Preparation and Reactions of Zincated Thymine Derivatives

Laurent Bérillon, Robert Wagner, and Paul Knochel*

Fachbereich Chemie der Philipps-Universität Marburg, Hans-Meerwein-Strasse, D-35032 Marburg, Germany

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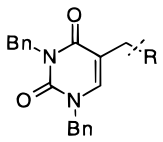
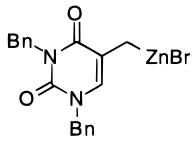
Heterocycle rings are partial structures of many pharmaceuticals, and general synthetic methods for coupling heterocyclic building blocks to other organic groups are required for the preparation of new molecules of biological interest.[1] Recently, we have shown that many heterocyclic iodides are readily converted to the corresponding zinc reagent by the direct insertion of zinc dust in THF.[2] This approach can be successfully applied to prepare zincated uracil and purine derivatives.[2,3] These metalated nucleosides undergo cross-coupling reactions with various aromatic and heterocyclic iodides in the presence of a Pd(0) catalyst.[2−4] Functionalized thymine derivatives of type **1** are potentially interesting target molecules for their antiviral activity.



1



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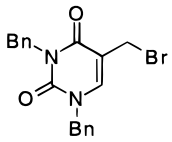

3

We have envisioned that these heterocycles could be prepared using the zincated thymine derivative **2**. Very few heterocyclic benzylic zinc reagents are known,[5,6] and no cross-coupling reactions have been performed with these reagents. Herein, we report a simple preparation of 1,3-dibenzyl-5-bromomethyluracil (**3**) starting from uracil (**4**), its straightforward conversion to the new heterocyclic benzylic zinc reagent (**2**), and its successful use in palladium(0)-catalyzed cross-coupling reactions.

Uracil (**4**) was converted to the corresponding hydroxymethyl derivative **5** according to a literature procedure[7] ((i) $Ba(OH)_2$ (0.2 equiv); (ii) aqueous CH_2O, rt, 24 h, 73% yield). The stepwise benzylation of **5** with benzyl alcohol (aqueous HCl cat., reflux, 30 min, 97% yield),[8] leading first to the monobenzylation product **6** followed by the treatment with benzyl bromide ((i) NaH, THF, rt, 1 h; (ii) $PhCH_2Br$ (excess, DMF, rt, 1 h), provides the tribenzylated product (**7**; 81% yield). The conversion of **7** to 1,3-dibenzyl-5-(bromomethyl)uracil (**3**) was performed by the reaction with a HBr solution in 1,4-dioxane (rt, 12 h; 71% yield),[9] completing the synthesis of **3** from uracil **4** in ca. 29% overall yield (Scheme 1). The zinc reagent **2** was obtained by the slow addition (1 drop each 5 s) of a 0.7 M THF solution of **3** to zinc dust (−325 mesh) previously activated by treatment with 1,2-dibromoethane (5 mol %) and TMSCl at 0 °C for 1 h.[6] A yield of ca. 80% is obtained as estimated by hydrolysis and iodolysis experiments. The zinc reagent **2** was treated with various aryl iodides in THF in the presence of catalytic amounts of bis(dibenzylideneacetone)palladium(0)[10] ($Pd(dba)_2$, 2.5 mol %) and (*o*-furyl)$_3$P[11] (tfp, 5 mol %). The reactions are completed after 12 h at room temperature, leading to the desired arylated products **1a**−**j** (Scheme 2 and Table 1). Interestingly, the cross-coupling with (*Z*)-1-iodohexene produces the expected cross-coupling product **1k** (100% *Z*, 85% yield) with complete retention of the stereochemistry (entry 11 of Table 1).

A selective deprotection of a benzyl group was realized. Thus, the treatment of **1b** with 10% Pd on charcoal and HCO_2NH_4 (excess, reflux, 24 h)[12] in methanol produces the monobenzylated product **8** in 77% yield (Scheme 3).

This cross-coupling reaction can be performed in the solid phase, and the zinc reagent **2** may be useful for the preparation of product libraries using combinatorial chemistry methods.[13,14] The reaction of Wang-resin-attached *o*- or *m*-iodobenzoates **9a**,**b** and Rink-resin-attached *p*-iodobenzoate **9c** with the zinc compound **2** (10 equiv) in the presence of Pd(dba) (5 mol %) and tfp (10 mol %) in THF (25 °C, 48 h) produces the expected cross-coupling products **10a**−**c**. After treatment with CF_3CO_2H in CH_2Cl_2, the corresponding *ortho*- and *meta*-substituted carboxylic acids **11a**,**b** and *para*-substituted amide **11c** were obtained with 92%, 89% and 93% purity, respectively, as indicated by HPLC analysis (UV detection at 254 nm; Scheme 4).

