dried (magnesium sulfate), and the solvent was evaporated under vacuum. The product was purified by radial thin-layer chromatography on silica gel eluting with dichloromethane/methanol (100:0 to 99:1) yielding a yellow oil (64.6 mg, 70%). ^{1}H NMR (400 MHz, CCl_3D): δ 7.46−7.44 (m, 4H), 7.39−7.35 (m, 4H), 6.26 (s, 1H), 4.96 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (400 MHz, CCl_3D): δ 178.3, 171.1, 164.6, 138.0, 134.1, 128.9, 128.8, 106.8, 55.0, 53.7. GC/MS (m/z): 369 (M^++1; 18), 368 (M^+; 100), 367 (48), 291 (12), 227 (29), 214 (12), 153 (12), 152 (33), 151 (18). ESI/APCI-HRMS Anal. Calcd for $C_{18}H_{18}AsN_2O_2$ ($M + H^+$) 369.0579, found 369.0594.

6-(3,3-Dimethyl-2-oxobutyl)uracil (19): Hydrolysis (Typical Procedure). Into a 50-mL round-bottomed flask equipped with a condenser and a magnetic stirrer were added1-(2,6-dimethoxypyrimidin-4-yl)-3,3-dimethylbutan-2-one (**6**) (47.1 mg, 0.20 mmol) and HCl 0.2 M (12 mL) then the solution was heated at reflux for 48 h. The reaction was allowed to cool to rt, the solution was neutralized with NaOH (1 M), and the solvent was evaporated under vacuum. Acetone was added to the residue and the solution was filtered to eliminate the inorganic salts. The filtrate was evaporated under vacuum and the residue was recrystallized in ethanol/water yielding a white solid (35.6 mg, 85%) with mp 242−245 C (partial decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 10.73 (s, 1H), 5.34 (s, 1H), 3.72 (s, 2H), 1.13 (s, 9H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 210.0, 164.5, 152.0, 151.2, 101.2, 44.3, 27.1, 26.2. ESI/APCI-HRMS Anal. Calcd for $C_{10}H_{15}N_2O_3$ ($M + H^+$) 211.1077, found 211.1081.

6-(2-Oxo-2-(1-adamantyl)ethyl)uracil (20). 1-(1-Adamantyl)-2-(2,6-dimethoxypyrimidin-4-yl)-ethanone (**8**) (57.0 mg, 0.18 mmol) and methanol (5 mL) were mixed. HCl 0.2 M (10 mL) was later introduced and the solution was heated at reflux for 48 h. A solid was formed. The mixture was concentrated to evaporate methanol and the product was filtered from the crude yielding a white solid (34.5 mg, 75%) with mp (methanol) 290 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 10.74 (s, 1H), 5.32 (s, 1H), 3.67 (s, 2H), 2.01 (s, 3H), 1.79 (m, 6H), 1.68 (dd, ^2J = 21.5 Hz, ^3J = 12.2 Hz, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 209.5. 164.5. 152.0. 151.3. 101.2. 46.3. 40.5. 38.0. 36.4. 27.8. ESI/APCI-HRMS Anal. Calcd for $C_{16}H_{21}N_2O_3$ ($M + H^+$) 289.1547, found 289.1550.

6-(Diphenylarsanyl)uracil (21). Diphenyl(2,4-dimethoxy-6-pyrimidyl)arsano (**18**) (58.7 mg, 0.16 mmol) was treated as in the case of compound **20** yielding a white solid (37.4 mg, 69%) with mp (methanol/water) 244−247 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 11.09 (s, 1H), 7.49−7.46 (m, 6H), 7.41−7.38 (m, 4H), 4.78 (t, J = 1.66, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 163.2, 159.0, 152.0, 136.0, 134.1, 130.1, 129.7, 106.3. GC/MS (m/z): 341 (M^++1, 7), 340 (M^+, 39), 262 (16), 229 (22), 227 (51), 154 (63), 153 (17), 152 (100), 151 (24), 68 (23). ESI/APCI-HRMS Anal. Calcd for $C_{16}H_{14}AsN_2O_2$ ($M + H^+$) 341.0266, found 341.0265.

