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Preparation and Reactions of New Zincated Nitrogen-Containing Heterocycles

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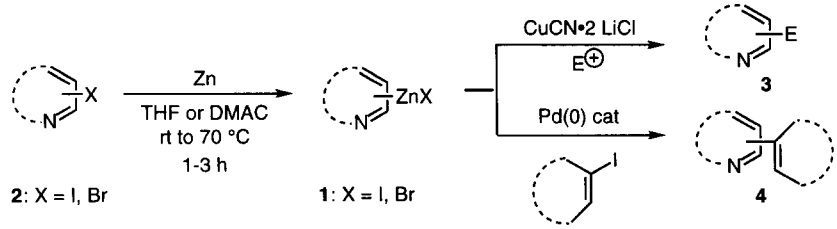
Key words : heteroarylzinc halides, zincated nucleosides, palladium (0) catalysis, copper(I) catalysis

Summary: A range of nitrogen-containing iodinated or in some cases brominated heterocycles were converted to the corresponding zincated heterocyclic derivatives by the direct insertion of zinc dust under mild conditions (25 °C to 70 °C, 1-3 h) in a solvent like THF or DMAC. This reaction was extended to the preparation of zincated nucleic acid bases and nucleosides. The reaction of these new zinc reagents toward various electrophiles with palladium (0) or copper(I) catalysis allows the preparation of a broad range of polyfunctional nitrogen-containing heterocycles. © 1997 Elsevier Science Ltd.

Introduction

Heterocyclic rings are present in many pharmaceuticals and agrochemicals [3] and much effort has been made to develop general synthetic methods for introducing heterocyclic moieties into organic molecules.[4] Especially interesting are reactions between metalated heterocyclic rings[5] and organic electrophiles, since this approach provides an access to a broad range of polyfunctionalized heterocyclic compounds. Some years ago, we have shown that aryl iodides insert zinc dust in a polar solvent like N,N-dimethylacetamide (DMAC).[6] More recently, we have extended this reaction to the preparation of zincated nucleosides.[7] Herein, we wish to report the preparation of various nitrogen containing heteroarylzinc halides **1** starting from heteroaryl iodides or bromides **2** using readily available zinc dust (Aldrich). In the presence of Cu(I)[8] or Pd(0)[9] as transition metal catalysts,[7] the new zinc organometallics **1** can be coupled with various organic electrophiles leading to products of type **3** or **4** (Scheme 1).

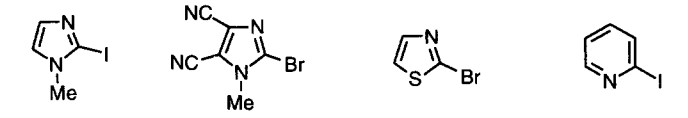


Scheme 1

Preparation of heterocyclic organozinc halides

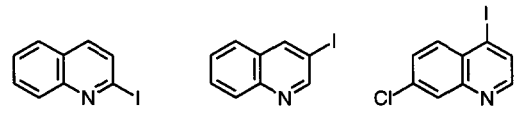
The insertion rate of zinc in heterocyclic halides strongly depends on the nature of the heterocycle. Both electron-rich heterocycles like 2-bromo- and 2-iodo-imidazoles **2a-b** and 2-bromothiazole **2c** or electron-poor heterocycles like 2-iodopyridine **2d** and iodoquinolines **2e-g** readily react with zinc dust in THF or DMAC at 25 °C to 70 °C leading to the desired heteroarylzinc derivatives **1a-g** in over 80% yield. As a rule, the electron-rich heterocycles undergo the zinc insertion very rapidly. No DMAC addition is necessary in the case of imidazole **2a** and the zinc insertion is usually complete within 1 h at 25 °C. In contrast to

previous work,[5d] it is not necessary to use highly activated zinc (Rieke-zinc) for preparing these zinc reagents, which makes these organometallics far more attractive for preparative applications.



2a **2b** **2c** **2d**

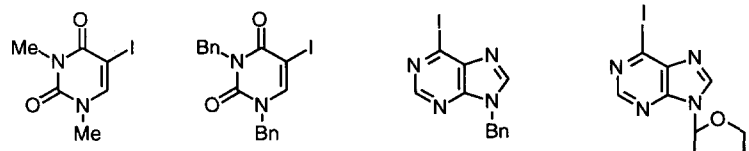
(THF, rt, 1 h)[a] (DMAC, rt, 1 h)[a] (THF, rt)[a] (DMAC, rt, 1 h)[a]



2e **2f** **2g**

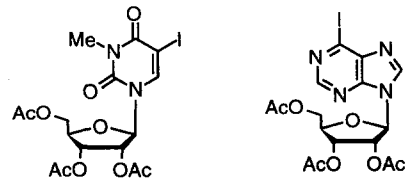
(DMAC, 70 °C, 1 h)[a] (DMAC, rt, 1 h)[a] (DMAC, rt, 1-3 h)[a]

Scheme 2. [a]The reaction conditions for the formation of the corresponding zinc derivatives are indicated in parenthesis.



5a **5b** **6a** **6b**

(THF, 70 °C, 3 h)[a] (THF, 70 °C, 5 min, then rt, 1 h)[a] (THF, 70 °C, 5 min, then rt, 2 h)[a] (THF, 70 °C, 5 min, then rt, 3 h)[a]



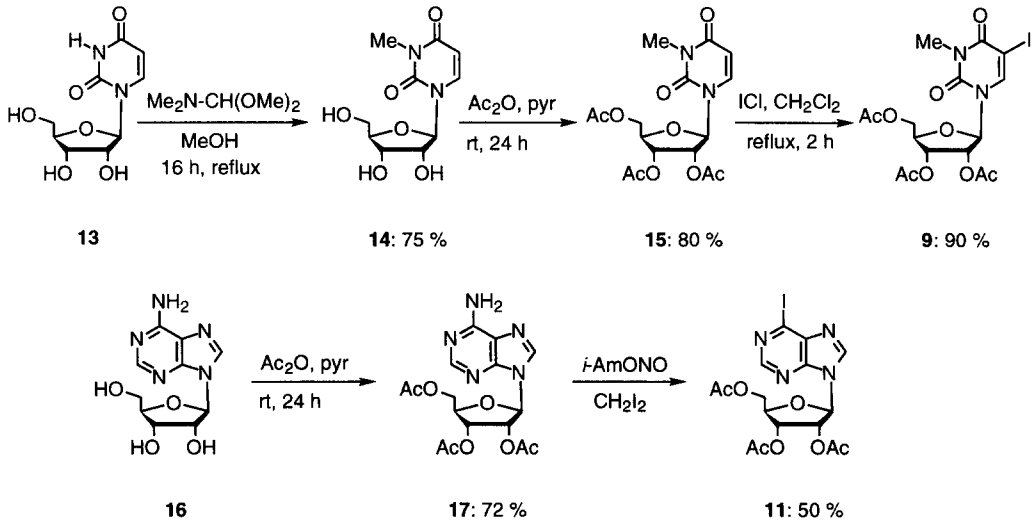
9 **11**

(DMAC, 70 °C, 3 h)[a] (THF, 70 °C, 5 min, then rt, 3 h)[a]

Scheme 3. [a]The reaction conditions for the formation of the corresponding zinc derivatives are indicated in parenthesis.

For these heterocycles, the insertion reaction of heteroaryl *bromides* is possible using DMAC (for **2b**) or THF (for **2c**) at rt. The electron-poor 2-pyridyl halides require somewhat harsher reaction conditions. Thus, whereas 2-iodopyridine is converted into the corresponding zinc reagent **1d** at 25 °C in DMAC (reaction time : 1 h), the corresponding 2-bromopyridine does not insert zinc even under reflux conditions. Similarly, the iodoquinolines **2e-g** are smoothly converted to the corresponding heteroarylzinc iodides **1e-g** in DMAC at temperatures between 25 °C and 70 °C within a few hours. In all these zinc insertions, the heteroaryl iodide or bromide concentration in THF or DMAC should be between 1.5 M and 2.5 M. An excess of zinc powder (-325 mesh, Aldrich; 3 equivalents) is always used. This zinc dust is conveniently activated with a small amount of 1,2-dibromoethane (ca. 5 mol%) and Me_3SiCl (ca. 1-2 mol%);[10] see experimental section. Although, the generality of this preparation method has not been examined more comprehensively, it appears to have a good generality and is superior to transmetalation procedures from organolithiums or Grignard reagents if functional groups are present in the heterocyclic ring. Thus, the 4,5-dicyanoimidazole **2b**[11] cannot be easily converted to the lithium or magnesium derivative due to the high reactivity of the cyano groups present in this molecule, whereas the zinc insertion smoothly proceeds in DMAC (rt, 1 h).

The functionalization of nucleosides is an important synthetic target since some nucleoside derivatives display antiviral activity or related biological activity.[12] Metalated nucleosides[13] have been used in cross-coupling reactions but difficulties in the formation of metalated forms of these polyfunctional molecules have been encountered. Several halogenated pyrimidines and purines have however been used as electrophiles in palladium catalyzed reactions.[14] The mild reaction conditions required for introducing a zinc metal in heteroaryl iodides should be especially well suited for the preparation of zincated nucleosides and nucleic acid bases.[7] Thus, several iodine-substituted uracils and purines such as **5a-b** and **6a-b** were prepared and converted by zinc insertion to the corresponding zincated species **7a-b** and **8a-b** (Scheme 3).