Interestingly, regardless of the substitution pattern, the expected cross-coupling products are obtained with excellent purities.

In summary, we have prepared in good yield the zincated thymine derivative **2** and have demonstrated its utility for the performance of palladium catalyzed cross-coupling reactions in solution and in the solid-phase.

Experimental Section

General Methods. Unless otherwise indicated, all reactions were carried out under an argon atmosphere. Solvents (THF

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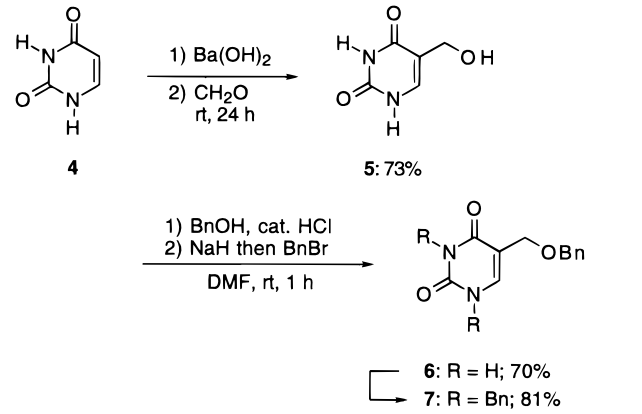
Scheme 1



Scheme 2

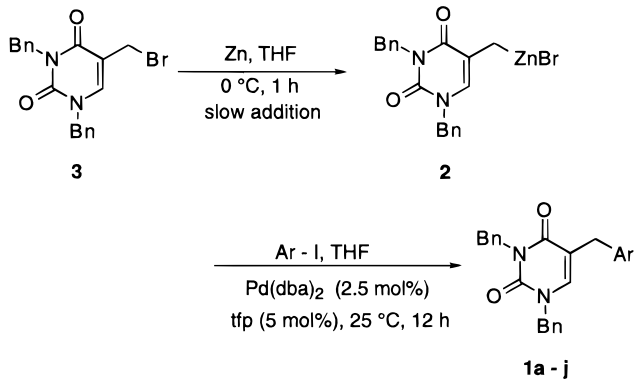
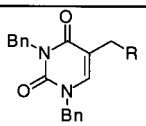
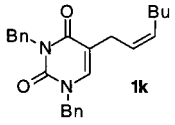
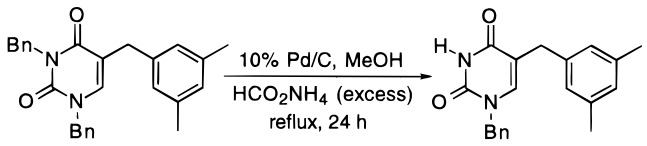


Table 1. Arylated and Alkenylated Thymine Derivatives 1a−k Obtained by the Reaction of the Heterocyclic Benzylic Zinc Reagent 2 with Aryl or Alkenyl Iodides in the Presence of Palladium(0) Catalysis

Entry	ArI	Product of type **1**	yield (%)[a]
1	PhI	 **1a**: R = Ph	89
2	3,5-diMeC$_6$H$_3$I	**1b**: R = diMeC$_6$H$_3$-	81
3	*p*-ClC$_6$H$_4$I	**1c**: R = *p*-ClC$_6$H$_4$-	80
4	*p*-BrC$_6$H$_4$I	**1d**: R = *p*-BrC$_6$H$_4$-	89
5	*p*-CF$_3$C$_6$H$_4$I	**1e**: R = *p*-CF$_3$C$_6$H$_4$-	86
6	*p*-MeOC$_6$H$_4$I	**1f**: R = *p*-MeOC$_6$H$_4$-	62
7	*o*-MeOC$_6$H$_4$I	**1g**: R = *o*-MeOC$_6$H$_4$-	66
8	*o*-NCC$_6$H$_4$I	**1h**: R = *o*-NCC$_6$H$_4$-	76
9	*m*-MeOC$_6$H$_4$I	**1i**: R = *m*-MeOC$_6$H$_4$-	80
10	*m*-C$_4$F$_9$SO$_3$C$_6$H$_4$I	**1j**: R = *m*-C$_4$F$_9$SO$_3$C$_6$H$_4$-	95
11		 **1k**	75

[a] Isolated yield of analytically pure products.

