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A Novel Approach to the Synthesis of 6-Substituted Uracils in Three-Step, One-Pot Reactions

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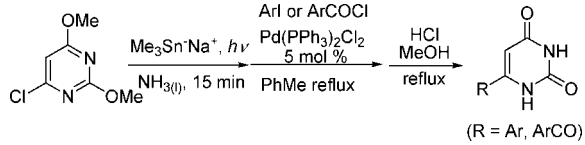

From the commercial 6-chloro-2,4-dimethoxypyrimidine (**1**) and by a photostimulated reaction with Me_3Sn^- ions, 2,4-dimethoxy-6-(trimethylstannyl)pyrimidine (**2**) was obtained in 95% yield. By the cross-coupling reaction of **2** with 1-iodonaphthalene as electrophile catalyzed by Pd (Stille reaction), 2,4-dimethoxy-6-(naphthalen-1-yl)pyrimidine (**9**) was obtained in 76% yield. By hydrolysis of **9**, 6-(1-naphthyl)uracil was obtained in 98% of isolated yield. When the three steps ($S_{RN}1$ reaction−cross coupling reaction−hydrolysis) were performed in a one-pot reaction, 6-substituted uracils (1-naphthyl, 4-chlorophenyl, 3-chlorophenyl, 2,3,4,5,6-pentafluorophenyl) were obtained (43−57%) of isolated pure products. When the electrophile was a benzoyl chloride, 6-benzoyl uracil (54%) and 6-(2-chlorobenzoyl) uracil (49%) were obtained in isolated pure products.

Introduction

Since the uracil unit is present in the DNA and related natural products, the preparation of functionalized uracil derivatives is of special interest. Uracils are privileged structures in drug discovery, widely used in oncology.[1] The functionalization of uracil derivatives at the C6 position is therefore of great synthetic importance.

6-Aminouracils were obtained by treatment of the corresponding substituted 6-chlorouracil derivatives with the appropriate amine.[2] These substrates react with 4-(dimethylamino)pyridine in boiling 1,2-dichlorobenzene to afford the uracilylpyridinium chloride.[3]

6-Thioether uracils were synthesized by reaction of 6-chloro or 6-tosylate with thiols.[4] Under microwave irradiation, the nucleophilic substitution reactions of 6-halouracils with selenium, sulfur, oxygen, and nitrogen nucleophiles after several minutes were completed with good yields.[5]

6-(Substituted phenyl)uracils and thiouracils were synthesized by the condensation of β-(substituted phenyl)-β-oxopropionates with thiourea.[6]

Lithiation of 1,3,6-trimethyluracil takes place at the methyl in the 6-position in an essentially regiospecific manner. Therefore this sequence was used for the preparation of several types of 6-alkyl-substituted uracil derivates that showed activity against Parainfluenza 1(Sendai) virus.[7]

Other functionalizations require the protection of carbonyl groups, and the introduction of functionality is implemented by directed lithiation[8] or bromine−lithium exchange[9] starting from 5-halo-2,4-dialkoxypyrimidines. These methods allow the preparation of various uracil derivatives. However, they require low temperatures and preclude the presence of sensitive functional groups. The magnesiation of 5-bromo-2,4-dialkoxypyrimidines has

(1) Newkome, G. R.; Pandler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, 1982.
(2) (a) Klein, R. S.; Lenzi, M.; Lim, T. H.; Hotchkiss, K. A.; Wilson, P.; Schwartz, E. L. *Biochem., Pharmacol.* **2001**, *62*, 1257. (b) Nencka, R.; Votruba, I.; Hrebabecký, H.; Tloustová, E.; Horská, K.; Masojídková, M.; Holý, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1335.
(3) Schmidt, A.; Kindermann, M. K. *J. Org. Chem.* **1997**, *62*, 3910.
(4) Benhida, R.; Aubertin, A.-M.; Grierson, D. S.; Monneret, C. *Tetrahedron Lett.* **1996**, *37*, 1031.
(5) Fang, W-P.; Cheng, Y.-T.; Cheng, Y.-R.; Cherng, Y.-J. *Tetrahedron* **2005**, *61*, 3107.
(6) Clark, J.; Munawar, Z. *J. Chem. Soc. (C)* **1971**, 1945.
(7) (a) Botta, M.; Saladino, R.; Delle Monache, G.; Gentile, G.; Nicoletti, R. *Heterocycles* **1996**, *43*, 1687. (b) Saladino, R.; Crestini, C.; Palamara, A. T.; Danti, M. C.; Manetti, F.; Corelli, F.; Garaci, E.; Botta, M. *J. Med. Chem.* **2001**, *44*, 4554.
(8) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841.
(9) (a) De Corte, B. L.; Kinney, W. A.; Liu, L.; Ghosh, S.; Brunner, L.; Hoekstra, W. J.; Santulli, R. J.; Tuman, R. W.; Baker, J.; Burns, C.; Proost, J. C.; Tounge, B. A.; Damiano, B. P.; Maryanoff, B. E.; Johnson, D. L.; Galemmo, R. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5227. (b) Reese, C. B.; Wu, Q. *Org. Biomol. Chem.* **2003**, *1*, 3160.