13 **14**: 75 % **15**: 80 % **9**: 90 %

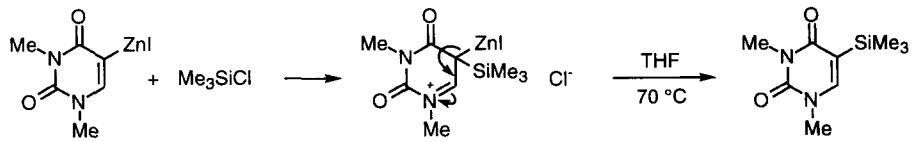
16 **17**: 72 % **11**: 50 %

Scheme 4

Interestingly in these zinc insertion reactions, the use of THF as reaction solvent is appropriate and for the heterocyclic iodides **5b**, **6a** and **6b** a brief heating of the reaction mixture to 70 °C (5 min) is sufficient. The formation of the desired zinc reagents is complete after 1-3 h of stirring at rt. For solubility reasons, the 5-iodouridine **9** is converted to the zinc derivative **10** in DMAC (70 °C, 3 h), whereas the more soluble 6-iodopurine riboside **11** reacts with zinc dust in THF. After a short heating to 70 °C, the reaction mixture is stirred 3 h at 25 °C leading to the expected zinc derivative **12** in over 80% yield. The 5-iodouridine **9** was readily prepared from the commercially available uridine **13**. After methylation using N,N-dimethyl formamide dimethyl acetal in methanol (reflux, 16 h, 75%),[15a] the resulting N-methyluridine **14** was acetylated leading to the triacetate **15** (Ac_2O, pyr, 25 °C, 24 h, 80% yield).[15b] The iodination of **15** with ICl[16] in CH_2Cl_2 (1.5 equiv, 40 °C, 2 h) affords the desired 5-iodouridine **9** in 90% yield. The acylation of adenosine **16** (Ac_2O, pyr, 25 °C, 24 h)[17] leads to the triacylated purine derivative which was converted with *i*-AmONO and CH_2I_2[18] (CH_3CN, 70 °C, 3.5 h, 50%) to the desired 6-iodopurine **11** (Scheme 4).

Copper Catalyzed reactions of heterocyclic organozinc halides

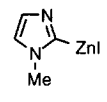
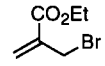
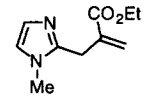
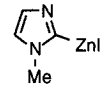
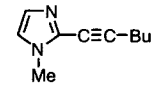
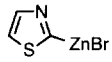
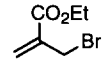
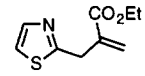
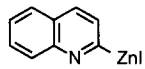
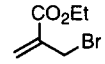
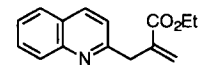
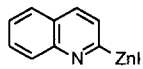
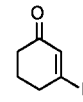
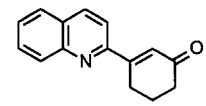
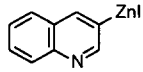
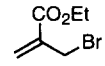
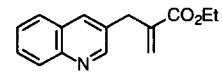
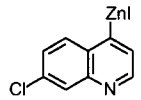
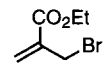
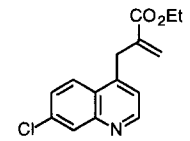
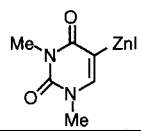
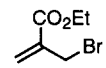
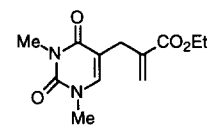
The reactivity of the carbon-zinc bond toward most organic electrophiles is rather low, therefore most reactions of organozincs with organic electrophiles require the use of a transition metal catalyst which will convert the carbon-zinc bond into a new carbon-metal bond. Because of the presence of low lying *d*-orbitals, new reaction pathways are possible allowing reactions with many organic electrophiles.[8] Of all the heteroarylzinc derivatives prepared above only the zincated uracil **7a** reacts with an electrophile (Me_3SiCl) in the absence of a catalyst. The exceptional reactivity of 5-zincated uracils may be explained by the enamine character of the double bond allowing a tentative low-energy addition-elimination mechanism via an intermediate of type **18** which leads to the product **19** (THF, 70 °C, 4 h) in 78% yield (Scheme 5). This high reactivity was also observed in palladium cross-coupling reactions and can be explained via a similar mechanism (see next section). Copper catalysis (5-10 mol%) with the THF soluble copper salt CuCN·2LiCl[10] allows allylation of various zincated heterocycles with ethyl (2-bromomethyl)acrylate[19] (see Table 1).



7a **18** **19**: 78 %

Scheme 5

Table 1. Products of type **3** obtained by the copper catalyzed reaction of zincated heteroaryls **1** with ethyl (2-bromomethyl)acrylate, 1-iodohexyne or 3-iodo-2-cyclohexen-1-one.

entry	zincated heterocycle		electrophile	product		yield (%)[a]
1		**1a**			**3a**	85
2		**1a**	Bu–C≡C–I		**3b**	68[b]
3		**1c**			**3c**	91
4		**1e**			**3d**	72
5		**1e**			**3e**	70[b]
6		**1f**			**3f**	74
7		**1g**			**3g**	57
8		**7a**			**3h**	71

[a]Isolated yield of analytically pure products. [b]One equivalent of CuCN·2LiCl has been used in this reaction.

Most allylation reactions occur readily at -30 °C to -20 °C and are complete within a few minutes by warming up to rt. The reaction of **1a** with 1-iodohexyne in the presence of CuCN·2LiCl (THF, -60 °C to -45 °C, 48 h) leads to the 2-alkynylimidazole **3b** in 68% yield (entry 2 of Table 1).[20] The addition-elimination of the zincated quinoline **1e** to 3-iodo-2-cyclohexen-1-one[21] in the presence of CuCN·2LiCl (1 equiv.) provides the 2-substituted quinoline **3e** in 70% yield. Very efficient palladium catalyzed cross-coupling reactions (Negishi-reaction)[9] were performed with all the zincated heterocycles. Several palladium catalysts were used but the *in situ* generation of the palladium catalyst from *bis*(dibenzylideneacetone) palladium (0)[22] ($Pd(dba)_2$; 1-2 mol%) and (*o*-furyl)$_3$P[23] (TFP; 4-8 mol%) gives the best results leading to the desired cross-coupling products of type **4** in good to excellent yields (Table 2).

Table 2. Products of type **4** obtained by the palladium (0) catalyzed reaction of zincated heterocycles **1** with unsaturated iodides.

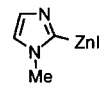
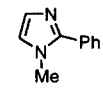
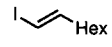
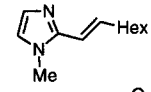
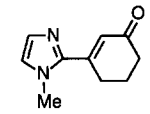
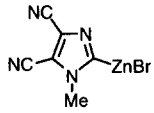
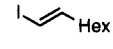
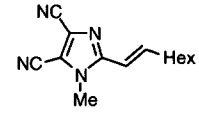
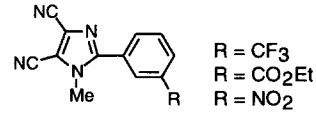
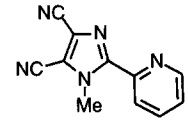
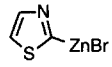
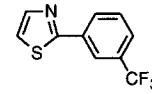
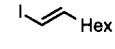
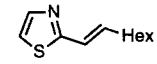
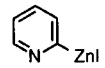
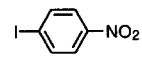
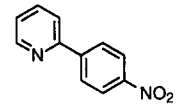
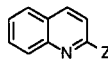
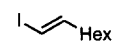
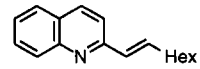
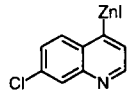
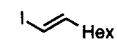
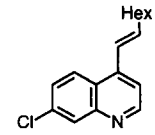
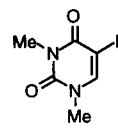
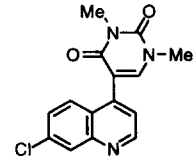
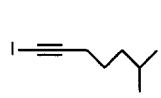
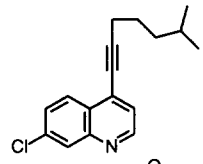
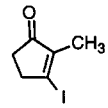
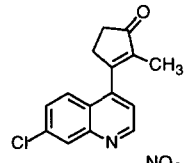
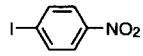
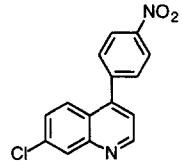
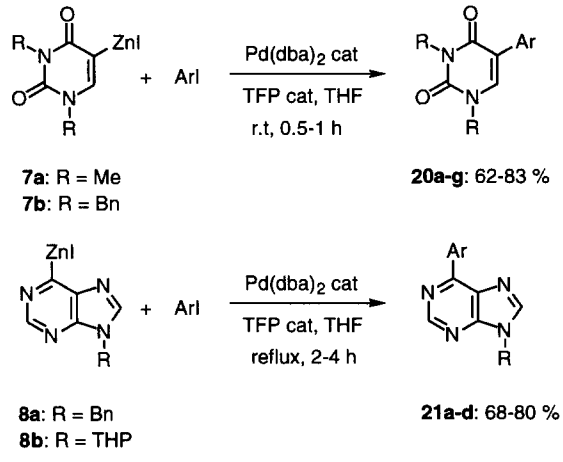
entry	zincated heterocycle	unsaturated iodide	product **4**		yield (%)[a]
1	 **1a**	PhI		**4a**	75
2	**1a**			**4b**	70
3	**1a**			**4c**	83
4	 **1b**			**4d**	85
5	**1b**	*m*-CF_3-C_6H_4-I	 R = CF_3	**4e**	70
6	**1b**	*m*-EtO_2C-C_6H_4-I	R = CO_2Et	**4f**	62
7	**1b**	*m*-NO_2-C_6H_4-I	R = NO_2	**4g**	68
8	**1b**			**4h**	83
9	 **1c**	*m*-CF_3-C_6H_4-I		**4i**	78
10	**1c**			**4j**	89
11	 **1d**			**4k**	84
12	 **1e**			**4l**	61
13	 **1g**			**4m**	72
14	**1g**			**4n**	73

Table 2 (continued)

15	**1g**			**4o**	55
16	**1g**			**4p**	71
17	**1g**			**4q**	86

[a]Isolated yield of analytically pure product.

