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A Direct Synthesis of Isocytosine Analogues by Carbonylative Coupling of α-Chloroketones and Guanidines

Martina Capua,[a] Serena Perrone,[a] Fabio Bona,[a] Antonio Salomone*,[a] and Luigino Troisi*,[a]

Abstract: A valuable and direct method to access 2-aminopyrimidin-4-one derivatives is described. The strategy relies on the Pd-catalyzed carbonylation of α-chloroketones in the presence of mono- and disubstituted guanidines. Although the strategy furnished also 2-aminoimidazoles derivatives as minor products, a good chemoselectivity, favouring the six-membered ring, has been achieved in all experiments. *In situ* formation of a β-oxoacylpalladium species has been invoked as the key step for a multicomponent process. Moreover, the method described can be considered of interest from a biological point of view because it constitutes a straightforward strategy for the synthesis of structural analogues of the unnatural nucleobase isocytosine.

Introduction

Among a plethora of palladium-catalyzed processes, a central role is played by carbonylation reactions for their exceptional efficiency in the direct and regioselective synthesis of carbonyl-containing molecules starting from simple substrates.[1] Since the original reports of Heck,[2] nowadays numerous synthetic methodologies have been set up thus expanding the scope of the carbonylations in terms of palladium ligands,[3] CO sources,[4] unconventional solvents[5] or peculiar structures of the target products.[6] In this field, we were involved in the carbonylative coupling of allyl and benzyl halides as a synthetic tool for the preparation of β-lactams,[7a-c] imides,[7d] esters,[7e] amides[7f] or acetylenic ketones[7g]. Subsequently, we have explored the carbonylation reaction of different unsaturated halides such as α-chloroketones, finding that new polyfunctionalized products, such as α-alkylidene-β-oxoamides[7h] and β-enaminoacid derivatives,[7i] could be easy made. More recently, the carbonylation of α-chloroketones was employed, by our group, as a useful strategy for the *one-pot* synthesis of 2-pyranones,[8a] uracil analogues[8b] and pyrazolones.[8c]

Unnatural nucleobase analogues have attracted much attention since they were recognized as potential probes[9] or modifiers[10] of the genetic information stored in nucleic acids. A symbolic example is represented by isocytosine (IsoC, Figure 1), a structural isomer of the natural nucleobase cytosine (C, FIgure 1), that can be incorporated in DNA and RNA, leading to the formation of a stable base pair with the synthetic nucleobase isoguanine (IsoG);[11] remarkably, in 2003, IsoC/IsoG was accepted as the third base pair in DNA thus suggesting a potential expansion of the genetic alphabet.[12]

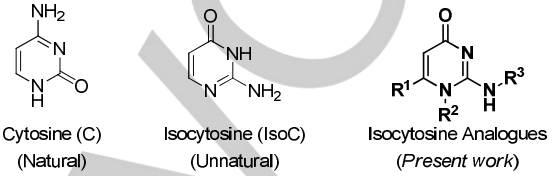

Figure 1. Natural nucleobase cytosine and its synthetic derivatives (Isocytosines)

Diverse nucleosides surrogates, bearing such synthetic nucleobases, display a wide range of interesting pharmaceutical activities as anticancer agents,[13a] inhibitors of xanthine oxidase[13b] and DNA polymerase;[9] furthermore they can be used also as investigation tools for the comprehension of molecular biology phenomena, e.g. for the DNA triplex formation[13c] and mechanistic studies about the RNA catalysis.[13d]

Most commonly, the 2-aminopyrimidin-4-one core of nucleobase derivatives is assembled following two main methodologies: (a) the cyclization of a β-ketoesters with guanidine;[14a-c] (b) the Biginelli reaction involving again a β-ketoester, an aldehyde and a guanidine.[15a-c] A limited number of other examples involve alternative strategies including carbonylation of *ortho*-iodoanilines in the presence of cyanamide,[16a] bacterial hydroxylation of 2-aminopyrimidines[16b], nucleophilic displacement with primary amines of 2-methylthio group on appropriate pyrimidinone derivatives,[16c] and Suzuki-Miyaura coupling of arylboronates with iodo-substituted pyrimidinones.[13b]

Therefore, progress in the synthesis of nucleobase analogues, with a range of stereo-electronic properties, will be highly important for potential biological as well as pharmaceutical purposes. Herein, we report new results about the carbonylative coupling of α-chloroketones with substituted guanidines, as an alternative and straightforward method for the assembly of di- and trisubstituted 2-aminopyrimidin-4-ones.