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also been described.[10] Recently a novel route for the synthesis of 5,6-difunctionalized uracils by using a chemo- and regioselective bromine/magnesium exchange reaction on 5-bromo-6-halo-2,4-dimethoxypyrimidines has been developed.[11]

In the present study, we explore the synthesis of 6-substituted uracils by $S_{RN}1$ reactions of 6-chloro-2,4-dimethoxypyrimidine with Me_3Sn^- ion, followed by cross-coupling reactions of the stannane obtained and finally by the hydrolysis of these products.

The unimolecular radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which an aromatic nucleophilic substitution is achieved. Since the scope of this process has increased considerably over the last decades, nowadays it serves as an important synthetic strategy.[12] The wide variety of nucleophiles that can be used, the great functional group tolerance, and the fact that many carbon−carbon and carbon−heteroatom bonds can be obtained make the $S_{RN}1$ reaction a powerful synthetic tool.

We have described the photostimulated reactions of Me_3Sn^- ions with several chloroarenes in liquid ammonia that afford $ArSnMe_3$ from very good to excellent yields, and these reactions occur by the $S_{RN}1$ mechanism.[13]

These reactions are an alternative route to the synthesis of stannanes, by which the use of Grignard reagents or organolithium compounds could be avoided. In addition, the $S_{RN}1$ reactions of Me_3Sn^- ions with chloroarenes are quite versatile. The products are of synthetic relevance and can be employed as intermediates in several reactions, such as the Stille reaction.[14]

Results and Discussion

In the photostimulated reaction of 6-chloro-2,4-dimethoxypyrimidine **1** (0.50×10^{-3} mol dissolved in 1 mL of ether) with Me_3Sn^- ions (prepared with Me_3SnCl and Na metal in liquid ammonia) (0.55×10^{-3} mol) the stannane **2** was obtained in 95% yield (76% isolated) (eq 1) (expt 1, Table 1). When the reaction was performed in the dark, the yield was 7%, and 73% of the substrate remained unaltered. The photostimulated reactions are also inhibited by 1,4-dinitrobenzene, a well-known inhibitor of $S_{RN}1$ reactions and di-*tert*-butyl nitroxide (a known radical trap).[12] This indicates that the reaction occurs by the $S_{RN}1$ mechanism. The fact that the yield of the dark reactions fell to zero in the presence of di-*tert*-butyl nitroxide led us to conclude that the dark component came from the same mechanism, through a spontaneous electron transfer (thermal initiation).

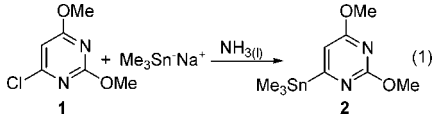


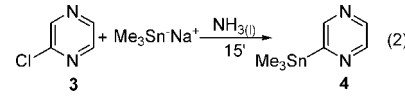
TABLE 1. $S_{RN}1$ Reactions of 1 with Me_3Sn^- Ions[a]

expt	**1**, 10^{-3} mol	$Me_3Sn^-Na^+$, 10^{-3} mol	conditions	**2**, yield (%)[b]
1	0.50	0.55	*hν*	95
2	0.25 (73%)[c]	0.26	dark	7
3[d]	0.50 (80%)[c]	0.55	dark	0
4[d]	0.23 (80%)[c]	0.26	*hν*	20
5[e]	0.24 (37%)[c]	0.26	*hν*	39

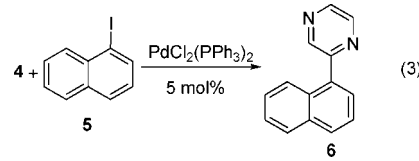
[a] All reactions were performed in liquid ammonia during 15 min; the substrate was added in 1 mL of Et_2O. Photostimulated reactions employed two water-cooled medium-pressure Hg lamps. [b] Product yields were determined by CG analysis, using authentic samples as references. [c] Yield of substrate recovered. [d] 30% of di-*tert*-butyl nitroxide was added. [e] 30 mol % of 1,4-dinitrobenzene was added.

Substrate 6-bromo-2,4-dimethoxypyrimidine only afforded the reduction product 2,4-dimethoxypyrimidine by a halogen metal exchange reaction.

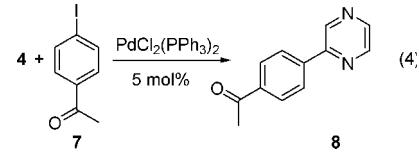
Prior to the next step in our synthesis, we decided to study the Stille reaction with stannane **4** (eq 2) as a model substrate. There is a fast reaction (15 min) of Me_3Sn^- ions and 2-chloropyrazine **3** to obtain **4** in excellent yield (97%) (eq 2).