Scheme 3



or DMF) were dried and freshly distilled over respectively sodium/benzophenone and CaH_2. Zinc dust (−325 mesh) was purchased from Aldrich or Riedel-de Haën (Germany). Reactions were monitored by thin-layer chromatography (TLC) analysis of worked-up reaction aliquots. Unless otherwise indicated, the reaction mixtures were worked up as follows: the reaction mixture was poured into a mixture of ethyl acetate and saturated aqueous NH_4Cl. The two-phase mixture was filtered to remove insoluble salts, and the two layers were separated. The combined organic extracts were washed successively with water (50 mL) and brine (20 mL), dried ($MgSO_4$), and filtered. The residue obtained after evaporation of the solvents was purified by flash chromatography. NMR data were recorded on a 200 and 300 MHz NMR spectrometer. The ionization methods used for the mass spectrometry were desorption chemical ionization (CI) and electron impact-ionization (EI, 70 eV).

Starting Materials. Most aryl iodides are commercially available. The following starting materials were prepared according to literature procedures: *m*-$C_4F_9SO_2OC_6H_4I$,[15] (*Z*)-1-iodo-1-hexene.[16]

Preparation of 5-(Hydroxymethyl)uracil (5).[7] Uracil (25 g, 223 mmol) was added to a filtered solution of $Ba(OH)_2 \cdot 8H_2O$ (15 g, 480 mmol) in water (0.5 L). A solution of 37% aqueous formaldehyde (54 mL, 720 mmol) was added, and the reaction mixture was refluxed for a few minutes in order to dissolve uracil. The reaction mixture was allowed to stand for 12 h at room temperature, and CO_2 (g) was bubbled into the reaction mixture in order to precipitate Ba_2CO_3. After filtration, the water was evaporated, and the viscous residue was dissolved at reflux in ethanol (250 mL). The desired product (**5**) crystallized in the refrigerator as a pure white solid (23 g, 73% yield. Mp: 220−230 °C (lit.[7] mp 235 °C). IR (KBr): 3371 (m), 3190 (m), 3037 (m), 1706 (s), 1678 (s), 1432 (m) cm^{-1}. ^1H NMR (200 MHz, D_2O): δ 7.60 (s, 1H), 4.37 (s, 2H). ^{13}C NMR (125 MHz, D_2O): δ 163.9, 150.9, 139.2, 110.2, 54.2. MS (EI): 142 (100), 141 (35), 124 (26), 113 (41). HRMS: calcd for $C_5H_6N_2O_3$ 142.0378, found 142.0375.

Preparation of 5-(Benzyloxymethyl)uracil (6).[8] A suspension of 5-(hydroxymethyl)uracil (**5**: 12.0 g, 84 mmol) and concentrated aqueous HCl (6 mL) in benzyl alcohol (300 mL) was refluxed for 1 h, resulting in the formation of a clear solution. After being cooled to room temperature, the reaction mixture was poured into ether (1.6 L). The resulting fine precipitate was filtered and washed several times with ether, affording the pure product (**6**; 15.4 g, 79% yield). Mp: 199−202 °C (lit.[8] mp 202−203 °C). IR (KBr): 3209 (br), 1751 (s), 1719 (s), 1669 (s), 1445 (m), 1431 (m) cm^{-1}. ^1H NMR (200 MHz, DMSO): δ 10.82 (s, 2H), 7.38 (s, 1H), 7.25 (s, 5H), 4.41 (s, 2H), 4.01 (s, 2H). ^{13}C NMR (50 MHz, DMSO): δ 164.2, 151.7, 141.1, 138.8, 128.6, 127.7, 109.4, 71.7, 64.6. MS (EI): 126 (100), 108 (24), 107 (30), 91 (39).

Preparation of 1,3-Dibenzyl-5-(benzyloxy)uracil (7). A suspension of 5-(benzyloxymethyl)uracil (**6**: 8 g, 34 mmol) in dry DMF (70 mL) was treated portionwise with sodium hydride

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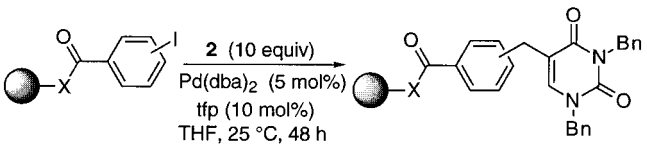
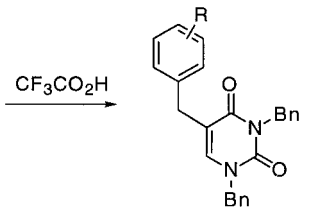
Scheme 4[a]



9a: *ortho*-subst; X = O
9b: *meta*-subst; X = O
9c: *para*-subst; X = NH

10a: *ortho*-subst; X = O
10b: *meta*-subst; X = O
10c: *para*-subst; X = NH



11a: R = *o*-CO_2H; 92%[a]
11b: R = *m*-CO_2H; 89%[a]
11c: R = *p*-$CONH_2$; 93%[a]

[a] HPLC-purity (UV, 254 nm).