Results and Discussion

On the basis of our previous research and few literature reports,[17] we theorize that the Pd-catalyzed carbonylation of α-chloroketones promotes *in situ* formation of reactive β-oxoacylpalladium species. Such organometallic intermediates can be considered as 1,3-biselectrophiles because of the

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presence of two carbonyl groups, for this reason, their reactions with bis-nucleophiles should afford cyclic products.

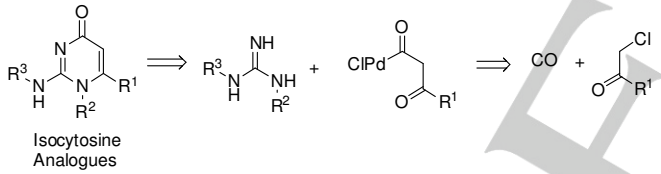
This general hypothesis, prompted us to start an investigation concerning the Pd-catalyzed carbonylation of α-chloroketones in the presence of guanidine derivatives, as bis-nucleophiles: a potential way for the assembly of the 2-aminopyrimidin-4-one core (Scheme 1).

To test this hypothesis, α-chloroacetophenone **1a** (1.5 mmol), *N,N'*-diphenylguanidine **2a** (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol) and NEt_3 (1.65 mmol) were dissolved in dioxane (10 mL); the resulting solution subjected to a pressure of CO (27 atm) in an autoclave. The reactor was then heated at 80 °C under magnetic stirring.

To our delight, the carbonylation reaction proceeded smoothly, and a full conversion of the starting chloroketone **1a** was observed after 10 h at 80 °C as determined by GC-MS analysis.

Further examination revealed that the reaction produced the 2-aminopyrimidin-4-one **3a** as the minor product (32% yield) along with 2-aminoimidazole **4a** (44% yield, Table 1, entry 1) as a major product.

This first experiment indicated that the carbonylation of **1a** was operative, also in the presence of a guanidine derivative, leading to the carbonyl-containing product **3a**; furthermore, a competitive uncatalyzed coupling between the starting reagents produced the five membered ring **4a**. Most likely it is formed by a nucleophilic attack of the guanidine **2a** to the chloroacetophenone **1a** followed by a ring closing condensation, as recently reported.[18]



Scheme 1. Retrosynthetic analysis for the preparation of di- and tri-substituted isocytosine analogues through β-oxoacylpalladium intermediates.

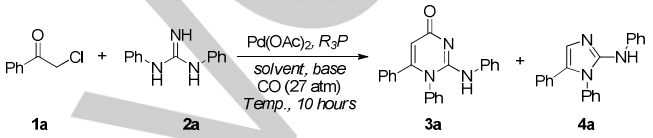
A brief screening regarding the solvent, phosphine, base and reaction temperature suggested that THF, PPh_3, NEt_3 and a temperature of 100 °C represent an efficient system to generate the target isocytosine analogue **3a** in a reasonable yield and chemoselectivity (Table 1, entries 1-9); moreover, the formation of the undesired 2-aminoimidazole **4a** was considerably reduced when 3.0 equivalents of **1a** were employed, affording the product **3a** in 72% yield (Table 1, entry 10).

Further examination of the experimental conditions highlighted that the presence of the NEt_3 is essential for the **3a** formation (Table 1, entry 11) and that the increase, or decrease, of the reaction temperature (120 °C or 80 °C) resulted in a lower **3a**/**4a** ratio, giving the product **4a** in a 18% or 22 % yield (Table 1, entries 12 and 13).

In order to test the range of applicability of the above mentioned catalytic system (Table 1, entry 10) we started a survey involving aliphatic and aromatic chloromethylketones **1b-i** and aryl guanidines **2a-c** (Table 2).