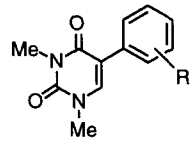
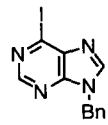
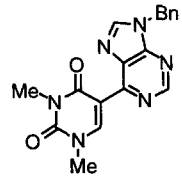
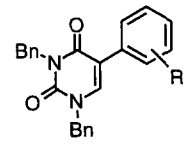
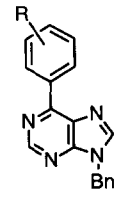
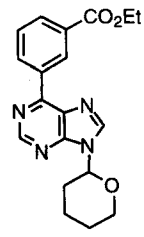
Thus, all the zincated heterocycles **1a-e** and **1g** react with various unsaturated iodides. The reaction proceeds at 25 °C with acyclic alkenyl or alkynyl iodides (entries 2, 4, 10, 12, 13 and 15 of Table 2) and is complete within a few hours. With less reactive cyclic alkenyl iodides (entries 3, 14 and 16) and functionalized aryl iodides (entries 1, 5-7, 9, 11 and 17) temperatures of 40 °C to 70 °C (12 h reaction time) are required. Uniformly good yields are obtained in these Pd-catalyzed reactions showing the generality of this synthetic method. Its extension to zincated nucleic acid derivatives **7a-b** and **8a-b** provides an entry to 5-aryl substituted uracils **20** and 6-arylsubstituted purines **21** (see Scheme 6 and Table 3).



Scheme 6

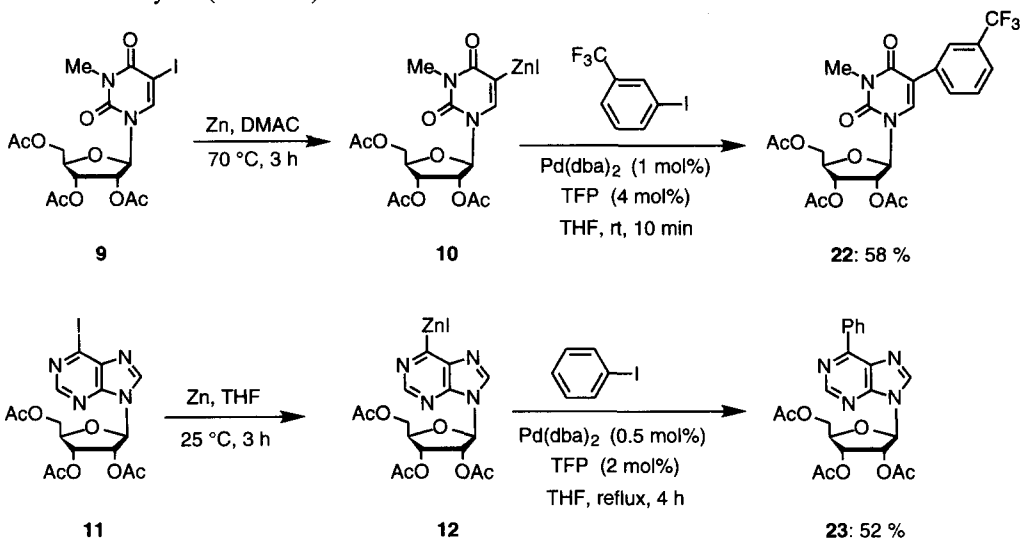
Remarkably, the zincated uracils react within a few minutes at 25 °C with various aryl iodides. Interestingly, the related zinc reagent 6-oxocyclohexenylzinc iodide[24] reacts with aryl iodides in the presence of palladium catalysts with much slower rates, showing the importance of the presence of a β-amino atom in the zincated uracils **7a-b** (compare with Scheme 5). The 6-zincated purines undergo the palladium catalyzed cross-coupling reactions under harsher conditions (60 °C, 2-4 h ; see entries 8-11 of Table 3).

Table 3. Arylated nucleoside bases **20a-g** and **21a-d** obtained by palladium (0) catalyzed cross-coupling of **7a-b** or **8a-b** with aryl iodides.

entry	zinc reagent **7** or **8**	aryl iodide	product **20** or **21**		yield (%)[a]
1	**7a**	Ph-I		**20a** : R = H	83
2	**7a**	*m*-CF_3-C_6H_4-I		**20b** : R = *m*-CF_3	78
3	**7a**	*p*-EtO_2C-C_6H_4-I		**20c** : R = *p*-CO_2Et	80
4	**7a**			**20d**	79
5	**7b**	*m*-CF_3-C_6H_4-I		**20e** : R = *m*-CF_3	68
6	**7b**	*m*-O_2N-C_6H_4-I		**20f** : R = *m*-NO_2	77
7	**7b**	*m*-EtO_2C-C_6H_4-I		**20g** : R = *p*-CO_2Et	62
8	**8a**	Ph-I		**21a** : R = H	80
9	**8a**	*p*-EtO_2C-C_6H_4-I		**21b** : R = *p*-CO_2Et	70
10	**8a**	*m*-CF_3-C_6H_4-I		**21c** : R = *m*-CF_3	74
11	**8b**	*m*-EtO_2C-C_6H_4-I		**21d**	68

[a]Isolated yield of analytically pure products.

The high functional compatibility of organozinc compounds allows the preparation of the zinc reagent of the 5-iodouridine derivative **9** and of the 6-iodopurine **11** respectively in DMAC (70 °C, 3 h) and THF (70 °C, 5 min, 25 °C, 3 h) by the direct insertion of zinc. The desired zinc reagents **10** and **12** are obtained in ca. 80% yield. Their cross-coupling with aryl iodides furnishes the arylated nucleosides **22** and **23** respectively in 58% and 52% yield (Scheme 7).



9 **10** **22**: 58 %

11 **12** **23**: 52 %

Scheme 7

In summary, we have described the preparation of various zincated nitrogen containing heterocycles using a practical insertion of zinc dust in either THF or DMAC ; the more reluctant insertion reactions being preferentially realized in the more polar solvent : DMAC. All these zinc compounds can be coupled with organic electrophiles like allylic bromides or 3-iodo-2-cyclohexenone in the presence of a copper catalyst or with alkenyl, alkynyl, aryl or heteroaryl iodides in the presence of a palladium catalyst.

Experimental Section

General methods. Unless otherwise indicated, all reactions were carried out under an argon atmosphere. Solvents (THF or DMAC) 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 gas-chromatography (GC) 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 sat. aq. NH_4Cl. The two phase mixture was filtered to remove insoluble salts and the two layers were separated. The combined organic extracts were washed with water (50 mL) and sat. aq. NaCl (20 mL), dried over $MgSO_4$ and filtered. The residue obtained after evaporation of the solvents was purified by flash chromatography. Fourier transform infrared spectra (FT-IR) were recorded on a Nicolet 5 DXB spectrometer. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Brucker AC-200 and AC 300 (200, 300 MHz (proton) and 50, 75.5 MHz (carbon)). Mass spectra (MS) and exact mass calculations were recorded on a VG-70-250 S mass spectrometer. The ionization methods used were desorption chemical ionization (CI) and electron impact ionization (EI, 70 eV).

Starting materials. The following starting materials were prepared according to literature procedures: ethyl (2-bromomethyl)acrylate,[19] 3-iodo-2-cyclohexen-1-one,[21] (E)-1-iodo-1-octene,[25] 1-iodo-5-methyl-1-hexyne,[26] 1-iodo-1-hexyne,[20,26] 3-iodo-2-methyl-2-cyclopenten-1-one,[27] 2-bromo-4,5-dicyano-1-methyl imidazole (**2b**),[11] 2-iodopyridine (**2d**),[28] 2-iodoquinoline (**2e**),[28] 3-iodoquinoline (**2f**),[29] 7-chloro-4-iodo

quinoline (**2g**),[28] 5-iodo-N,N-dimethyluracil (**5a**),[30] 5-iodo-N,N-dibenzyluracil (**5b**),[31] 6-iodo-9-benzyl purine (**6a**),[32] 6-iodo-9-tetrahydropyranylpurine (**6b**),[33] 6-iodo-9β-(2',3',5'-tri-O-acetyl)-D-ribofuranosyl purine (**11**),[18] 3-methyluridine (**14**),[15] 3-methyl-(2',3',5'-tri-O-acetyl)uridine (**15**).[34]

2-Iodo-1-methylimidazole (2a):[35] A three-necked flask equipped with an argon inlet, a thermometer and an addition funnel was charged with 1-methylimidazole (8.20 g, 100 mmol) and THF (100 mL). The solution was cooled to -90 °C and treated with n-BuLi (2.40 M, 42 mL, 100 mmol), then warmed to 0 °C. After 5 min the reaction mixture was cooled to -60 °C and treated slowly with a solution of I_2 (27.92 g, 110 mmol) in THF (20 mL), and stirred at 0 °C for 20 min. The reaction mixture was quenched by adding $Na_2S_2O_3$ solution (100 mL) and extracted with $CHCl_3$ (4 x 50 mL). The combined organics were dried over Na_2CO_3 and the solvent distilled off. Distillation of the crude product gave a colorless oil of **2a** (68 °C, 0.03 mm Hg). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.90 (s, 1H), 6.86 (s, 1H), 3.46 (s, 3H).

5-Iodo-3-methyl-(2',3',5'-tri-O-acetyl)uridine (9):[16] 3-Methyl-(2',3',5'-tri-O-acetyl)uridine **15**[34] (1.7 g, 4.5 mmol) was dissolved in CH_2Cl_2 and ICl (1.1 g, 6.8 mmol) in CH_2Cl_2 (40 mL) was added. The reaction mixture was refluxed for 2 h, cooled to rt and diluted with CH_2Cl_2 (40 mL). Excess of ICl was reduced with a minimum of diluted aqueous $NaHSO_3$ solution at 5 °C. The organic layer was separated, washed successively with water, brine, dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by flash chromatography (ether : EtOAc 95:5) leading to the iodouridine **9** (2.06 g, 4.0 mmol, 90 %) as a foam. IR (KBr): 1750 (s), 1715 (m), 1668 (s), 1228 (s), 1098 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.31 (s, 1H), 5.93 (d, 1H, J = 4.4 Hz), 5.53 (t, 1H, J = 6.1 Hz), 5.40 (t, 1H, J = 5.9 Hz), 4.24-4.41 (m, 3H), 3.24 (s, 3H), 2.12 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 169.9, 169.2, 159.6, 150.1, 144.0, 89.5, 79.1, 72.3, 69.2, 69.0, 62.7, 28.8, 20.6, 20.2; Mass (EI): 510 (M^+, 0.1), 259 (25), 139 (46), 127 (2), 97 (36). Exact mass calcd. for $C_{16}H_{19}IN_2O_9$: 510.27. Observed: 510.01.