(2.08 g, 69 mmol, 80% in oil). After the end of gas evolution, the reaction mixture was stirred for 1 h at room temperature, benzyl bromide (10 mL, 84 mmol) was slowly added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water (150 mL), and the solvent was evaporated using a rotatory evaporator and then a vacuum pump (0.1 mmHg). The residue was dissolved in ethyl acetate (100 mL) and was washed with water (50 mL). The aqueous phase was washed with ethyl acetate (2 × 25 mL), and the combined organic phase was washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the crude residue was purified by chromatography (ethyl acetate/pentane 1:4), providing the desired product **7** (11.1 g, 79% yield) as a colorless oil. IR (neat): 1701 (s), 1663 (s), 1642 (s), 1454 (s), 1060 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42−7.15 (m, 16H), 5.07 (s, 2H), 4.83 (s, 2H), 4.48 (s, 2H), 4.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 150.6, 138.5, 136.7, 135.8, 134.4, 128.1, 127.4, 127.4, 127.0, 126.8, 126.6, 110.3, 72.2, 64.0, 51.4, 43.6. MS (EI): 412 (M+, 0.1), 306 (66), 215 (41), 91 (100). Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.64; H, 5.86, N, 6.79, found C, 75.40; H, 5.46; N, 6.74.

Preparation of 1,3-Dibenzyl-5-(bromomethyl)uracil (3). A solution of HBr in dry 1,4-dioxane (30 mL, ca. 44 mmol) was added to 5-(benzyloxy)-1,3-dibenzyluracil (**7**: 9 g, 22 mmol), resulting in the formation of a clear solution. The reaction mixture was stirred 12 h at room temperature, and the solvent was removed by vacuum to afford an oily residue that crystallizes after the addition of a few seed crystals. The remaining dioxane was removed by evaporation (0.1 mmHg), and the residue was triturated with ether, filtrated and washed with ether (10 mL). The resulting product (**3**; 7.5 g, 89% yield) was analytically pure. Mp: 133 °C. IR (KBr): 1704 (s), 1657 (s), 1459 (s), 1452 (s), 1384 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49−7.46 (m, 2H), 7.37−7.24 (m, 9H), 5.15 (s, 2H), 4.91 (s, 2H), 4.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 151.3, 141.5, 136.5, 134.9, 129.2, 129.1, 128.7, 128.4, 128.1, 127.7, 111.1, 52.5, 44.9, 25.9. MS (EI): 384 (M+, 0.1), 306 (17), 305 (52), 92 (16), 91 (100). HRMS: calcd for $C_{19}H_{17}BrN_2O_2$ 384.0474, found 384.0480.

Preparation of the Zinc Reagent (2). A dry 50 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar, and a thermometer was charged with zinc dust (Aldrich-325 mesh, 1.96 g, 30 mmol). The flask was flushed with argon and 1,2-dibromoethane (ca. 200 mg, 0.1 mmol) in THF (2 mL) was added. The zinc suspension was heated three times to reflux with a heat gun for ca. 30 s and was allowed to cool to room temperature. TMSCl (ca. 0.3 mL) was added, and the reaction mixture was stirred for 5 min and cooled to 0 °C with an ice bath. The heterocyclic bromide **3** (3.84 g, 10 mmol) in THF (14 mL) was slowly added using a syringe pump (1 drop each 5 s), and the reaction mixture was stirred for further 30 min at room temperature after the end of the addition. The yield of zinc reagent was estimated to be ca. 80% according to deuteriolysis experiments. Less than 10% of homocoupling products was obtained (^1H NMR analysis).