The carbonylative coupling of **2a** with 4-chlorophenyl substituted ketone **1b** proceeded efficiently, giving the desired 6-membered heterocyclic product **3b** in good yield (68%) (Table 2, entry 1) with a chemoselectivity slowly lowered due to the simultaneous uncatalysed formation of the imidazole derivative **4b** (11% Yield). Similarly, other α-chloroacetophenones **1c-e** having electrondonating substituent (MeO, Me) or a fluorine atom, on the phenyl ring, afforded the expected isocytosine analogues in satisfactory yields (61–74%) via a carbonylation and following coupling reaction with guanidine **2a** (Table 1, entries 2-4).

Table 1. Optimization of the model reaction between chloroacetophenone **1a**, *N,N'*-diphenylguanidine **2a** and carbon monoxide.[a]



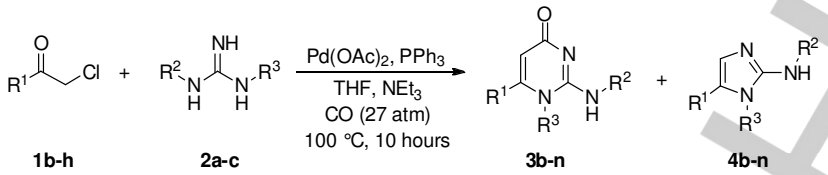
1a **2a** **3a** **4a**

Entry	R_3P	Base	Solvent	Temp (°C)	Yield % **3a**[b]	Yield % **4a**[b]
1	PPh_3	NEt_3	Dioxane	80	32	44
2	PPh_3	NEt_3	DMF	80	49	28
3	PPh_3	NEt_3	Toluene	80	21	25
4	PPh_3	K_2CO_3	THF	80	38	27
5	PPh_3	DABCO	THF	80	45	35
6	P(*o*-Tol)$_3$	NEt_3	THF	80	39	32
7	P(*t*-Bu)	NEt_3	THF	80	12	61
8	–	NEt_3	THF	80	<5	70
9	PPh_3	NEt_3	THF	100	65	15
10	PPh_3	NEt_3	THF	100	72[c]	10
11	PPh_3	–	THF	100	<5	17
12	PPh_3	NEt_3	THF	120	70[c]	18
13	PPh_3	NEt_3	THF	80	50	22

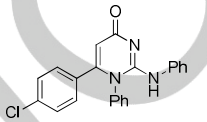
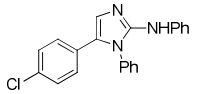
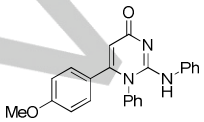
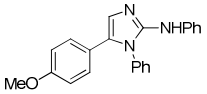
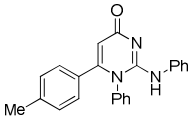
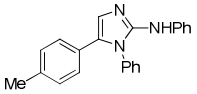
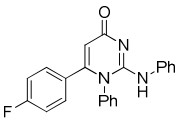
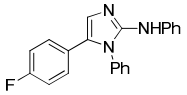
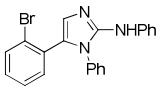
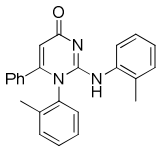
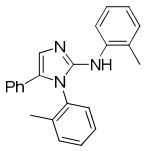
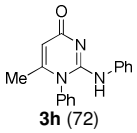
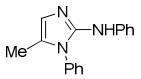
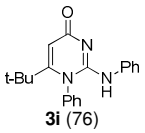
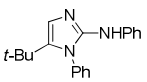
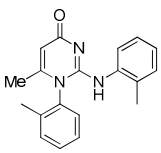
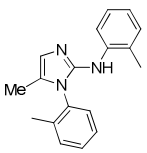
[a] Reaction conditions: chloroacetophenone **1a** (1.5 mmol), *N,N'*-diphenylguanidine (1.5 mmol), base (1.65 mmol), $Pd(OAc)_2$ (0.05 mmol), phosphine (0.2 mmol), CO (27 atm), solvent (10 mL). All reactions were run in duplicate. [b] Calculated by GC analysis of the crude reaction mixture by means of the internal standard technique. [c] 3.0 mmol of α-chloroacetophenone and 3.3 mmol of NEt_3 were used.