With stannane **4** thus obtained we performed the cross-coupling reaction with 1-iodonaphthalene **5** as a model electrophile under different conditions (Table 2) to obtain 2-(1-naphthyl)pyrazine **6** (eq 3).



The nonpolar solvent (PhMe) was better than polar ones (DMF and NMP, Table 2, expts 1, 6 and 7). Under the best conditions **6** was obtained in 79% yield when CsF, CuI, and Ph_3P were added (Table 2, expt 3). 4-Iodoacetophenone **7** was another electrophile studied, and good yields of the cross-coupling product **8** were obtained (Table 2, expt 8) (eq 4). However, its yield decreased when the best condition found for **5** was used (Table 2, expt 9).



The possibility of performing the synthesis of **4** and the Stille reaction in a two-step, one-pot reaction was also explored. Therefore, we carried out the $S_{RN}1$ reaction employing **3** (0.97×10^{-3} mol), in 50 mL of dry liquid ammonia and Me_3Sn^- ions (0.97×10^{-3} mol), under an atmosphere of nitrogen during 15 min to obtain stannane **4**. Then the ammonia was allowed to evaporate, PhMe was added (20 mL), and iodoarene **5** (0.97×10^{-3} mol) and the catalyst system $PdCl_2(Ph_3P)_2$ (5 mol %) were added, the reaction was refluxed for 4 h, and product **6** was obtained in 57% yield (duplicate experiments).[15] However,

(10) (a) Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Masataka, Y. *J. Org. Chem.* **1998**, *63*, 7207. (b) Shimura, A.; Momotake, A.; Togo, H.; Yokoyama, M. *Synthesis* **1999**, 495.

(11) Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737.

(12) For reviews, see: (a) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71. (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.

(13) (a) Yammal, C. C.; Podesta, J. C.; Rossi, R. A. *J. Org. Chem.* **1992**, *57*, 5720. (b) Corsico, E. F.; Rossi, R. A. *Synlett* **2000**, 227. (c) Santiago, A. N.; Basso, S. M.; Montañez, J. P.; Rossi, R. A. *J. Phys. Org. Chem.* **2006**, *19*, 829.

(14) (a) Corsico, E. F.; Rossi, R. A. *Synlett* **2000**, 230. (b) Corsico, E. F.; Rossi, R. A. *J. Org. Chem.* **2002**, *67*, 3311. (c) Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, 359.

(15) There was no substrate left.

TABLE 2. Cross-Coupling Reactions of 4 with 5[a]

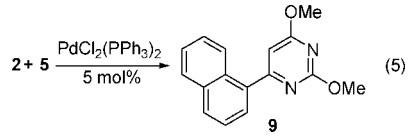
expt	**2**, 10^{-3} mol	**5**, 10^{-3} mol	conditions	**4**, yield (%)[b]
1	0.23	0.23	PhMe, 4 mL, reflux, 18 h	70[c]
2	0.30	0.31	PhMe, 5 mL, 60 °C, 5 days	25[d]
3[e]	0.20	0.21	PhMe, 2 mL, 80 °C, 24 h	79[c]
4[f]	0.21	0.22	PhMe, 2 mL, 80 °C, 13 h	19[c]
5[g]	0.25	0.26	PhMe, 5 mL, 85 °C, 3 h	42[c]
6	0.26	0.27	DMF, 5 mL, 80 °C, 3 h	12[h]
7[f]	0.25	0.26	NMP, 2 mL, 80 °C, 3 h	50[c]
8[i]	0.22	0.24	PhMe, 10 mL, reflux, 10 h	88[c]
9[i,e]	0.21	0.23	PhMe, 10 mL, 80 °C, 24 h	78[c]

[a] The catalyst was $PdCl_2(Ph_3P)_2$ (5 mol %). In addition to the cross-coupling product **4**, small amounts of homocoupling products were detected, but not quantified. [b] Quantified by GC, using the internal standard method. [c] There was no substrate left. [d] Substrate was recovered in 43% yield. [e] CsF (0.4×10^{-3} mol), CuI (10 mol %), and Ph_3P (10 mol %) were added. [f] CsF (0.4×10^{-3} mol), CuI (10 mol %), and Ph_3P (20 mol %) were added. [g] The catalyst was $Pd(Ph_3P)_4$. [h] Substrate was recovered in 60% yield. [i] The electrophile was **7**.

when the optimized reaction conditions obtained for the Stille reaction (conditions of Table 2, expt 3) were used, **6** was formed in 55% yield, the same yield when no additive was used.