Typical Procedure for the Palladium(0)-Catalyzed Cross-Coupling of the Zincated Thymine Derivative (2) and Aryl or Alkenyl Iodides. A dry three-necked flask equipped with an argon inlet, septum, and thermometer was charged with $Pd(dba)_2$ (11.5 mg, 2.5 mol %) and tfp (9.2 mg, 5 mmol %) followed by THF (1 mL). The initial red color disappeared after 1 min, leading to a yellow solution. The aryl iodide (0.8 mmol) was added followed by the zincated thymine **2** (ca. 2.5 mmol). The reaction mixture was stirred for 12 h at room temperature and worked up by pouring in aqueous saturated NH_4Cl solution and extracting with ethyl acetate. The organic layer was washed with brine and dried ($MgSO_4$), and the residual oil obtained after evaporation of the solvent was purified by flash chromatography (pentane/EtOAc).

Analytical Data of the Products 1a−k of Table 1. 1,3,5-Tribenzyluracil (1a). Compound **1a** was prepared according to the typical procedure starting from phenyl iodide (163 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6 mL, 1.9 mmol, 0.32 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 2:1), the product **1a** was obtained as a pale yellow solid (270 mg, 89%). Mp: 101 °C. IR (KBr): 1697 (s), 1659 (s), 1450 (s), 1337 (m), 1215 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.55−7.46 (m, 2H), 7.29−7.16 (m, 13 H), 6.72 (s, 1H), 5.13 (s, 2H), 4.78 (s, 2H), 3.16 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 151.4, 139.0, 138.2, 136.9, 135.5, 129.0, 128.9 (2), 128.6, 128.4, 128.3, 127.8, 127.5, 126.6, 114.3, 52.2, 44.7, 33.2. MS (EI): 383 (18), 382 (43), 291 (57), 91 (100). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; H, 7.32, found C, 78.70; H, 5.95; N, 7.15.

1,3-Dibenzyl-5-(3,5-dimethylbenzyl)uracil (1b). Compound **1b** was prepared according to the typical procedure starting from 3,5-dimethylphenyl iodide (186 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 6:1), the product **1b** was obtained as a yellow oil (262 mg, 80%). IR (neat): 1705 (m), 1664 (s), 1452 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.33−7.17 (m, 8 H), 6.84 (s, 1H), 6.74−6.72 (m, 3H), 5.15 (s, 2H), 4,0.83 (s, 2H), 3.55 (s, 2H), 2.25 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 151.6, 139.1, 138.1 (2), 137.1, 135.7, 129.1, 129.0, 128.4 (2), 128.3, 127.9, 127.6, 126.8, 114.7, 52.2, 44.8, 33.0, 21.3. MS (EI): 411 (20), 410 (33), 319 (45), 91 (100). HRMS: calcd for $C_{27}H_{26}N_2O_2$ 410.1994, found 410.1990.

1,3-Dibenzyl-5-(4-chlorobenzyl)uracil (1c). Compound **1c** was prepared according to the typical procedure starting from 4-chlorophenyl iodide (191 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6 mL, 1.9 mmol, 0.32 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 4:1), the product **1c** was obtained as a white solid (266 mg, 80%). Mp: 110 °C. IR (KBr): 1695 (s), 1659 (s), 1489 (m), 1452 (s), 1366 (m), 1348 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.46−7.06 (m, 14H), 6.74 (s, 1H), 5.13 (s, 2H), 4.84 (s, 2H), 3.57 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.4, 139.0, 136.8, 135.3, 132.4, 130.2, 129.0, 128.7, 128.4, 127.8, 127.6, 113.8, 52.2, 44.7, 32.7. MS (EI): 418 (11), 416 (28), 327 (12), 325 (38), 91 (100). HRMS: calcd for $C_{25}H_{21}ClN_2O_2$ 416.1292, found 416.1287.

1,3-Dibenzyl-5-(4-bromobenzyl)uracil (1d). Compound **1d** was prepared according to the typical procedure starting from 4-bromophenyl iodide (226 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 5:1), the product **1d** was obtained as a white solid (327 mg, 89%). Mp: 90 °C. IR (KBr): 1709 (m), 1700 (m), 1656 (s), 1452 (m), 1367 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.46−7.20 (m, 12H), 7.04−7.00 (m, 2H), 6.74 (s, 1H), 5.13 (s,

2H), 4.84 (s, 2H), 3.56 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.4, 139.0, 137.3, 136.8, 135.3, 131.6, 130.5, 129.0, 128.3, 127.8, 127.6, 120.4, 113.6, 52.1, 44.7, 32.7. MS (EI): 462 (21), 460 (20), 371 (20), 369 (2), 91 (100). Anal. Calcd for $C_{25}H_{21}BrN_2O_2$: C, 65.08; H, 4.59; N, 6.07, found C, 64.81; H, 4.55; N, 5.90.