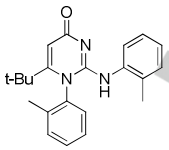
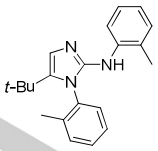
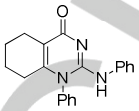
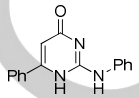
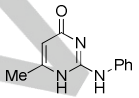
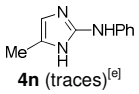
Several efforts to synthesize the 2-aminopyrimidine-4-one core starting from the sterically demanding 2-bromo derivative **1f** and *N,N*-diphenylguaninide **2a** failed, affording in a major extent the 5-membered ring **4f** (37% yield, Table 2, entry 5). Such result can be also justified by considering that a competitive oxidative addition of Pd(0) to the C–Br bond may be operative under the reaction conditions adopted, thus opening unexplored reaction pathways far from the target isocytosine derivative.

Table 2. Synthesis of 2-aminopyrimidin-4-one derivatives **3b-n** and 2-aminoimidazoles **4b-n**.[a]

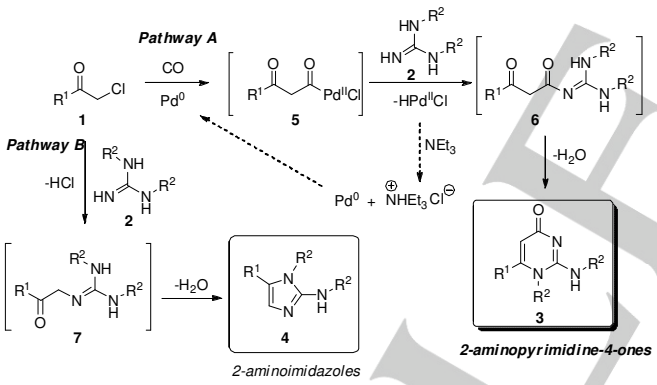


1b-h **2a-c** **3b-n** **4b-n**

entry[a]	Chloroketone **1**	R^1	Guanidine **2**	R^2	R^3	2-Aminopyrimidin-4-one **3** (Yield %)[b]	2-Aminoimidazole **4** (Yield %)[b]
1	**1b**	4-ClC_6H_4	**2a**	Ph	Ph	 **3b** (68)	 **4b** (11)
2	**1c**	4-$MeOC_6H_4$	"	"	"	 **3c** (61)	 **4c** (15)
3	**1d**	4-MeC_6H_4	"	"	"	 **3d** (74)	 **4d** (9)
4	**1e**	4-FC_6H_4	"	"	"	 **3e** (69)	 **4e** (16)
5	**1f**	2-BrC_6H_4	"	"	"	–	 **4f** (37)
6	**1a**	Ph	**2b**	2-MeC_6H_4	2-MeC_6H_4	 **3g** (56)	 **4g** (25)
7	**1g**[c]	Me	**2a**	Ph	Ph	 **3h** (72)	 **4h** (12)
8	**1h**[c]	*t*-Bu	"	"	"	 **3i** (76)	 **4i** (15)
9	**1g**[c]	Me	**2b**	2-MeC_6H_4	2-MeC_6H_4	 **3j** (59)	 **4j** (22)

10	**1h**[c]	*t*-Bu	**2b**	2-MeC_6H_4	2-MeC_6H_4	 **3k** (63)	 **4k** (28)
11	**1i**[c],[d]		**2a**	Ph	Ph	 **3l** (65)	–
12	**1a**	Ph	**2c**	Ph	H	 **3m** (34)	–
13	**1g**[c]	Me	**2c**	Ph	H	 **3n** (18)	 **4n** (traces)[e]

[a] Reaction conditions: chloroketone **1** (3.0 mmol), guanidine (1.5 mmol), NEt_3 (3.3 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), CO (27 atm), dry THF (10 mL 100 °C. All reactions were run in duplicate. [b] Calculated after isolation of the product by column chromatography on silica gel. [c] 2.0 mmol of chloroketone wer used. [d] The structure showed in the column R^1 is intended to be as the whole chloroketone and not a substituent. [e] Significant amounts of acetophenone (30° yield) were isolated after column chromatography. [e] Not isolated, detected in traces by GC-MS analysis of the crude reaction mixture.