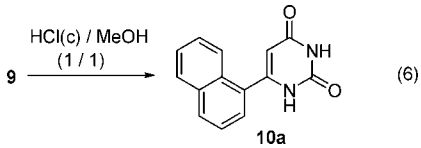
These results, and the fact that the use of additives seems to be deleterious for other electrophiles in the Stille reactions (see Table 2, expt 8 and 9), prompted us to perform the Stille reaction without additives in the "one-pot" synthesis of uracil derivates.

After studying the Stille reaction, we resumed our target synthesis and performed the reaction with stannane **2** (0.25×10^{-3} mol) and electrophile **5** (0.32×10^{-3} mol) in the presence of $PdCl_2(Ph_3P)_2$ as catalyst (5 mol %) in refluxing toluene (5 mL) during 15 h; 2,4-dimethoxy-6-(naphthalen-1-yl)pyrimidine **9** was obtained in 67% yield (eq 5).



The $S_{RN}1$−Stille sequence was performed in a two-step, one-pot reaction as indicated before for the model reaction. The $S_{RN}1$ reaction was carried out with **1** (0.50×10^{-3} mol), and Me_3Sn^- ions (0.51×10^{-3} mol), **5** (0.51×10^{-3} mol), and the catalyst system $PdCl_2(Ph_3P)_2$ (5 mol %): product **9** was obtained in 61% yield (duplicate experiments).

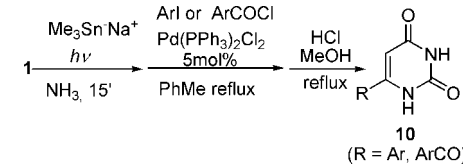
To end the reaction sequence to yield 6-subtituted uracil, product **9** (0.23×10^{-3} mol) was hydrolyzed with HCl−MeOH (1:1, 10 mL) and boiled for 18 h, and 6-(naphthalen-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione **10a** was obtained quantitatively (98% isolated yield, eq 6).



Finally, we studied the possibility of performing a three-step, one-pot reaction $S_{RN}1$−Stille−hydrolysis from the commercial pyrimidine **1** to obtain 6-aryl and 6-acyl substituted uracils (Scheme 1) without the need to isolate the intermediate product (Table 3).

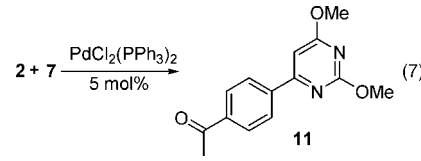
We proceeded as indicated before for the $S_{RN}1$−Stille one-pot reactions, then toluene was evaporated, MeOH/HCl was added, and the mixture was refluxed for 20−24 h. After

SCHEME 1. Three-Step, One-Pot Synthesis of 6-Substituted Uracils



extraction of the final mixture the solid products were obtained in high purity in good yields, after being washed with Et_2O.

Surprisingly, eletrophile **7**, which worked well in the cross-coupling of the model reaction (Table 2, expt 8), only gave a low yield (30%) of the desired product. In view of these results, we performed the Stille reaction of **2** with electrophile **7** and obtained a 60% yield of product **11** (eq 7).



However, with this yield of the Stille reaction, a yield of about 50% of the global reaction $S_{RN}1$−Stille−hydrolysis is expected; therefore it is believed that there has been some problem in the conditions of the last step for the synthesis of this compound. Yet, its reasons are still unclear.

Conclusions

In summary, we have shown that the reactions of commercial 6-chloro-2,4-dimethoxypyrimidine (**1**) in liquid ammonia afford 6-substituted uracils with good yields in a three-step, one-pot reaction. Considering the availability/simplicity of the starting materials, the readiness and mild reaction conditions of the procedure, we believe that this procedure might become a general method for the synthesis of this family of compounds.

Experimental Section

2,4-Dimethoxy-6-(trimethylstannyl)pyrimidine (2). Reactions of $Me_3Sn^-Na^+$ in liquid ammonia: 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. $ClSnMe_3$ (109.6 mg, 0.55 mmol) was then added, and Na metal (30.6 mg, 1.33 mmol) in small pieces was introduced, waiting for total discoloration between each addition. A lemon yellow solution of Me_3Sn^- ions is obtained. Then 6-chloro-2,4-dimethoxypyrimidine (87.3 mg, 0.50 mmol) was dissolved in 1 mL of dried ethyl ether and added to the solution. The reaction mixture was irradiated for 15 min with use of two medium-pressure mercury lamps emitting maximally at 350 nm. The reaction was quenched by adding ammonium nitrate in excess. The ammonia was allowed to evaporate, and water (50 mL) was added. The aqueous phase was extracted with Et_2O (3×40 mL), the organic phase was dried (magnesium sulfate), and the solvent was evaporated in vacuum. The product was purified by radial thin-layer chromatography on aluminum oxide eluting with petroleum ether/ethylic ether 90:10. Colorless oil was isolated in 76% yield (115.1 mg, 0.38 mmol). ^1H NMR (400 Mhz, CCl_3D) δ 6.56 (s, $^{H-Sn}J = 12.4$, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 0.31 (s, $^{H-Sn}J = 27.7$, 9H). ^{13}C NMR (100.6 MHz, CCl_3D) δ 184.8, 169.5, 164.1, 110.1, 54.4, 53.1, −9.6. CG/MS (*m*/*z*) 304 (M^+ (^{120}Sn), 1), 289 (isotopic cluster, M^+ (^{120}Sn) − CH_3, 100), 259 (43), 165 (15), 163 (12), 162 (10), 151 (15), 149