1,3-Dibenzyl-5-[4-(trifluoromethyl)benzyl]uracil (1e). Compound **1e** was prepared according to the typical procedure starting from 4-(trifluoromethyl)phenyl iodide (272 mg, 1.0 mmol), $Pd(dba)_2$ (115 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (11.4 mL, 4 mmol, 0.35 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 3:1), the product **1e** was obtained as a yellow oil (388 mg, 86%). IR (neat): 1699 (s), 1664 (s), 1453 (s), 1324 (s), 1160 (m), 1119 (s), 1065 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41−7.08 (m, 14H), 6.70 (s, 1H) 5.04 (s, 2H), 4.74 (s, 2H), 3.55 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 151.5, 142.7, 139.2, 136.8, 135.3, 129.1, 128.5, 127.9, 127.7, 125.6, 113.3, 52.2, 44.8, 33.2. MS (EI): 450 (31), 360 (12), 359 (35), 316 (16), 91 (100). Anal. Calcd for $C_{26}H_{21}F_3N_2O_2$: C, 69.33; H, 4.70; N, 6.22, found C, 68.89; H, 4.62; N, 6.13.

1,3-Dibenzyl-5-(4-methoxybenzyl)uracil (1f). Compound **1f** was prepared according to the typical prodecure starting from 4-methoxyphenyl iodide (187 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mol), and zinc reagent **2** (6 mL, 1.94 mmol, 0.32 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 4:1), the product **1f** was obtained as a white solid (330 mg, 62%). Mp: 95 °C. IR (KBr): 1709 (s), 1665 (s), 1510 (m), 1461 (m), 1243 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47−7.05 (m, 12H), 6.82−6.78 (m, 2H), 6.71 (s, 1H), 5.14 (s, 2H), 4.80 (s, 2H), 3.76 (s, 3H), 3.56 (2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 158.3, 151.5, 138.9, 136.9, 135.5, 130.0, 129.0, 128.4, 127.8, 127.5, 114.8, 114.0, 55.2, 52.2, 44.7, 32.4. MS (EI): 413 (11), 412 (57), 321 (29), 278 (10), 91 (100). Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79, found C, 75.50; H, 5.80; N, 6.44.

1,3-Dibenzyl-5-(2-methoxybenzyl)uracil (1g). Compound **1g** was prepared according to the typical procedure starting from 2-methoxyphenyl iodide (187 mg, 0.8 mmol), $Pd(dba)_2$ (11,5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.2 mL, 2.4 mmol, 0.39 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatrography (pentane/EtOAc 5:1), the product **1g** was obtained as a colorless solid (219 mg, 66%). Mp: 80 °C. IR (KBr): 1696 (s), 1638 (s), 1656 (s), 1450 (s), 1246 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50−7.48 (m, 12H), 6.88−6.79 (m, 3H), 5.14 (s, 2H), 4.82 (s, 2H), 3.60 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.1, 157.3, 151.5, 139.0, 137.0, 135.7, 131.0, 129.1, 128.9, 128.3, 128.2, 128.0, 127.9, 127.5, 126.2, 120.6, 113.0, 110.2, 54.9, 51.9, 44.6, 28.0. MS (EI): 413 (11), 412 (57), 321 (29), 278 (10), 91 (100). HRMS: calcd for $C_{26}H_{24}N_2O_3$ 412.1787, found 412.1789.

1,3-Dibenzyl-5-(2-cyanobenzyl)uracil (1h). Compound **1h** was prepared according to the typical procedure starting from 2-cyanophenyl iodide (206 mg, 0.9 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (7.4 mL, 2.3 mmol, 0.31 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 4:1), the product **1h** was obtained as a white solid (278 mg, 76%). Mp: 131 °C. IR (KBr): 1700 (m), 1661 (s), 1452 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58−7.25 (m, 15H), 5.10 (s, 2H), 4.89 (s, 2H), 3.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 151.4, 142.5, 140.3, 136.8, 135.3, 132.9 (2), 131.1, 129.1, 129.0, 128.4 (2), 128.3, 127.6, 127.2, 119.0, 112.2, 111.6, 52.6, 44.8, 32.4. MS (EI): 408 (14), 407 (38), 317 (20), 316 (68), 273 (13), 91 (100). HRMS: calcd for $C_{26}H_{21}N_3O_2$ 407.1634, found 407.1639.