Typical procedure for the preparation of an heteroarylzinc halide in THF or DMAC. Preparation of 2-quinolylzinc iodide (1e): A dry, three-necked 25 mL flask equipped with an argon inlet, a magnetic stirring bar and a thermometer was charged with zinc dust (-325 mesh, Aldrich, 0.98 g, 15 mmol). The flask was flushed with argon and 1,2-dibromoethane (ca. 100 mg, 0.05 mmol) in DMAC (1.5 mL) was added. The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred (30 s to 1 min). This heating was repeated twice and the zinc suspension was allowed to reach 25 °C (5 min). TMSCl (ca. 0.15 mL) was added neat and the reaction mixture was allowed to stir for 5 min. A 2.5 M solution of 2-iodoquinoline (**2e**) (1.28 g, 5 mmol) in DMAC was added at 50 °C. The reaction mixture was heated at 70 °C for 1 h, cooled to rt, diluted with THF (3 mL). Stirring was stopped and the remaining zinc dust was allowed to settle (ca. 1 h). The supernatant liquid containing the zinc reagent **1e** can be easily transferred in a syringe and was ready to use for the next step. The concentration of the heteroarylzinc iodide **1e** was determined by GC-analysis of an aliquot using an internal standard. Thus, the starting iodide (**2e**) was mixed with a small amount of undecane or decane as internal standard. The initial ratio A_0 between the integration of the heteroaryl iodide and the internal standard is determined. After the end of the zinc insertion, it is checked that no or negligible amounts (less than 5 %) of the iodide is present by performing a hydrolysis on a reaction aliquot. A second aliquot is taken and submitted to an iodolysis. The ratio At between the reformed aryl iodide and internal standard is determined. The ratio between A_t and A_0 (A_t/A_0) leads to the reaction yield with a precision of 1-2 %.

Typical procedure for the copper(I) catalyzed allylation of a heteroarylzinc halide. The preparation of ethyl 2-(2-quinolylmethyl)propenoate (3d): A dry, three-necked 25 mL flask equipped with an argon inlet, a magnetic stirring bar and a low temperature thermometer was charged with CuCN (ca. 90 mg, 1 mmol), dry LiCl (ca. 90 mg, 2 mmol) and THF (2 mL). The resulting solution was cooled to -30 °C and the DMAC : THF solution of the zinc reagent (**1e**) ((5 mmol) as determined by GC analysis; see above) was added. The greenish resulting solution was shortly warmed up to 0 °C and cooled back to -40 °C and ethyl (2-bromomethyl)acrylate[19] (680 mg, 3.5 mmol) was added. The reaction mixture was allowed to warm up to rt and was worked up by extracting with ether, washing successively with sat. aq. NH_4Cl solution (2 x 30 mL), water (2 x 10 mL), brine (10 mL) and dried ($MgSO_4$). The crude residue obtained after evaporation of the solvent was purified by flash chromatography (EtOAc : hexane 1:9) affording the desired product **3d** (610 mg, 72 % yield) as an oil.

Typical procedure for the copper(I) mediated addition-elimination of an heteroarylzinc iodide with 3-iodo-2-cyclohexen-1-one. The preparation of 3-(2-quinolyl)-2-cyclohexen-1-one (3e): A dry, three-necked 25 mL flask equipped with an argon inlet, a magnetic stirring bar and two glass-stoppers was charged with LiCl (420 mg, 10 mmol) and was heated 2 h at 140 °C under reduced pressure (0.1 mm Hg). It was cooled to rt and the glass-stopper was replaced by a low temperature thermometer. CuCN (450 mg, 5

mmol) and THF (10 mL) was added resulting in the formation of a greenish solution which was cooled to -30 °C. A DMAC : THF solution of the 2-quinolylzinc iodide (5 mmol) was added via syringe. The reaction mixture was warmed up to 0 °C for 5 min and was cooled back to -30 °C. A THF solution of 3-iodo-2-cyclohexen-1-one [21] (780 mg, 3 mmol in THF (2 mL)) was added and the reaction mixture was stirred at -10 °C for 24 h. The reaction mixture was worked up as described above. The crude residue obtained after evaporation of the solvent was purified by flash chromatography (EtOAc : hexane 1:19) affording the enone **3e** as a white solid (mp = 85-86 °C).

Typical procedure for the palladium (0) catalyzed cross-coupling between an heteroarylzinc iodide and an unsaturated iodide. Preparation of 2-(4-nitrophenyl)pyridine (4k); (entry 11 of Table 2):
Preparation of the zinc reagent: A two-necked flask equipped with argon inlet, rubber septum was charged with zinc dust (325 mg, 5 mmol, 2.5 eq), DMAC (2 mL) and was activated as previously described. A solution of 2-iodopyridine (410 mg, 2 mmol) in DMAC (2 mL) is added dropwise and the temperature rose to 60 °C. After stirring for 1 h at rt, the reaction is completed as judged by GC analysis of hydrolyzed and iodolyzed aliquots.
Coupling reaction: In a dry three-necked round bottom flask equipped with argon inlet, rubber septum and thermometer, $Pd(dba)_2$ (9.6 mg, 1.3 mol %) and TFP (7.5 mg, 2.6 mol %) were dissolved in THF (2 mL). After the red wine color discharged (4 min at rt), 1-iodo-4-nitrobenzene (311 mg, 1.25 mmol) was added followed by the previously prepared 2-pyridylzinc iodide. The reaction mixture was stirred at rt for 14 h then poured into sat. aq. NH_4Cl and extracted with EtOAc. The organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane : EtOAc 4:1) yielding 2-(4-nitrophenyl)pyridine (210 mg, 1.05 mmol, 84 % yield) as a pale yellow solid (mp = 124 °C).

Typical procedure for the palladium catalyzed cross-coupling between a zincated nucleoside and an aryl iodide. Preparation of 3-methyl-5-[(3-trifluoromethyl)phenyl]-2',3',5'-tri-O-acetyluridine (24): (Scheme 7). A 5 mL three-necked flask was charged under Ar with zinc dust (200 mg, 3 mmol; Aldrich, -325 mesh) and dry DMAC (1 mL). After successive activation with 1,2-dibromoethane and TMSCl as reported above, the iodide **9** (510 mg, 1 mmol) in DMAC (1 mL) was added. The reaction mixture was heated to 70 °C for 3 h. TLC analysis indicated the completion of the formation of the zinc reagent. The excess zinc dust was allowed to settle and the resulting clear solution of the zinc reagent was added at 0 °C to a solution of 3-iodotrifluoromethylbenzene (200 mg, 0.75 mmol), $Pd(dba)_2$ (6 mg, ca. 10 µmol), TFP (10 mg, 40 µmol) in THF (2 mL). The reaction mixture was allowed to stir for 10 min at rt and was quenched with aq. NH_4Cl solution, extracted with ethyl acetate (2 x 10 mL), washed with water, brine and dried ($MgSO_4$). The crude residue obtained after solvent evaporation was purified by flash chromatography (ether) affording the pure uridine derivative **24** (230 mg, 58 % yield) as a white foam.

Analytical data of the products (3a-h) of Table 1:
Ethyl 2-(1-methyl-2-imidazolylmethyl)propenoate (3a): 570 mg, 85 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (680 mg, 3.5 mmol) with **1a** (5 mmol). Reaction conditions: -60 °C to 0 °C , 1 h. Purification by flash chromatography (EtOAc : hexane 1:4). IR (neat): 1723 (s), 1634 (s), 1369 (s), 1095 (s), 821 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.93 (s, 1H), 6.78 (s, 1H), 6.28 (s, 1H), 5.41 (s, 1H), 4.17 (q, 2H, J = 6.8 Hz), 3.66 (s, 2H), 3.54 (s, 3H), 1.26 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.2, 144.8, 136.6, 127.3, 126.3, 120.6, 60.7, 32.5, 29.0, 13.9; MS (EI): 194 (M^+, 46), 165 (14), 146 (16), 121 (100), 119 (34), 95 (16). Exact mass calcd. for $C_{10}H_{14}N_2O_2$: 194.1055. Observed: 194.1062.

1-Methyl-2-(1-hexynyl)imidazole (3b): 385 mg, 68 % yield obtained by the reaction of 1-iodo-1-hexyne (710 mg, 3.5 mmol) with **1a** (5 mmol). Reaction conditions: -60 °C to -45 °C, 48 h. One equivalent of CuCN·2LiCl was used for generating the zinc-copper reagent. The crude reaction mixture was purified by flash chromatography (EtOAc : acetone 5:1). IR (neat): 2872 (s), 2239 (s), 1380 (s), 1285 (s), 751 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.95 (s, 1H), 6.83 (s, 1H), 3.67 (s, 3H), 2.44 (t, 2H, J = 6.8 Hz), 1.58-1.66 (m, 2H), 1.45-1.56 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.6, 128.6, 120.4, 94.0, 70.1, 33.1, 30.2, 21.7, 18.8, 13.3; MS (EI): 162 (M^+, 54), 147 (28), 133 (36), 119 (100), 106 (10). Exact mass calcd. for $C_{10}H_{14}N_2$: 162.1157. Observed: 162.1148.

Ethyl 2-(2-thiazolylmethyl)propenoate (3c): 630 mg, 91 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (680 mg, 3.5 mmol) with **1c** (5 mmol). Reaction conditions: -60 °C to 0 °C, 1 h. Purification by flash chromatography (EtOAc : hexane 1:7). IR (neat): 2983 (s), 1717 (s), 1633 (s), 1177 (m), 875 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, 1H, J = 3.4 Hz), 7.21 (d, 1H, J = 3.3 Hz), 6.36 (s, 1H), 5.74 (s, 1H), 4.20 (q, 2H, J = 7.1 Hz), 4.03 (s, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.4, 165.8, 142.2, 137.2, 127.5, 118.7, 60.7, 35.5, 13.9; MS (EI): 197 (M^+, 31), 168 (16), 152 (42), 151 (66), 124 (73), 123 (100). Exact mass calcd. for $C_9H_{11}NO_2S$: 197.0511. Observed: 197.0497.