TABLE 3. Three-Step, One-Pot Synthesis of 6-Substituted Uracils[a]

expt	**1** (10^{-3} mol)	Me_3Sn^- Na^+ (10^{-3} mol)	ArI or ArCOCl (10^{-3} mol)	product (yield %)[b]
1	0.42	0.44	**5** (0,44)	**10a**(57)
2	0.47	0.50	**7** (0.58)	**10b**(30)
3	0.37	0.39	1-chloro-4-iodobenzene (0.49)	**10c**(55)
4	0.50	0.57	1-chloro-3-iodobenzene (0.58)	**10d**(43)
5	0.39	0.43	1,2,3,4,5-pentafluoro-6-iodobenzene (0.46)	**10e**(50)
6	0.48	0.50	benzoyl chloride (0.65)	**10f** (54)
7	0.37	0.40	2-chlorobenzoyl chloride (0.46)	**10g**(49)

[a] The $S_{RN}1$ reactions were performed in ca. 50 mL of liquid ammonia. The Stille reaction was in PhMe (ca. 10 mL) at reflux during 16−20 h. The catalyst was $PdCl_2(Ph_3P)_2$ (5 mol %). The hydrolysis was performed with HCl(c)/MeOH (1:3, 13 mL) at reflux during 20−24 h. [b] Isolated yield (>95% purity by ^{1}H NMR).

(14), 135 (33), 134 (11), 133 (26), 131 (17), 72 (10), 66 (11). ESI/APCI-HRMS Anal. calcd for $C_9H_{16}N_2O_2Sn$ 304.0234, found 304.0225.

2-(Trimethylstannyl)pyrazine[16] (4). To a lemon yellow solution of Me_3Sn^- ions (0.55 mmol) was added 2-chloropyrazine (57.3 mg, 0.50 mmol) dissolved in 1 mL of dried ethyl ether. The reaction mixture was allowed to react for 15 min and treated as previously described. The product was purified by radial thin-layer chromatography on aluminum oxide eluting with petroleum ether/diethyl ether 90:10. A colorless oil was isolated (78.9 mg, 0.33 mmol, yield 65%). ^{1}H NMR (400 MHz, CCl_3D) δ 8.69 (dd, ^3J = 2.27 Hz, ^4J = 1.73 Hz, 1H), 8.58 (d, ^4J = 1.58 Hz, 1H), 8.39 (d, ^3J = 2.51 Hz, 1H), 0.42 (s, ^{H-Sn}J = 27.8 Hz, 9H). ^{13}C NMR (100.6 MHz, CCl_3D) δ 169.0, 150.6, 146.6, 143.2, −9.4. CG/MS (*m*/*z*) 244 (isotopic cluster, M^+ (^{120}Sn), 12), 229 (isotopic cluster, $M^+ - CH_3$ (^{120}Sn), 100), 199 (39), 165 (25), 164 (26), 163 (21), 162 (21), 161(16), 160 (10), 146(11), 145 (10), 135 (54), 134 (17), 133 (43), 132 (15), 131(25), 120 (13), 118 (10), 52(11).

2-(Naphthalen-1-yl)pyrazine[17] (6). General procedure for cross-coupling reactions: Into a 2-necked round-bottomed flask equipped with a nitrogen inlet and magnetic stirrer were added 4 mL of toluene, 2-(trimethylstannyl)pyrazine (55.9 mg, 0.23 mmol), and 1-iodonaphthalene (58.4 mg, 0.23 mmol). Then cesium fluoride (69.9 mg, 0.46 mmol), dichlorobis(triphenylphosphine)palladium(II) (8.4 mg, 0.012 mmol, 5 mol %), and triphenylphosphine (6.3 mg, 0.024 mmol, 10 mol %) were introduced and the reaction mixture was stirred for 5 min. Copper(I) iodide (4.6 mg, 0.024 mmol, 10 mol %) was added and the mixture was warmed at the temperature and the time indicated (see Table 2). Water was added (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic phase was dried (magnesium sulfate), and the solvent was evaporated in vacuum. The product was separated and isolated by radial thin-layer chromatography on silica gel eluting with petroleum ether/diethyl ether. A colorless oil was isolated. Spectral data for **6** (^{1}H and ^{13}C NMR, MS) agree with those previously reported.[17]