6-(4,7,7-Trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)uracil (22). **10** (36.0 mg, 0.12 mmol) and methanol (5 mL) were mixed. HCl (0.2 M, 10 mL) was later introduced and the solution was heated at reflux for 48 h. The solution was neutralized with NaOH and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), and the solvent was evaporated under vacuum yielding a white solid (16.5 mg, 50%) with mp (methanol) 230 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 10.74 (s, 1H), 5.12 (s, 1H), 3.51 (d, J = 4.47 Hz, 1H), 2.53 (br s, 1H), 1.74−1.72 (m, 2H), 1.26−1.21 (m, 2H), 0.98 (s, 3H), 0.85 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 213.7, 164.3, 152.7, 151.9, 99.0, 58.9, 52.2, 47.1, 45.8, 29.6, 21.2, 19.5, 19.4, 9.8. ESI/APCI-HRMS Anal. Calcd for $C_{14}H_{19}N_2O_3$ ($M + H^+$) 263.1390, found 263.1395.

Typical Procedure for the Hydrolysis with MW Heating. Into a 5-mL tube equipped with a magnetic stirrer were added substrate and HCl (aq). The tube was sealed and irradiated with MW at 120 °C for the time indicated. The temperature was measured with a noncontact infrared sensor. After the irradiation time the mixture was treated as indicated for the hydrolysis with conventional heating for each compound.

"One-Pot" Reactions: 6-(2-Oxopropyl)uracil (24): Typical Procedure for "One-Pot" Reactions (Hydrolysis with Conventional Heating). After distillation of ammonia (50 mL), potassium *tert*-butoxide (121.0 mg, 1.05 mmol) and acetone (73 μL, 1.00 mmol) were added as previously described in the synthesis of **6**. The irradiation was started and then **1** (43.6 mg, 0.25 mmol) was added to the solution dissolved in 1 mL of dried ethyl ether. The reaction mixture was irradiated for 15 min. Ammonium nitrate was added (84 mg, 1.0 mmol) and the ammonia was allowed to evaporate. HCl 0.2 M was added (15 mL) and the coldfinger condenser was changed for a condenser. The mixture was heated at reflux for 48 h. The reaction was allowed to cool to rt, the solution was neutralized with NaOH (1 M), and the solvent was evaporated under vacuum. Acetone was added to the residue and the solution was filtered to eliminate the inorganic salts. The filtrate was evaporated under vacuum and the residue was analyzed for HPLC; yielding a yellow solid (37.7 mg, 90%, 95% purity). The solid was recrystallized from ethanol/water yielding a white solid with mp 290 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 10.71 (s, 1H), 5.34 (s, 1H), 3.58 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 203.0, 164.5, 151.9, 150.3, 101.3, 46.5, 30.3. ESI/APCI-HRMS Anal. Calcd for $C_7H_9N_2O_3$ ($M + H^+$) 169.0608, found 169.0649.

6-(Diphenylphosphoryl)uracil (25). After distillation of ammonia (50 mL) $Ph_2P^-Na^+$ (0.26 mmol) as described above. The

irradiation was started and then **1** (43.6 mg, 0.25 mmol) was added to the solution dissolved in 1 mL of dried ethyl ether. The reaction mixture was irradiated for 10 min. Ammonium nitrate was added (42 mg, 0.5 mmol) and the ammonia was allowed to evaporate. Hydrogen peroxide 20 vol (2 mL) and HCl 0.2 M were added (15 mL) and the coldfinger condenser was changed for a condenser. The mixture was heated at reflux for 48 h. The reaction was allowed to cool to rt, the solution was neutralized with NaOH (1 M), and the solvent was evaporated under vacuum. Acetone was added to the residue and the solution was filtered to eliminate the inorganic salts. The solvent was allowed to evaporate slowly to improve crystallization and the residue was washed with diethyl ether yielding a yellow solid (42.8 mg, 55%, 95% purity). The solid was recrystallized from acetone yielding a white solid with mp 243 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 11.31 (d, ^{H-P}J = 5.0 Hz, 1H), 7.78−7.71 (m, 6H), 7.64−7.60 (m, 4H), 5.53 (d, ^{H-P}J = 11.4 Hz, 1H). ^{31}P NMR (162 MHz, DMSO-d_6): δ 22.12. ^{13}C NMR (400 MHz, DMSO-d_6): δ 163.1 (d, ^{P-C}J = 15.6 Hz), 151.8 (d, ^{P-C}J = 11 Hz), 149.4, 148.5, 133.7, 133.6, 132.4, 132.3, 129.7, 129.6, 129.5, 128.6, 108.9 (^{P-C}J = 10.5 Hz). ESI/APCI-HRMS Anal. Calcd for $C_{16}H_{14}N_2O_3P$ ($M + H^+$) 313.0737, found 313.0740.