Ethyl 2-(2-quinolylmethyl)propenoate (3d): For the reaction conditions, see the typical procedure. IR (neat): 3058 (m), 1714 (s), 1632 (s), 1303 (s), 1139 (m), 829 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 1H, J = 8.6 Hz), 8.03 (d, 1H, J = 7.6 Hz), 7.76 (d, 1H, J = 8.1 Hz), 7.66 (dd, 1H, J = 8.5 Hz, 1.5 Hz), 7.50 (t, 1H, J = 7 Hz), 7.33 (d, 1H, J = 8.4 Hz), 6.34 (s, 1H), 5.60 (s, 1H), 4.18 (q, 2H, J = 7.1 Hz), 4.02 (s, 2H), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.6, 159.3, 147.8, 138.5, 136.1, 129.2, 128.9, 127.3, 126.9, 125.8, 121.3, 60.6, 41.2, 14.0. MS (EI): 241 (M^+, 3), 212 (4), 196 (5), 168 (43), 143 (3), 129 (100), 128 (23), 102 (22). Exact mass calcd. for $C_{15}H_{15}NO_2$: 241.1102. Observed: 241.1086.

3-(2-Quinolyl)-2-cyclohexen-1-one (3e): For the reaction conditions, see the typical procedure. IR (KBr): 3056 (m), 1668 (s), 1265 (s), 1140 (s), 784 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (d, 1H, J = 8.6 Hz), 8.11 (d, 1H, J = 8.5 Hz), 7.82 (d, 1H, J = 8.2 Hz), 7.72 (dt, 2H, J = 8.6 Hz, 6.9 Hz), 7.56 (t, 1H, J = 6.9 Hz), 6.81 (s, 1H), 3.31 (t, 2H, J = 6 Hz), 2.55 (t, 2H, J = 6.3 Hz), 2.18-2.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 200.0, 158.9, 155.5, 147.6, 136.3, 129.9, 129.7, 127.7, 127.5, 127.2, 127.2, 118.1, 37.6, 26.2, 22.5; MS (EI): 223 (M^+, 100), 194 (80), 180 (26), 167 (59), 154 (7), 140 (6), 128 (14). Exact mass calcd. for $C_{15}H_{13}NO$: 223.0997. Observed: 223.0997.

Ethyl 2-(3-quinolylmethyl)propenoate (3f): 800 mg, 74 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (870 mg, 4.5 mmol) with **1f** (6 mmol). Reaction conditions: -60 °C to 0 °C, 0.5 h. Purification by flash chromatography (ether : hexane 1:3). IR (neat): 2982 (s), 1716 (s), 1634 (s), 1189 (s), 862 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.81 (s, 1H), 8.07 (d, 1H, J = 8.4 Hz), 7.96 (d, 1H, J = 1.5 Hz), 7.78 (dd, 1H, J = 8.9 Hz, 1.2 Hz), 7.69 (dd, 1H, J = 8.4 Hz, 6.9 Hz), 7.53 (dd, 1H, J = 8.1 Hz, 6.9 Hz), 6.33 (s, 1H), 5.60 (s, 1H), 4.18 (q, 2H, J = 7.1 Hz), 3.80 (s, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.1, 151.7, 146.8, 139.2, 134.8, 131.4, 128.9, 128.6, 127.8, 127.2, 126.3, 60.6, 35.3, 13.9; MS (EI): 241 (M^+, 28), 212 (14), 196 (16), 184 (3), 167 (100), 139 (13), 128 (4), 115 (23). Exact mass calcd. for $C_{15}H_{15}NO_2$: 241.1102. Observed: 241.1082.

Ethyl 2-[4-(7-chloroquinolylmethyl)]propenoate (3g): 540 mg, 57 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (680 mg, 3.5 mmol) with **1g**. Reaction conditions: -60 °C to 0 °C, 1 h. Purification by flash chromatography (EtOAc : hexane 15:85). Solid (mp = 51-52 °C). IR (KBr): 2982 (s), 1716 (s), 1632 (s), 1173 (s), 847 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.81 (d, 1H, J = 4.4 Hz), 8.01 (d, 1H, J = 2 Hz), 7.88 (d, 1H, J = 9 Hz), 7.50 (dd, 1H, J = 6.8 Hz, 2 Hz); 7.21 (d, 1H, J = 4.4 Hz), 6.31 (s, 1H), 5.30 (s, 1H), 4.21 (q, 2H, J = 7.2 Hz), 4.05 (s, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.3, 151.2, 148.9, 144.9, 138.0, 134.9, 129.0, 127.4, 127.3, 125.8, 125.2, 121.9, 61.0, 33.8, 14.0; MS (EI): 275 (M^+, 28), 246 (20), 230 (15), 211 (5), 202 (80), 167 (100), 166 (98), 139 (23), 127 (2), 114 (6). Exact mass calcd. for $C_{15}H_{14}O_2NCl$: 275.0713. Observed: 275.0714.

5-(2-Carboethoxy-2-propenyl)-1,3-dimethyluracil (3h): 540 mg, 71 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (580 mg, 3 mmol) with **7a**. Reaction conditions: -60 °C to 0 °C, 1 h. Purification by flash chromatography (EtOAc : hexane 1:1). IR (neat): 3068 (w), 2939 (w), 1701 (s), 1680 (s), 819 (s), 773 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16 (s, 1H), 6.27 (s, 1H), 5.81 (s, 1H), 4.21 (q, 2H, J = 7.2 Hz), 3.41 (s, 3H), 3.33 (s, 3H), 3.30 (s, 2H), 1.31 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.3, 162.9, 151.4 , 140.7, 136.9, 126.9, 110.2, 60.5, 36.5, 29.2, 27.6, 13.9; MS (EI): 252 (M^+, 8), 207 (26), 206 (79), 179 (40), 178 (100), 153 (5), 138 (2). Exact mass calcd. for $C_{12}H_{16}N_2O_4$: 252.1110. Observed: 252.1118.

Analytical data of the products (4a-q) of Table 2:

1-Methyl-2-phenylimidazole (4a): 345 mg, 75 % yield obtained by the reaction of iodobenzene (612 mg, 3 mmol) with **1a** (5 mmol). Reaction conditions: 25 °C, 48 h. Purification by flash chromatography (EtOAc : hexane 1:1). IR (neat): 3056 (w), 1396 (s), 1044 (m), 773 (s), 710 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.64 (m, 2H), 7.38-7.48 (m, 3H), 7.1 (s, 1H), 6.95 (s, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 147.6, 130.5, 128.4, 128.3, 128.2, 128.2, 122.1, 34.1; MS (EI): 158 (M^+, 55), 157 (65), 116 (4). Exact mass calcd. for $C_{10}H_{10}N_2$: 158.0844. Observed: 158.0837.

(E)-1-Methyl-2-(1-octenyl)imidazole (4b): 475 mg, 70 % yield obtained by the reaction of (*E*)-1-iodo-1-octene (833 mg, 3.5 mmol) with **1a** (5 mmol). Reaction conditions: 25 °C, 24 h. Purification by flash chromatography (EtOAc : hexane 1:1). IR (neat): 3104 (m), 2925 (s), 1650 (m), 725 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.00 (s, 1H), 6.78 (s, 1H), 6.64-6.78 (m, 1H), 6.20-6.30 (m, 1H), 3.63 (s, 3H), 2.24 (t, 2H, J = 7 Hz), 1.42-1.56 (m, 2H), 1.28-1.40 (m, 6H), 0.9 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.5, 135.9, 127.8, 120.4, 115.4, 32.8, 32.8, 31.4, 28.7, 28.6, 22.3, 13.8; MS (EI): 192 (M^+, 26),

177 (3), 163 (6), 149 (15), 135 (100), 121 (41). Exact mass calcd. for $C_{12}H_{20}N_2$: 192.1626. Observed: 192.1634.

1-Methyl-2-(3-oxocyclohexenyl)imidazole (4c): 445 mg, 83 % yield obtained by the reaction of 3-iodo-2-cyclohexen-1-one (670 mg, 3 mmol) with **1a** (5 mmol). Reaction conditions: 25 °C, 72 h. Purification by flash chromatography (EtOAc : hexane 1:3), solid (mp = 88-89 °C). IR (KBr):1655 (s), 1607 (s), 1262 (s), 1154 (m), 773 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.11 (s, 1H), 6.95 (s, 1H), 6.19 (s, 1H), 3.75 (s, 3H), 2.90 (t, 2H, J = 5.9 Hz), 2.44 (t, 2H, J = 5.7 Hz), 2.06-2.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.1, 149.3, 144.6, 129.2, 125.5, 125.2, 37.0, 35.5, 27.7, 22.1; MS (EI): 176 (M^+, 100), 161 (3), 147 (48), 133 (15), 120 (53), 119 (74). Exact mass calcd. for $C_{10}H_{12}N_2O$: 176.0949. Observed: 176.0962.

(E)-4,5-Dicyano-1-methyl-2-(1-octenyl)imidazole (4d): 720 mg, 85 % yield obtained by the reaction of (E)-1-iodooctene (833 mg, 3.5 mmol) with **1b**. Reaction conditions: 25 °C, 2 h. Purification by flash chromatography (EtOAc : hexane 1:9). IR (neat): 2928 (s), 2232 (s), 1653 (s), 757 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.02 (dt, 1H, J = 15.4 Hz, 7.0 Hz), 6.20 (d, 1H, J = 15.4 Hz), 3.76 (s, 3H), 2.29 (q, 2H, J = 7.1 Hz), 1.28-1.52 (m, 8H), 0.87 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 150.5, 145.6, 121.9, 113.0, 112.2, 111.8, 108.4, 33.0, 32.4, 31.4, 28.7, 28.2, 22.4, 13.9; MS (EI): 242 (M^+, 10), 214 (9), 199 (14), 185 (58), 171 (33), 159 (100), 158 (43), 146 (70), 131 (8). Exact mass calcd. for $C_{14}H_{18}N$: 242.1531. Observed: 242.1525.