1,3-Dibenzyl-5-(3-methoxybenzyl)uracil (1i). Compound **1i** was prepared according to the typical procedure starting from 3-methoxyphenyl iodide (187 mg, 0.8 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (6.3 mL, 2.4 mmol, 0.33 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 4:1), the product **1i** was obtained as a colorless oil (265 mg, 80%). IR (neat): 1699 (s), 1642 (s), 1602 (m), 1452 (s) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60−7.47 (m, 2H), 7.32−7.18 (m, 9H), 6.75−6.72 (m, 4H), 5.14 (s, 2H), 4.80 (s, 2H), 3.71 (s, 3H), 3.59 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.9, 159.8, 151.4, 139.8, 139.1, 136.9, 135.5, 129.6, 129.0 (2), 128.4, 128.3, 127.8, 127.5, 121.2, 114.3, 112.2, 55.1, 52.2, 44.7, 33.2. MS (EI): 413 (16), 412 (533), 321 (53), 91 (100). HRMS: calcd for $C_{26}H_{24}N_2O_3$: 412.1787, found 412.1780.

1,3-Dibenzyl-5-[3-(nonafluorobutylsulfonyl)benzyl]-uracil (1j). Compound **1j** was prepared according to the typical procedure starting from 3-(nonafluorobutylsulfonyl)phenyl iodide (351 mg, 0.7 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (5.8 mL, 1.8 mmol, 0.31 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 4:1), the product **1j** was obtained as a colorless oil (450 mg, 95%). IR (neat): 1699 (m), 1663 (m), 1643 (s), 1458 (m), 1450 (m), 1430 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.11 (m, 14H), 6.83 (s, 1H), 5.14 (s, 2H), 4.87 (s, 2H), 3.66 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.9, 151.5, 149.9, 141.7, 139.4, 136.9, 135.4, 130.4, 129.1, 128.5, 128.0, 127.7, 121.8, 119.5, 113.1, 52.3, 44.9, 33.1. MS (EI): 680 (40), 590 (13), 589 (39), 91 (100). HRMS: calcd for $C_{29}H_{21}F_9N_2O_5S$ 680.1028, found 680.1039.

1,3-Dibenzyl-5-[(2)-2-heptenyl]uracil (1k). Compound **1k** was prepared according to the typical procedure starting from (*Z*)-1-iodohexene (210 mg, 1.0 mmol), $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.2 mg, 0.04 mmol), and zinc reagent **2** (11.4 mL, 4 mmol, 0.35 M in THF). Reaction time: 12 h at room temperature. After purification by flash chromatography (pentane/EtOAc 5:1), the product **1k** was obtained as a yellow oil (330 mg, 85%). IR (neat): 2956 (s), 2929 (s), 1701 (s), 1665 (s), 1452 (s), 1382 (s), 1350 (s) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70−7.25 (m, 10H), 6.88 (s, 1H), 5.59−5.32 (m, 2H), 5.16 (s, 2H), 4.89 (s, 2H), 3.07 (d, J = 7.2, 2H), 1.97 (m, 2H), 1.23 (m, 4H), 0.85 (tr, J = 6.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.2, 151.6, 137.9, 137.0, 135.6, 133.6, 129.1, 128.4, 127.8, 127.5, 124.2, 113.3, 112.9, 52.2, 44.7, 31.6, 26.8, 24.6, 22.3, 13.9. MS (EI): 388 (15), 305 (22), 91 (100). HRMS: calcd for $C_{25}H_{28}N_2O_2$ 388.2151, found 388.2157.

Hydrogenation Procedure. Preparation of 3-Benzyl-5-(3,5-dimethylbenzyl)uracil (8). To a stirred suspension of **1b** (140 mg, 0.34 mmol) and an equal weight of 10% Pd−C in dry methanol (2 mL) was added anhydrous formate (108 mg, 1.7 mmol) in a single portion under argon. The resulting mixture was stirred at reflux, and the reaction was monitored by TLC. After completion of the reaction (24 h), the catalyst was removed by filtration through a Celite pad, which was washed with chloroform (20 mL). The filtrate after evaporation under reduced pressure afforded the pure uracil derivative **8** as a colorless solid (84 mg, 77%). Mp: 149−152 °C. IR (KBr): 3217 (m), 3076 (m), 2944 (m), 1713 (s), 1648 (s), 1447 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.21 (s, 1H), 7.36−7.17 (m, 5H), 6.79−6.63 (m, 4H), 5.02 (s, 2H), 3.48 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.5, 153.3, 138.3, 138.0, 136.7, 135.8, 128.8, 128.5, 127.7, 127.0, 114.7, 44.1, 33.0, 21.4. MS (EI): 321 (10), 320 (40), 229 (56), 186 (40), 143 (11), 91 (100). HRMS: calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1523.