1-(4-(Pyrazin-2-yl)phenyl)ethanone (8). Toluene, **4**, 4-iodoacetophenone (**7**), and the catalyst (and additives) were added and refluxed for 10 h. Product **8** was isolated as a yellow oil. ^{1}H NMR (400 MHz, CCl_3D) δ 9.09 (d, J = 1.44 Hz, 1H), 8.68 (dd, J = 2.32 Hz, 1.64 Hz, 1H), 8.57 (d, J = 2.45 Hz, 1H), 8.11 (m, 4H), 2.66 (s, 3H). ^{13}C NMR (100.6 MHz, CCl_3D) δ 197.5, 151.5, 144.3, 143.7, 142.4, 140.4, 137.8, 128.9, 127.0, 26.7. CG/MS (*m*/*z*) 199 (M^+ + 1, 5), 198 (M^+, 38), 184 (13), 183 (100), 155 (45), 128 (10), 102 (10), 101 (11), 43 (11). ESI/APC -HRMS Anal. calcd for $C_{12}H_{10}N_2O$ 198.0793, found 198.0787.

2,4-Dimethoxy-6-(naphthalen-1-yl)pyrimidine (9). Toluene (5 mL), **2** (75.7 mg, 0.25 mmol), 1-iodonaphthalene (81.3 mg, 0.32 mmol), and 5 mol % (8.8 mg, 0.0125 mmol) of the catalyst (dichlorobis(triphenylphosphine)palladium(II)) were added and the mixture was refluxed for 15 h. The product was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether to yield 44.6 mg (0.17 mmol, 67%) of a white solid. Mp 78−80 °C. ^{1}H NMR (400 MHz, CCl_3D) δ 8.25 (m, 1H), 7.91 (m, 2H), 7.65 (dd, ^3J = 7.09 Hz, ^4J =1.16 Hz, 1H), 7.51 (m, 3H), 6.67 (s, 1H), 4.07 (superimposed s, 3H), 4.06 (superimposed s, 3H). ^{13}C NMR (100.6 MHz, CCl_3D) δ 172.0, 168.4, 165.2, 136.2, 133.8, 130.6, 129.9, 128.4, 127.3, 126.5, 126.0, 125.4, 125.1, 102.4, 54.9, 53.9. CG/MS (*m*/*z*) 267 (M^+ + 1, 10), 266 (M^+, 61), 265 (100), 250 (13), 194 (12), 193 (38), 166 (13), 165 (14), 152 (9), 126 (10), 83 (10). ESI/APCI-HRMS Anal. calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1057.

1-(4-(2,4-Dimethoxypyrimidin-6-yl)phenyl)ethanone (11). Toluene (4 mL), **2** (60.6 mg, 0.20 mmol), 4-iodoacetophenone (51.7 mg, 0.21 mmol), and 5 mol % (7 mg, 0.01 mmol) of the catalyst (dichlorobis(triphenylphosphine)palladium(II)) were added and the mixture was refluxed for 16 h. The product was purified by column chromatography on silica gel eluting with a petroleum ether/diethyl ether mixture, and 31 mg (0.12 mmol, 60%) of a white solid was obtained. Mp 121−123 °C. ^{1}H NMR (400 MHz, CCl_3D) δ 8.14 (m, 2H), 8.04 (m, 2H), 6.83 (m, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (100.6 MHz, CCl_3D) δ 197.5, 172.6, 165.5, 164.6, 140.9, 138.4, 128.6, 127.2, 98.0, 54.8, 54.0, 26.7. CG/MS (*m*/*z*) 260 (M^+ + 2, 2), 259 (M^+ + 1, 15), 258 (M^+, 100), 257 (57), 244 (13), 243 (75), 229 (16), 228 (34), 215 (21), 172 (12), 143 (35), 115 (12), 99 (17), 72 (12), 43 (22). ESI/APCI-HRMS Anal. calcd for $C_{14}H_{14}N_2O_3$ 258.1004, found 258.1011.

6-(Naphthalen-1-yl)uracil (10a). General procedure for hydrolysis: To a solution of MeOH (10 mL) was added **9** (61.2 mg, 0.23 mmol) and the mixture was stirred for 5 min until total dissolution, then HCl concentrate (36%, 10 mL) was introduced and the mixture was refluxed until **9** was completely consumed (18 h). A saturated solution of $NaHCO_3$ was carefully introduced to neutralize the acid, water was added (20 mL), and the aqueous phase was extracted with AcOEt (3 × 50 mL), the organic phase was dried (magnesium sulfate), and the solvent was evaporated in vacuum. A pure product was obtained as a white solid in 98% (53.7 mg, 0.22 mmol) isolated yield. Mp 317 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.26 (superimposed s, 1H), 11.23 (superimposed s, 1H), 8.03 (m, 3H), 7.61 (m, 4H), 5.57 (s, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 163.9, 152.5, 151.4, 132.9, 130.6, 130.1, 129.7, 128.3, 127.1, 126.6, 126.4, 125.1, 124.6, 101.4. CG/MS (*m*/*z*) 239 (M^+ + 1, 4), 238 (M^+, 59), 237 (19), 222 (15), 221 (100), 194 (13), 179 (15), 168 (12), 167 (75), 166 (59), 140 (15), 139 (27), 127 (26), 126 (13), 84 (12), 84(13), 70 (12), 63 (10). ESI/APCI-HRMS Anal. calcd for $C_{14}H_{10}N_2O_2$ 238.0742, found 238.0739.