4,5-Dicyano-1-methyl-2-(3-trifluoromethylphenyl)imidazole (4e): 290 mg, 70 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (400 mg, 1.5 mmol) with **1b** (2.5 mmol). Reaction conditions: 70 °C, 12 h. Purification by flash chromatography (EtOAc : hexane 1:3); solid (mp = 108 °C). IR (KBr): 2242 (s), 1399 (m), 1326 (s), 1165 (m), 833 (m), 729 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.84 (d, 1H, J = 4.5 Hz), 8.14 (d, 1H, J = 2.1 Hz), 7.98 (d, 1H, J = 9 Hz), 7.15-7.50 (m, 1H), 4.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.4, 148.9, 146.7, 138.3, 135.0, 129.1, 128.8, 128.8, 127.5, 126.8, 125.3, 122.1, 38.2; MS (EI): 276 (M^+, 77), 275 (100), 257 (5), 207 (5), 145 (4), 138 (2). Anal. calcd. for C: 56.53, H: 2.55, N: 20.28; Found: C: 56.41, H: 2.78, N: 20.12.

4,5-Dicyano-1-methyl-2-(3-carboethoxyphenyl)imidazole (4f): 260 mg, 62 % yield obtained by the reaction of ethyl 3-iodobenzoate (414 mg, 1.5 mmol) with **1b** (2.5 mmol). Reaction conditions: 70 °C, 12 h. Purification by flash chromatography (EtOAc : hexane 1:2), solid (mp = 100-101 °C). IR (KBr): 2233 (s), 1723 (s), 1270 (s), 1111 (m), 734 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.20 (m, 2H), 7.77 (m, 1H), 7.57 (t, 1H, J = 7.83 Hz), 4.32 (q, 2H, J = 7 Hz), 3.86 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 165.3, 151.5, 133.2, 132.1, 131.6, 129.8, 129.5, 127.3, 122.2, 114.3, 111.6, 108.2, 61.6, 34.8, 14.3; MS (EI): 280 (M^+, 87), 252 (34), 235 (100), 207 (43), 130 (2). Anal. calcd. for C: 64.28, H: 4.32, N: 19.99; Found: C: 64.23, H: 4.57, N: 19.98.

4,5-Dicyano-1-methyl-2-(3-nitrophenyl)imidazole (4g): 260 mg, 68 % yield obtained by the reaction of 1-iodo-3-nitrobenzene (374 mg, 1.5 mmol) with **1b** (2.5 mmol). Reaction conditions: 70 °C, 12 h. Purified by flash chromatography (EtOAc : hexane 2:3). Solid (mp = 138 °C). IR (KBr): 2244 (s), 1531 (s), 1475 (m), 793 (s), 717 (s) cm^{-1}; ^1H NMR (C_3D_6O, 300 MHz): δ 8.62 (m, 1H), 8.44 (m, 1H), 8.23 (m, 1H), 7.92 (t, 1H, J = 8 Hz), 4.14 (s, 3H); ^{13}C NMR (C_3D_6O, 75.5 MHz): δ 151.1, 149.4, 136.1, 131.5, 130.1, 126.2, 124.9, 122.2, 116.1, 112.8, 109.2, 35.6; MS (EI): 253 (M^+, 100), 252 (17), 207 (54), 206 (26), 192 (9). Anal. calcd. for: C: 56.92, H: 2.79, N: 27.66; Found: C: 56.77, H: 2.81, N: 27.44.

4,5-Dicyano-1-methyl-2-(2-pyridyl)imidazole (4h): 260 mg, 83 % yield obtained by the reaction of 2-bromopyridine (233 mg, 1.5 mmol) with **1b** (2.5 mmol). Reaction conditions: 70 °C, 12 h. Purified by flash chromatography (EtOAc : hexane 2:3), solid (mp = 166 °C). IR (KBr): 2241 (s), 1327 (w), 802 (s), 743 (m) cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz): δ 8.60 (m, 1H), 8.12 (m, 1H), 7.80 (m, 1H), 7.35 (m, 1H), 4.21 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ 149.6, 148.4, 138.1, 125.7, 125.1, 122.2, 116.1, 112.6, 109.0;MS (EI): 209 (M^+, 80), 208 (100), 105 (25). Anal. calcd. for C: 63.15, H: 3.37, N: 33.48; Found: C: 62.94, H: 3.27, N: 33.60.

2-[(3-Trifluoromethyl)phenyl]thiazole (4i): 625 mg, 78 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (952 mg, 3.5 mmol) with **1c** (5 mmol). Reaction conditions: 25 °C, 12 h. Purification by flash chromatography (EtOAc : hexane 1:19). IR (neat): 1595 (w), 1330 (s), 1238 (s), 1169 (s), 1129 (s), 802 (m), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.19 (s, 1H), 8.05 (d, 1H, J = 7.8 Hz), 7.84 (d, 1H, J = 3.2 Hz), 7.60 (d, 1H, J = 8 Hz), 7.49 (t, 1H, J = 7.8 Hz), 7.32 (d, 1H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 166.5, 144.0, 134.3, 132.2, 131.7, 131.3, 130.9, 129.7, 129.7, 129.5, 126.4, 126.4,

126.3, 126.3, 123.4, 123.3, 123.3, 123.2, 119.6; MS (EI): 229 (M^+, 30), 210 (2), 58 (100). Anal. calcd. for C: 52.40, H: 2.64, N: 6.11; Found: C: 52.50, H: 2.66, N: 6.11.

(E)-2-(1-Octenyl)thiazole (4j): 610 mg, 89 % yield obtained by the reaction of (E)-1-iodo-1-octene (833 mg, 3.5 mmol) with **1c** (5 mmol). Reaction conditions: 25 °C, 6 h. Purification by flash chromatography (EtOAc : hexane 1:19). IR (neat): 2957 (s), 2871 (s), 1649 (s), 1142 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.69 (d, 1H, J = 3.3 Hz), 7.14 (d, 1H, J = 3.3 Hz), 6.58-6.62 (m, 2H), 2.21-2.28 (m, 2H), 1.47-1.54 (m, 2H), 1.30-1.37 (m, 6H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.5, 142.9, 138.1, 123.7, 117.2, 32.6, 31.6, 28.7, 28.5, 22.5, 13.9; MS (EI): 195 (M^+, 50), 180 (6), 166 (13), 152 (20), 138 (100). Exact. mass calcd. for $C_{11}H_{17}NS$: 195.1082. Observed: 195.1082.

2-(4-Nitrophenyl)pyridine (4k): 210 mg, 84 % yield obtained by the reaction of 1-iodo-4-nitrobenzene (311 mg, 1.25 mmol) with **1d** (2 mmol). Reaction conditions: 25 °C, 14 h. Purification by flash chromatography (EtOAc : hexane 1:4). Solid (mp = 124 °C). IR (KBr): 3035 (w), 1585 (m), 1515 (s), 1346 (s), 1326 (m), 741 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.64 (d, 1H, J = 4.7 Hz), 8.23 (d, 2H, J = 8.9 Hz), 8.15 (d, 2H, J = 8.9 Hz), 7.78 (m, 2H), 7.24 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.0, 150.2, 148.3, 145.3, 137.2, 127.8, 124.1, 123.6, 121.3; MS (EI): 200 (M^+, 100), 154 (83), 127 (29). Anal. calcd. for C: 65.99, H: 4.03, N: 13.99; Found: C: 65.51, H: 4.25, N: 13.59.

(E)-2-(1-Octenyl)quinoline (4l): 510 mg, 61 % yield obtained by the reaction of (E)-1-iodo-1-octene (830 mg, 3.5 mmol) with **1e** (5 mmol). Reaction conditions: 25 °C, 4 h. Purification by flash chromatography (EtOAc : hexane 1:24). IR (neat): 2955 (s), 1652 (m), 1503 (s), 1117 (m), 750 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 1H, J = 8.2 Hz), 8.02 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 8.1 Hz), 7.66 (t, 1H, J = 8.4 Hz), 7.43-7.53 (m, 2H), 6.83 (dt, 1H, J = 15.9, 6.5 Hz), 6.73 (d, 1H, J = 15.9 Hz), 2.30-2.36 (m, 2H), 1.50-1.60 (m, 2H), 1.29-1.43 (m, 6H), 0.90 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 156.5, 148.3, 137.9, 135.9, 131.0, 129.4, 129.1, 127.3, 127.1, 125.7, 118.7, 32.9, 31.6, 28.9, 28.8, 22.5, 13.9; MS (EI): 239 (M^+, 20), 210 (23), 196 (18), 182 (100). Exact mass calcd. for $C_{17}H_{21}N$: 239.1673. Observed: 239.1654.

(E)-[7-Chloro-4-(1-octenyl)]quinoline (4m): 590 mg, 72 % yield obtained by the reaction of (E)-1-iodo-1-octene (710 mg, 3 mmol) with **1g**. Reaction conditions: 25 °C, 4 h. Purification by flash chromatography (EtOAc : hexane 1:19). IR (neat): 2955 (s), 1645 (s), 1503 (s), 1158 (m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.80 (d, 1H, J = 4.6 Hz), 8.06 (d, 1H, J = 2.1 Hz), 8.01 (d, 1H, J = 9 Hz), 7.46 (dd, 1H, J = 6.8 Hz, 2 Hz), 7.40 (d, 1H, J = 4.6 Hz), 7.00 (d, 1H, J = 15.6 Hz), 6.48 (dt, 1H, J = 15.9 Hz, 6.5 Hz), 2.31-2.38 (m, 2H), 1.41-1.54 (m, 2H), 1.29-1.39 (m, 6H), 0.91 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.2, 149.1, 143.8, 139.2, 134.9, 128.9, 127.1, 125.1, 124.7, 124.1, 117.4, 33.5, 31.6, 28.9, 28.9, 22.6, 13.9; MS (EI): 273 (M^+, 47), 216 (11), 202 (57), 189 (34), 177 (25), 167 (75), 154 (100). Exact mass calcd. for $C_{17}H_{20}NCl$: 273.1284. Observed: 273.1275.

1,3-Dimethyl-5-(7-chloro-4-quinolyl)uracil (4n): 660 mg, 73 % yield obtained by the reaction of 1,3-dimethyl-5-iodouracil (800 mg, 3 mmol) with **1g** (5 mmol). Reaction conditions: 45 °C, 24 h. Purification by flash chromatography (EtOAc). Solid (mp = 185-186 °C). IR (KBr): 3081 (w), 1699 (s), 1649 (s), 1579 (s), 776 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.91 (d, 1H, J = 4.4 Hz), 8.13 (d, 1H, J = 2.1 Hz), 7.70 (d, 1H, J = 9.0 Hz), 7.48 (dd, 1H, J = 9.0 Hz, 2.8 Hz), 7.36 (s, 1H), 7.29 (d, 1H, J = 4.4 Hz), 3.52 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.6, 151.2, 150.8, 148.8, 142.8, 139.6, 135.2, 128.6, 127.5, 126.7, 125.5, 122.5, 110.5, 37.0, 28.1; MS (EI): 301 (M^+, 80), 266 (14), 243 (18), 216 (27), 140 (42), 83 (19), 56 (36), 42 (100). Exact mass calcd. for $C_{15}H_{12}ClN_2O_3$: 301.0618. Observed: 301.0626.