Scheme 2. Hypothesized reaction mechanism accounting for the formation of pyrimidin-4-ones **3** (*Pathway A*) and imidazoles **4** (*Pathway B*).

On the contrary, guanidines bearing sterically demanding groups, were compatible with the methodology; in fact, the carbonylative coupling between ketone **1a** and *N,N'*-bis(ortho-tolyl) derivative **2b** furnished, in satisfactory yield, the 2-aminopyrimidin-4-one **3g** (61% Yield). In this case, a slight reduction of the chemoselectivity was also noticed being the **3g**/**4g** ratio close to 70/30, Table 2, entry 6).

We then started to investigate the efficiency of the methodology in the synthesis of 6-alkyl-substituded isocytosines by employing aliphatic α-chloroketones. The carbonylation of chloroacetone **1g** and chloropinacolone **1h**, in the presence of guanidine **2a**, gave the expected 6-methyl and 6-*tert*-butyl derivatives **3h** and **3i** in 72 and 76% yield, respectively (Table 2, entries 7 and 8). In addition, small quantities (12-15%) of 5-alkyl-2-aminoimidazoles **4h,i** were isolated after column chromatography.

Aliphatic ketones **1g,h** were also coupled with the bis(*ortho*-tolyl)guanidine **2b**; both reactions smoothly furnished the expected isocytosines **3j,k** in moderate yields (59-63%, entries 9-10, Table 2) but with a somewhat reduced chemoselectivity (ratio **3**/**4** = 73/27 to 69/31). Such result can be justified by considering that the carbonylative coupling could be slowed down because of the steric hindrance in both guanidine **2b** and the triphenylphosphine acylpalladium complex deriving from the carbonylation step (*vide infra* for the reaction mechanism, Scheme 2).

An additional experiment suggested that the formation of the 2-aminopyrimidin-4-one core is accessible also when cyclic chloroketones are employed; indeed, the carbonylative coupling of 2-chlorocyclohexanone **1i** with guanidine **2a** afforded the bicyclic compound **3l** in a satisfactory yield (65%, Table 2, entry 11). Furthermore, no trace of the corresponding 2-aminoimidazole could be detected by ^{1}H-NMR and GC-MS analyses of the crude reaction mixture.

It is of mention that, all aliphatic ketones tested (**1g-i**) can be used in a smaller amount (1.3 equiv. respect to the guanidine), if compared with the aromatic ones (**1a-e**, 2 equiv.) to produce the expected isocytosine analogues **3i-l** in a similar chemical yield and chemoselectivity.

The stereoelectronic nature of the nucleophile was then significantly changed. In particular we tested the method by using the monosubstituted *N*-phenylguanidine **2c** as the nucleophile. The latter was coupled firstly with α-

cloroacetophenone **1a** and then with the aliphatic derivative **1g**. Again, the expected isocytosine derivatives **3m** and **3n** were formed with a very high chemoselectivity in both cases (Table 2, entries 12,13) although in a minor extent (34 and 18% yield, respectively). In fact, beside the hetherocyclic product **3**, a considerable amount of acetophenone (30% yield) was detected by ^{1}H NMR analysis of the crude reaction mixture.

With respect to the reaction mechanism, as before anticipated, we hypothesize the formation of a *β*-oxoacylpalladium intermediate **5** (*Pathway A*, Scheme 2) deriving from the carbonylation of the corresponding chloromethylketone **1**. Such palladium complex **5**, could then acylate the guanidine **2**, at the sp^2-nitrogen, affording the acyclic intermediate **6**. The final condensation should afford the expected 2-aminopyrimidin-4-one nucleus **3**. On the same time, the uncatalyzed *Pathway B* (Scheme 2) is operative; particularly, the 2-aminoimidazole ring should be simply obtained after a nucleophilic attack of the guanidine to the *α*-carbon of the ketone leading to the formation of intermediate **7**. The latter is involved in an intramolecular condensation reaction giving the aromatic derivative **3**.