General Procedure for Three-Step, One-Pot Reactions ($S_{RN}1$−Stille−Hydrolysis). Ammonia (50 mL), previously dried with Na metal under nitrogen, was condensed into a 3-necked, 100-mL round-bottomed flask equipped with a coldfinger condenser charged with ethanol, a nitrogen inlet, and a magnetic stirrer. Me_3SnCl was then added, and Na metal in small pieces was introduced, waiting for total discoloration between each addition. A lemon yellow solution of Me_3Sn^- ions was obtained. Then 6-chloro-2,4-dimethoxypyrimidine was dissolved in 1 mL of dried ethyl ether and added to the solution. The reaction mixture was

(16) Yang, Y.; Martin, A. R. *Synth. Commun.* **1992**, *22*, 1757.
(17) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2007**, *68*, 4302.

irradiated for 15 min with use of two medium-pressure mercury lamps emitting maximally at 350 nm. The ammonia was allowed to evaporate under N_2. Then toluene (10 mL) was added followed by the addition of electrophile (ArI or ArCOCl) and the catalyst ($PdCl_2(PPh_3)_2$). The reaction was refluxed overnight. Then MeOH was added (20 mL) and the solution was evaporated in vacuum. MeOH (10 mL) was added and the solution was stirred for 5 min, HCl (36%, 3 mL) was introduced, and the mixture was refluxed for 20−24 h. A saturated solution of $NaHCO_3$ was carefully added to neutralize the acid. Water (20 mL) was added and the aqueous phase was extracted with AcOEt (3 × 50 mL), the organic phase was dried (magnesium sulfate), and the solvent was evaporated in vacuum. The solid residue was washed with boiling ethyl ether (5 mL) and the product was isolated with >95% purity (H^1 RMN).

6-(Naphthalen-1-yl)uracil (10a). Substrate **1** (73.3 mg, 0.42 mmol) was used with 1-iodonaphthalene (111.8 mg, 0.44 mmol) as the electrophile. The product was obtained as a yellow solid. Isolated yield 57% (57 mg, 0.24 mmol). Recrystallization from MeOH gave a white solid. Mp: 317 °C decomposed.

6-(4-Acetylphenyl)uracil (10b). Substrate **1** (82.0 mg, 0.47 mmol) was used with 4-iodoacetophenone (142.7 mg, 0.58) as the electrophile. The product was obtained as a yellow solid. Isolated yield 30% (32.4 mg, 0.14 mmol). Recrystallization from EtOH gave a white solid. Mp: up to 390 °C (at this temperature the solid turned brown). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.20 (superimposed s, 1H), 11.17 (superimposed s, 1H), 8.03 (d, ^3J = 8.36 Hz, 2H), 7.86 (d, ^3J = 8.37 Hz, 2H), 5.89 (s, 1H), 2.62 (s, 3H).^{13}C NMR (100.6 MHz, d_6-DMSO) δ 197.9, 164.3, 152.2, 151.8, 138.9, 136.1, 128.8, 127.8, 99.6, 27.3. ESI/APCI-HRMS Anal. calcd for $C_{12}H_{10}N_2O_3$ 230.0691, found 230.0696.

6-(4-Chlorophenyl)uracil[6] (10c). Substrate **1** (64.6 mg, 0.37 mmol) was used with 1-chloro-4-iodobenzene (116.8 mg, 0.49 mmol) as the electrophile. The product was obtained as a yellow solid. Isolated yield 55% (45.3 mg, 0.22 mmol). Recrystallization from EtOH gave a white solid. Mp: 325 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.17, (br s, 2H), 7.74 (d, ^3J = 8.64 Hz, 2H), 7.56 (d, ^3J = 8.63 Hz, 2H), 5.84 (d, J = 1.52 Hz, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 163.8, 151.6, 151.2, 135.7, 130.3, 128.8, 128.7, 98.3. CG/MS (*m*/*z*) 225 (M^+ + 3, 4), 224 (M^+ + 2, 37), 223 (M^+ + 1, 16), 222 (M^+, 100), 181 (19), 180 (15), 179 (52), 151 (21), 140 (25), 139 (12), 138 (78), 137 (11), 111 (13), 102 (13), 89 (12), 76 (13), 75 (25), 68 (15), 50(11).