Typical Procedure for the Pd(0)-Catalyzed Cross-Coupling of the Zincated Thymine Derivative (2) and Resin-Attached *o*-, *m*- or *p*-Iodobenzoates (9a−c).[17] Resin (80 mg, ca. 0.6 mmol/g substitution) was placed into a Schlenk flask. THF (2 mL) containing $Pd(dba)_2$ (1.4 mg, 2.5 μmol) and tfp (1.2 mg, 5.0 μmol) and zinc reagent **2** (1.7 mL, 0.5 mmol, 0.30 M in THF) were added, and the reaction mixture was stirred 48 h at room temperature. The resin was then treated with MeOH and washed with DMF and repeatedly with MeOH and CH_2Cl_2 (four times). The desired compound was cleaved from the resin by treatment with a $CF_3CO_2H/H_2O/CH_2Cl_2$ (9:1:1) solution for Wang resin or a CF_3CO_2H/H_2O (1:1) solution for Rink resin and evaporated under reduced pressure.

2-(3-Benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl)benzoic acid (11a). Compound **11a** was prepared according to the typical procedure starting from Wang-resin-attached *o*-iodobenzoate[17] (92% HPLC purity, UV 254 nm). ^{1}H NMR (300 MHz, DMSO): δ 7.64−7.00 (m, 15H), 4.79 (s, 2H), 4.71 (s, 2H), 3.77 (s, 2H). ^{13}C NMR (75 MHz, DMSO): δ 167.9, 161.8, 150.2, 140.75, 139.0, 136.4, 135.9, 130.9, 129.6, 129.5, 127.9, 127.6, 126.9, 126.7, 126.6, 126.4, 125.6, 111.1, 50.9, 43.1,

29.8. MS (EI): 426 (31), 408 (30), 335 (13), 317 (24), 132 (16), 91 (100), 28 (44). HRMS: calcd for $C_{26}H_{22}N_2O_4$ 426.1579, found 426.1582.

3-(3-Benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl)benzoic Acid (11b). Compound **11b** was prepared according to the typical procedure starting from Wang-resin-attached *m*-iodobenzoate[17] (88% HPLC purity, UV 254 nm). ^{1}H NMR (300 MHz, DMSO): δ 8.01−7.28 (m, 15H), 5.03 (s, 2H), 5.00 (s, 2H), 3.71 (s, 2H). ^{13}C NMR (75 MHz): δ 167.1, 162.0, 150.0, 141.4, 139.7, 136.7, 136.3, 132.4, 130.5, 128.7, 128.2, 128.0, 127.9, 127.3, 127.0, 126.9, 126.7 (2), 111.2, 51.1, 43.4, 31.9. MS (EI): 426.0 (27), 380 (15), 335 (47), 292 (13), 91 (100). HRMS: calcd for $C_{26}H_{22}N_2O_4$ 426.1579, found 426.1581.

4-(3-Benzyl-2,4-dioxo-1-phenethyl-1,2,3,4-tetrahydro-5-pyrimidinylmethyl)benzamide (11c). Compound **11c** was prepared according to the typical procedure starting from Rink-attached *p*-iodobenzoate[17] (93% HPLC purity, UV 254 nm). ^{1}H NMR (300 MHz, DMSO): δ 7.81−7.09 (m, 15H), 4.90 (s, 2H), 4.87 (s, 2H), 3.55 (s, 2H). ^{13}C NMR (75 MHz, DMSO): δ 167.3, 162.0, 150.6, 142.6, 141.3, 136.7, 136.3, 131.8, 111.1, 51.1, 43.4, 31.9. MS (EI): 279 (11), 167 (38), 150 (12), 149 (82), 113 (20), 112 (17), 97 (12), 83 (23), 71 (46), 57 (100), 43 (71), 41 (28), 32 (23), 29 (11), 28 (97).

(17) The substrates were attached to resin through coupling with *N*,*N*-diisopropylcarbodiimide and DMAP following literature procedures: (a) Deshpande, M. S. *Tetrahedron Lett.* **1994,** *35*, 5613. (b) Sucholeiki, I. *J. Org. Chem.* **1995**, *60*, 523.

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **1a**−**k**, **3**, **5**−**8**, and **11a**−**c** (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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