7-Chloro-4-(1-hexynyl)quinoline (4o): 424 mg, 55 % yield obtained by the reaction of 1-iodo-5-methyl-1-hexyne (670 mg, 3 mmol) with **1g** (5 mmol). Reaction conditions: 25 °C, 3 h. Purification by flash chromatography (EtOAc : hexane 1:20). IR (neat): 2958 (s), 2233 (s), 1186 (m), 880 (s), cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, 1H, J = 4.4 Hz), 8.18 (d, 1H, J = 8.89 Hz), 8.07 (d, 1H, J = 2 Hz), 7.52 (dd, 1H, J = 4.9 Hz, 2 Hz), 7.40 (d, 1H, J = 4.5 Hz), 2.59 (t, 2H, J = 7.4 Hz), 1.77-1.86 (m, 1H), 1.61 (q, 2H, J = 7.2 Hz), 0.98 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 150.7, 149.2, 135.6, 130.7, 128.7, 127.8, 127.4, 126.9, 123.6, 101.5, 76.3, 37.4, 27.5, 22.1, 17.8; MS (EI): 257 (M^+, 44), 242 (91), 214 (47), 200 (37), 179 (19), 166 (100). Exact mass calcd. for $C_{16}H_{16}ClN$: 257.0971. Observed: 257.0957.

7-Chloro-4-(2-methylcyclopenten-2-one)quinoline (4p): 550 mg, 71 % yield obtained by the reaction of 3-iodo-2-methyl-cyclopentenone (670 mg, 3 mmol) with **1g** (5 mmol). Reaction conditions: 45 °C, 24 h. Purification by flash chromatography (EtOAc : hexane 1:3). Solid (mp = 119-120 °C). IR (KBr): 1707 (s), 1651 (s), 1572 (s), 1119 (s), 848 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.95 (d, 1H, J = 4.4 Hz), 8.16 (d,

1H, J = 1.4 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.44 (dd, 1H, J = 8.0 Hz, 2.0 Hz), 7.19 (d, 1H, J = 4.9 Hz), 2.88-2.91 (m, 2H), 2.59-2.62 (m, 2H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 207.9, 164.1, 150.9, 148.8, 144.0, 140.8, 135.7, 129.2, 128.1, 126.1, 122.9, 118.7, 34.2, 31.7, 9.0; MS (EI): 257 (M^+, 7), 234 (4), 219 (22), 194 (4), 180 (4), 105 (100). Exact mass calcd. for $C_{15}H_{12}ClNO$: 257.0607. Observed: 257.0601.

7-Chloro-4-(4-nitrophenyl)quinoline (4q): 610 mg, 86 % yield obtained by the reaction of 1-iodo-4-nitrobenzene (622 mg, 2.5 mmol) with **1g** (4 mmol). Reaction conditions: 60 °C, 2 h. Purification by flash chromatography (EtOAc : hexane 1:1). Solid (mp = 163 °C). IR (KBr): 3063 (w), 1601 (m), 1576 (m), 1517 (s), 1351 (s), 865 (m), 841 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (d, 1H, J = 4.3 Hz), 7.43 (dd, 1H, J = 9 Hz, J = 2 Hz), 7.62 (m, 3H), 8.19 (d, 1H, J = 2 Hz), 8.38 (d, 2H, J = 8.7 Hz), 8.87 (d, 1H, J = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.3, 149.4, 146.4, 144.4, 136.3, 130.9, 129.5, 128.8, 128.1, 126.8, 124.8, 124.4, 121.7; MS(EI): 184 (M^+, 100), 238 (20), 203 (69), 88 (17). Anal. calcd. for C: 63.28, H: 9.84, N: 3.19. Found C: 63.51, H: 9.65, N: 3.38.

1,3-Dimethyl-5-trimethylsilyluracil (19): 750 mg, 78 % yield obtained by the reaction of TMSCl (648 mg, 6 mmol) with **7a** (10 mmol). Reaction conditions: 70 °C, 4 h. Purification by flash chromatography (EtOAc : hexane 1:3). IR (neat): 2954 (s), 1703 (s), 1643 (s), 785 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.86 (s, 1H), 3.22 (s, 3H), 3.13 (s, 3H), 0.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 165.4, 152.1, 146.8, 109.2, 36.6, 27.2, -1.92; MS (EI): 212 (M^+, 5), 198 (14), 197 (100), 83 (5), 73 (2), 42 (8). Exact mass calcd. for $C_9H_{16}N_2O_2Si$: 212.0981. Observed: 212.0974.

Analytical data of the products (20a-g and 21a-d) (Table 3):

1,3-Dimethyl-5-phenyluracil (20a): 610 mg, 83 % yield obtained by the reation of iodobenzene (918 mg, 4.5 mmol) with **7a** (3.4 mmol). Reaction conditions: 25 °C, 0.5 h. Purification by flash chromatography (EtOAc : ether 1:3). Solid (mp = 146-147 °C). IR (KBr): 2900 (w), 1692 (s), 1648 (s), 1640 (s), 1600 (w), 1483 (m), 1351 (m), 748 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31-7.53 (m, 6H), 3.48 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.1, 151.3, 140.3, 132.7, 128.3, 128.1, 127.7, 114.2, 36.9, 28.1; MS (EI): 216 (M^+, 100), 158 (70), 118 (45). Anal. calcd. for C: 66.70, H: 5.60, N: 12.98, Found: C: 66.62, H: 5.48, N: 12.85.

1,3-Dimethyl-5-(3-trifluoromethylphenyl)uracil (20b): 750 mg, 78 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (1.10 g, 4 mmol) with **7a** (3 mmol). Reaction conditions: 25 °C, 0.5 h. Purification by flash chromatography (ether). Solid (mp = 152-153 °C). IR (KBr): 2950 (w), 1702 (s), 1657 (s), 1489 (m), 1461 (m), 1372 (m), 1346 (m), 1279 (m), 1116 (s), 809 (m), 711 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40-7.74 (m, 4H), 7.30 (s, 1H), 3.43 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.0, 151.7, 141.4, 134.1, 132.1, 129.3, 125.3, 124.9, 113.4, 37.6, 28.7; MS (EI): 284 (M^+, 100), 226 (50), 186 (45), 42 (85). Anal. calcd. for C: 54.93, H: 3.90, N: 9.85; Found: C: 54.61, H: 3.77, N: 9.80.

1,3-Dimethyl-5-(4-carboethoxyphenyl)uracil (20c): 785 mg, 80 % yield obtained by the reaction of ethyl 4-iodobenzoate (1.10 g, 4 mmol) with **7a** (3.4 mmol). Reaction conditions: 25 °C, 0.5 h. Purification by flash chromatography (EtOAc : ether 1:6). Solid (mp = 122-123 °C). IR (KBr): 2900 (w), 1697 (s), 1651 (s), 1605 (m), 1456 (m), 1409 (m), 1278 (s), 1112 (s), 786 (m), 707 (m) cm^{-1} ; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.97 (dd, 2H, J = 5 Hz, 1.6 Hz), 7.52 (dd, 2H, J = 5 Hz, 1.8 Hz); 7.32 (s, 1H), 4.30 (q, 2H, J = 7.2 Hz), 3.43 (s, 3H), 3.36 (s, 3H), 1.33 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.7, 162.3, 152.0, 141.5, 137.8, 130.0, 128.4, 113.7, 61.4, 37.6, 28.7, 14.7; MS (EI): 288 (M^+, 100), 243 (75), 230 (60), 145 (30). Anal. calcd. for C: 62.49, H: 5.59, N: 9.72; Found: C: 62.33, H: 5.37, N: 9.70.

1,3-Dimethyl-5-[6-(9-benzyl)purine]uracil (20d): 760 mg, 79 % yield obtained by the reaction of 6-iodo-9-benzylpurine (960 mg, 2.8 mmol) with **7a** (3.4 mmol). Reaction conditions: 25 °C, 0.5 h. Recrystallized using acetonitrile as solvent. Needles (mp = 229-230 °C). IR (KBr): 3069 (w), 2950 (w), 1710 (s), 1664 (s), 1621 (m), 1578 (m), 1443 (s), 1360 (m), 1324 (m), 744 (m), 724 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.82 (s, 1H), 8.07 (s, 1H), 7.87 (s, 1H), 7.06-7.19 (m, 5H), 5.26 (s, 2H), 3.34 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): 163.4, 155.4, 154.7, 154.1, 153.8, 149.5, 147.0, 137.8, 134.1, 132.0, 131.4, 130.7, 112.4, 50.2, 40.4, 31.2; MS (EI): 348 (M^+, 50), 257 (60), 91 (100). Anal. calcd. for C: 62.42, H: 4.63, N: 24.12; Found: C: 62.13, H: 4.83, N: 24.02.

1,3-Dibenzyl-5-(3-trifluoromethylphenyl)uracil (20e): 890 mg, 68 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (1.09 g, 4 mmol) with **7b** (3 mmol). Reaction conditions: 25 °C, 1 h. Purified by flash chromatography (ether : hexane 1:1) and the product was isolated as a foam. IR (KBr): 3110 (w), 1705 (s), 1650 (s), 1450 (m), 1330 (m), 1260 (m), 1120 (s), 810 (m), 737 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41-7.60 (m, 4H), 7.18-7.25 (m, 11H), 5.16 (s, 2H), 4.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ

162.1, 151.7, 140.5, 137.1, 135.6, 134.1, 132.2, 131.6, 130.9, 129.6, 129.3, 129.1, 128.9, 128.4, 128.2, 127.1, 125.5, 125.4, 125.1, 125.0, 121.7, 114.1, 53.0, 45.5; MS (EI): 436 (M^+, 40), 91 (100). Anal. calcd. for C: 68.80, H: 4.55, N: 6.43; Found C: 68.70, H: 4.59, N: 6.45.