6-(3-Chlorophenyl)uracil[6] (10d). Substrate **1** (87.3 mg, 0.50 mmol) was used with 1-chloro-3-iodobenzene (138.3 mg, 0.58 mmol) as the electrophile. The product was obtained as a yellow solid. Isolated yield 43% (47.9 mg, 0.22 mmol). Recrystallization from EtOH gave a white solid. Mp: 280−283 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.20 (superimposed s, 1H), 11.17 (superimposed s, 1H), 7.81 (br s, 1H), 7.68 (m, 1H), 7.60 (m, 1H), 7.52 (t, ^2J = 7.90 Hz, 1H), 5.88 (s, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 163.9, 151.6, 150.9, 133.6, 133.4, 130.7, 130.5, 126.8, 125.7, 98.8. CG/MS (*m*/*z*) 225 (M^+ + 3, 3), 224 (M^+ + 2, 35), 223 (M^+ + 1, 16), 222 (M^+, 100), 181 (20), 180 (13), 179 (61), 151 (18), 140 (22), 138 (70), 111 (17), 89 (11), 75 (21), 68 (16).

6-(Perfluorophenyl)uracil (10e). Substrate **1** (68.1 mg, 0.39 mmol) was used with 1,2,3,4,5-pentafluoro-6-iodobenzene (135.2 mg, 0.46 mmol) as the electrophile. The product was obtained as a yellow solid. Isolated yield 50% (54.2 mg, 0.20 mmol). **10e** was purified by short column chromatography on silica gel eluting with ethyl ether. White solid. Mp: 64−267 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.46 (superimposed s, 1H), 11.44 (superimposed s, 1H), 5.82 (d, J = 1.58 Hz, 1H). ^{19}F NMR (376.4 MHz, d_6-DMSO) δ −139.14 (d, J = 18.39 Hz, 2F), −151.08 (t, J = 22.43 Hz, 1F), −161.48 (m, 2F). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ[18] 163.2, 151.0, 139.0, 104.0. CG/MS (*m*/*z*) 279 (M^+ + 1, 4), 278 (M^+, 38), 277 (100), 201 (12), 199 (21), 183 (14), 152 (11), 77 (18), 51 (12). ESI/APCI-HRMS Anal. calcd for $C_{10}H_3F_5N_2O_2$ 278.0115, found 278.0117.

6-Benzoyluracil (10f). Substrate **1** (83.8 mg, 0.48 mmol) was used with benzoyl chloride (91.4 mg, 0.65 mmol) as the electrophile. The product was obtained as a light brown solid. Isolated yield 54% (56.0 mg, 0.26 mmol). Filtration over silica gel followed by recrystallization from EtOH gave a white solid. Mp: 221 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.37 (superimposed s, 1H), 11.21 (superimposed s, 1H), 7.92 (m, 2H), 7.76 (m, 1H), 7.60 (t, ^3J = 7.76 Hz, 2H), 5.70 (s, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 189.3, 164.2, 151.4, 148.1, 135.0, 134.5, 130.3, 129.4, 103.9. CG/MS (*m*/*z*) 217 (M^+ + 1, 7), 216 (M^+, 54), 188 (17), 145 (29), 105 (100), 77 (78), 68 (46), 51 (30). ESI/APCI-HRMS Anal. calcd for $C_{11}H_8N_2O_3$ 216.0535, found 216.0532.

6-(2-Chlorobenzoyl)uracil (10g). Substrate **1** (64.6 mg, 0.37 mmol) was used with 2-chlorobenzoyl chloride (80.5 mg, 0.46 mmol) as the electrophile. The product was obtained as a light brown solid. Isolated yield 49% (45.4 mg, 0.18 mmol). Filtration over silica gel followed by recrystallization from EtOH gave a white solid. Mp ∼215 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.50 (br s, 1H), 11.30 (br s, 1H), 7.67 (m, 3H), 7.53 (m, 1H), 5.55 (d, J = 1.54 Hz, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 188.9, 164.3, 151.2, 146.5, 134.9, 133.8, 131.1, 130.9, 130.7, 127.9, 107.2, CG/MS (*m*/*z*) 253 (M^+ + 3, 2), 252 (M^+ + 2, 15), 251 (M^+ + 1, 5), 250 (M^+, 43), 215 (39), 179 (16), 172 (19), 144 (27), 141 (31), 139 (100), 113 (13), 111 (38), 75 (31), 68 (74), 50 (12). ESI/APCI-HRMS Anal. calcd for $C_{11}H_7ClN_2O_3$ 250.0145, found 250.0142.

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Supporting Information Available: General methods, ^{1}H NMR, and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The aromatic carbons were not observed due to the low relaxations of the C system and the large coupling C−F.