6-(3,3-Dimethyl-2-oxobutyl)uracil (19). The reaction was treated as described for compound **24**. **1** (43.7 mg, 0.25 mmol), potassium *tert*-butoxide (117.0 mg, 1.04 mmol), and pinacolone (125 μL, 1.00 mmol) were used yielding a yellow solid (44.2 mg, 84%, 96% purity).

6-(2-Oxo-2-(1-adamantyl)ethyl)uracil (20). Anion **7** was prepared and the reaction was performed as described in the synthesis of compound **8**. After evaporation of ammonia, methanol (5 mL) and HCl (0.2 M) were added (15 mL) and the hydrolysis was performed as described for this compound above. **1** (43.7 mg, 0.25 mmol), potassium *tert*-butoxide (117.0 mg, 1.04 mmol), and 1-adamantylmethyl ketone (177.8 mg, 1.0 mmol) were used. The solid was washed with diethyl ether yielding a yellow solid (32.5 mg, 45%, 98% purity).

6-(Diphenylarsanyl)uracil (21). Anion **15** was prepared and the first reaction was performed as described in the synthesis of compound **18**. After evaporation of ammonia, methanol (5 mL) and HCl (0.2 M, 15 mL) were added and the hydrolysis was performed as described above for this compound. **1** (43.6 mg, 0.25 mmol) and $AsPh_3$ (80.2 mg, 0.26 mmol) were used. The solid was washed with diethyl ether yielding a yellow solid (58.5 mg, 69%, 97% purity).

Typical Procedure for "One-Pot" Reactions (Hydrolysis with MW Irradiation). The first reaction was performed as described above for each compound. The second reaction was performed as described in the typical procedure for MW hydrolysis. The final concentration of HCl was 0.1 M in all cases.

6-(3,3-Dimethyl-2-oxobutyl)uracil (19). 1 (43.2 mg, 0.247 mmol), potassium *tert*-butoxide (118.0 mg, 1.05 mmol), and pinacolone (125 μL, 1.00 mmol) were used. The irradiation time was 10 min yielding a yellow solid (43.3 mg, 82%, 97% purity).

6-(2-Oxo-2-(1-adamantyl)ethyl)uracil (20). Methanol (20%) was used as cosolvent in the hydrolysis reaction. **1** (43.60 mg, 0.25 mmol), potassium *tert*-butoxide (117.5 mg, 1.05 mmol), and 1-adamantyl methyl ketone (177.6 mg, 1.0 mmol) were used. The irradiation time was 20 min. The solid was washed with diethyl ether yielding a yellow solid (30.5 mg, 42%, 96% purity).

6-(Diphenylarsanyl)uracil (21). Methanol (20%) was used as cosolvent in the hydrolysis reaction. **1** (42.5 mg, 0.24 mmol) and $AsPh_3$ (77.1 mg, 0.25 mmol) were used. The irradiation time was 20 min. The solid was washed with diethyl ether yielding a yellow solid (46.0 mg, 56%, 98% purity).

6-(Diphenylphosphoryl)uracil (25). 1 (44.6 mg, 0.255 mmol) and PPh_3 (69.4 mg, 0.26 mmol) were used with an irradiation time was 20 min, yielding a yellow solid (35.3 mg, 44%, 98% purity).

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Supporting Information Available: Additional conditions, tables and graphical, ^{1}H NMR, ^{13}C NMR, and 2D experiment. This material is available free of charge via the Internet at http://pubs.acs.org.