1,3-Dibenzyl-5-(3-nitrophenyl)uracil (20f): 950 mg, 77 % yield obtained by the reaction of 1-iodo-3-nitrobenzene (996 mg, 4 mmol) with **7b** (3 mmol). Reaction conditions: 25 °C, 1 h. Purification by flash chromatography (ether : hexane 1:2). Solid (mp = 144-145 °C). IR (KBr): 3110 (w), 1705 (s), 1650 (s), 1516 (s), 1459 (s), 1450 (m), 1384 (s), 737 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.11-8.13 (m, 1H), 7.90 (d, 1H, J = 7.4 Hz), 7.65 (d, 1H, J = 7.6 Hz), 7.12-7.39 (m, 12H), 5.06 (s, 2H), 4.87 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.9, 151.6, 148.7, 140.8, 136.9, 135.4, 134.9, 129.7, 129.2, 128.9, 128.5, 128.3, 123.4, 123.0, 113.2, 53.1, 45.6; MS (EI): 413 (M^+, 30), 91 (100). Anal. calcd. for C: 69.72, H: 4.60, N: 10.18; Found C: 69.58, H: 4.89, N: 10.16.

1,3-Dibenzyl-5-(4-carboethoxyphenyl)uracil (20g): 820 mg, 62 % yield obtained by the reaction of ethyl 3-iodobenzoate (1.10 g, 4 mmol) with **7b** (3 mmol). Reaction conditions: 25 °C, 1 h. Purification by flash chromatography (ether : hexane 1:1). The product was isolated as a foam. IR (KBr): 3110 (w), 1700 (s), 1650 (s), 1450 (m), 1420 (m), 1360 (m), 1250 (s), 1170 (s), 780 (m), 710 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.95 (s, 1H), 7.84 (d, 1H, J = 7.6 Hz), 7.57 (d, 1H, J = 7.2 Hz), 7.15-7.44 (m, 11H), 5.10 (s, 2H), 4.86 (s, 2H), 4.25 (q, 2H, J = 7.2 Hz), 1.25 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.7, 162.2, 151.7, 140.7, 137.3, 136.0, 133.7, 133.4, 131.1, 130.5, 129.6, 129.5, 129.2, 128.9, 128.4, 128.1, 114.2, 61.5, 52.9, 45.4, 14.8; MS (EI): 440 (M^+, 50), 91 (100). Exact mass. calcd. for $C_{27}H_{24}N_2O_4$: 440.2266. Observed: 440.1729.

9-Benzyl-6-phenylpurine (21a): 495 mg, 80 % yield obtained by the reaction of iodobenzene (612 mg, 3 mmol) with **8a** (2.15 mmol). Reaction conditions: 60 °C, 4 h. Purification by flash chromatography (EtOAc : hexane 1:2). Solid (mp = 123-125 °C). IR (KBr): 3080 (w), 2925 (w), 1580 (s), 1564 (s), 1456 (m), 766 (s), 729 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.99 (s, 1H), 8.68-8.73 (m, 2H), 8.03 (s, 1H), 7.46-7.50 (m, 3H), 7.28 (s, 5H), 5.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.3, 153.0, 144.5, 136.1, 135.6, 131.4, 130.2, 129.6, 129.1, 129.0, 128.2, 47.7; MS (EI): 286 (M^+, 59), 285 (64), 258 (4), 209 (8), 195 (12), 91 (100), 77 (3). Anal. calcd. for C: 75.51, H: 4.93, N: 19.57; Found: C: 75.38, H: 4.68, N: 19.24.

9-Benzyl-6-(4-carboethoxyphenyl)purine (21b): 540 mg, 70 % yield obtained by the reaction of ethyl 4-iodobenzoate (828 mg, 3 mmol) with **8a** (2.15 mmol). Reaction conditions: 60 °C, 4 h. Purification by flash chromatography (ether : hexane 3:1) and the product was isolated as a foam. IR (KBr): 2972 (w), 1708 (s), 1584 (m), 1561 (m), 1294 (s), 1107 (m), 775 (m), 726 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.90 (s, 1H), 8.70 (d, 2H, J = 8.2 Hz), 8.01 (d, 2H, J = 8.4 Hz), 7.94 (s, 1H), 7.18 (s, 5H), 5.40 (s, 2H), 4.22 (q, 2H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.2, 153.4, 152.7, 152.4, 144.4, 139.6, 134.9, 132.2, 131.2, 129.6, 129.5, 129.0, 128.5, 127.7, 61.0, 42.2, 14.2; MS (EI): 358 (M^+, 49), 357 (40), 329 (8), 313 (20), 285 (4), 209 (2), 91 (100). Anal. calcd. for C: 70.38, H: 5.06, N: 15.63; Found: C: 70.18, H: 5.13, N: 15.70.

9-Benzyl-6-(3-trifluoromethyl)phenylpurine (21c): 565 mg, 74 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (816 mg, 3 mmol) with **8a** (2.15 mmol). Reaction conditions: 60 °C, 4 h. Purification by flash chromatography (ether : hexane 2:1). Solid (mp = 121-122 °C). IR (KBr): 3100 (w), 1571 (s), 1342 (s), 1326 (m), 1272 (m), 1179 (m), 729 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.98-9.05 (m, 3H), 8.06 (s, 1H), 7.57-7.72 (m, 2H), 7.28 (s, 5H), 5.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.3, 153.2, 145.0, 136.9, 135.4, 133.5, 131.8, 131.5, 131.2, 129.6, 129.5, 129.1, 128.3, 127.8, 127.7, 127.5, 126.9, 126.9, 121.8, 47.8; MS (EI): 354 (M^+, 59), 353 (64), 335 (2), 263 (5), 91 (100), 77 (1). Anal. calcd. for C: 64.39, H: 3.70, N: 15.81; Found C: 64.08, H: 3.68, N: 15.53.

6-(3-carboethoxyphenyl)-9-tetrahydropyranylpurine (21d): 720 mg, 68 % yield obtained by the reaction of ethyl-3-iodobenzoate (1.10 g, 4 mmol) with **8b** (3 mmol). Reaction conditions: 65 °C, 2.5 h. Purification by flash chromatography (ether : hexane 3:2). Solid (mp = 93-94 °C). IR (KBr): 2900 (s), 1700 (s), 1580 (m), 1565 (m), 1435 (m), 1292 (s), 1107 (m), 775 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.27-9.29 (m, 1H), 8.94 (s, 1H), 8.88-8.93 (m, 1H), 8.25 (s, 1H), 8.07-8.12 (m, 1H), 7.49-7.57 (m, 1H), 5.71-5.77 (m, 1H), 4.32 (q, 2H, J = 7.2 Hz), 4.05-4.13 (m, 1H), 3.60-3.91 (m, 1H), 1.96-2.05 (m, 3H), 1.62-1.68 (m, 3H), 1.30 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.8, 154.2, 152.8, 152.2, 142.8, 136.4, 134.6, 132.2, 131.6, 131.5, 131.0, 129.2, 82.4, 69.3, 61.6, 32.2, 25.3, 23.2, 14.8; MS (EI): 352 (M^+, 20), 269 (70), 223 (25), 196 (50), 85 (100). Anal. calcd. for C: 64.76, H: 5.72, N: 15.90; Found: C: 64.61, H: 5.74, N: 15.93.

3-Methyl-5-[(3-trifluoromethyl)phenyl]-2',3',5'-tri-O-acetyluridine (22): 230 mg, 58 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (200 mg, 0.75 mmol) with **22** (1 mmol). Reaction conditions: 0 °C to 25 °C, 10 min. Purification by flash chromatography (ether). The product was isolated as a foam. IR (KBr): 2950 (w), 1754 (s), 1715 (m), 1669 (s), 1467 (m), 1229 (s), 1103 (w), 756 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.46-7.68 (m, 5H), 6.03 (d, 1H, J = 5 Hz), 5.39 (t, 1H, J = 5.7 Hz), 5.28 (t, 1H, J = 4.6 Hz), 4.30-4.32 (m, 3H), 3.40 (s, 3H), 2.06 (s, 6H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.0, 169.6, 169.5, 161.3, 150.4, 135.4, 133.7, 131.9, 131.9, 131.4, 130.7, 130.3, 128.9, 125.2, 125.1, 124.9, 124.8, 114.2, 88.8, 80.0, 72.9, 70.0, 62.8, 28.3, 20.4, 20.3; MS (EI): 528 (M^+, 0.3), 509 (0.6), 269 (0.1), 259 (34), 43 (100). Anal. calcd. for C: 52.28, H: 4.39, N: 5.30; Found: C: 52.00, H: 4.63, N: 5.11.

6-Phenyl-9β-(2',3',5'-tri-O-acetyl)-D-ribofuranosylpurine (23): 355 mg, 52 % yield obtained by the reaction of iodobenzene (510 mg, 2.5 mmol) with **8a** (1.5 mmol). Reaction conditions: 65 °C, 4 h. Purification by flash chromatography (ether : hexane 3:1). The product was isolated as a foam. IR (KBr): 2926 (m), 1749 (s), 1583 (s), 1566 (s), 1439 (m), 1220 (s), 1101 (m), 766 (m), 693 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.95 (s, 1H), 8.65-8.69 (m, 2H), 8.21 (s, 1H), 7.45-7.55 (m, 3H), 6.22 (d, 1H, J = 5.2 Hz), 5.94 (t, 1H, J = 5.2 Hz), 5.63 (t, 1H, J = 4.4 Hz), 4.32-4.41 (m, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.7, 170.7, 169.9, 155.8, 153.0, 152.4, 142.9, 135.7, 132.0, 131.5, 130.2, 129.0, 86.7, 80.7, 73.4, 71.0, 63.4, 21.1, 20.9, 20.7; MS (EI): 454 (M^+, 2), 411 (2), 395 (7), 259 (14), 216 (2), 195 (2), 141 (1), 139 (52), 127 (3), 77 (1), 43 (100). Exact mass calcd. for $C_{22}H_{22}N_4O_7$: 454.2168. Observed: 454.1508.

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References and Notes

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