Conclusions

In summary, we have reported a direct methodology for the synthesis of 2-aminopyrimidin-4-one derivatives through a one-pot multicomponent carbonylative coupling of *α*-chloroketones and guanidines, under the palladium catalysis.

Although the synthetic way showed a partial chemoselectivity, giving also 2-aminoimidazole derivatives, the optimization of the reaction conditions allowed us to obtain the target isocytosine analogues as the major products in all the cases examined, except one. On the basis of our hypothesis about the reaction mechanism, the present strategy constitutes an useful example of synthetic employment of *β*-oxoacylpalladium species as key intermediates for the preparation of heterocycles.

Furthermore, the Pd-catalyzed carbonylation exhibits a broad substrate scope, representing an easy way for the preparation of variously 6-substituted-2-aminopyrimidine-4-ones as biologically valuable products for their structural analogy with unnatural nucleobase isocytosine.

Experimental Section

ExperimentalSection

General: Triethylamine, $Pd(OAc)_2$, 2-chloro-1-phenylethanone, 2-chloro-1-(4-chlorophenyl)ethanone, 2-chloro-1-(*p*-tolyl)ethanone, 2-chloro-1-(4-fluorophenyl)ethanone, 1-(2-bromophenyl)-2-chloroethanone, 1-chloropropan-2-one, 1-chloro-3,3-dimethylbutan-2-one, 2-chlorocyclohexanone, 1,3-diphenylguanidine, 1,3-di-*o*-tolylguanidine, 1-phenylguanidine were of commercial grade (Aldrich) and used without further purification. THF, dioxane, DMF and toluene were purified by standard laboratory methods before use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded with a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as the solvent and TMS as an internal standard (δ = 7.26 ppm for ^{1}H spectra; δ = 77.0 ppm for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. Gas chromatography (GC) was conducted on an Rt_x-5 30-m fused silica capillary column (split ratio 100:1). The following program was used: method A = initial temperature of 100 °C for 0.0 min, ramp 10 °C/min to 280 °C, and hold for 15 min; the standard operating conditions were 300 °C injector temperature and 290 °C detector temperature. GC-MS analyses, conducted using method A temperature programme, were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenylpolymethylsiloxane capillary column, 30 m, 0.25 mmi.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV. LC-MS/MS analyses were performed using Agilent 1260 Infinity Series HPLC system coupled to Agilent 6420 triple quadrupole detector equipped with an Electrospray ionization (ESI). The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion-spray ionization source. MS (+) spectra were acquired by direct infusion (5 mL min^{-1}) of a solution containing the appropriate sample (10 pmol mL^{-1}) dissolved in a solution 0.1% acetic acid, methanol/water (50:50) at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Chromatographic separations were performed on silica gel (63–200 mesh) using petroleum ether/ethyl acetate (AcOEt) mixture as eluent. All reactions involving air-sensitive reagents were performed under an atmosphere of nitrogen in oven-dried glassware by using syringe/septum cap techniques.

General procedure for the synthesis of 2-aminopyrimidin-4-one derivatives 3a-e, g-n and 2-aminoimidazoles 4a-k, n: A solution of guanidine (1.5 mmol), chloroketone (3.0 mmol for aromatic derivatives and 2.0 mmol for aliphatic ones), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (52 mg, 0.2 mmol) NEt_3 (333 mg, 3.3 mmol) in anhydrous THF (10 mL) was placed in a 45 mL autoclave. The autoclave was purged, pressurized with CO (27 atm) and then heated at 100 °C under magnetic stirring, for 10 hours. The crude mixture was then purified by chromatography on silica gel (petroleum ether/AcOEt 70:30 to 40:60 to obtain the corresponding2-aminopyrimidin-4-one derivatives **3a-e**, **g-n** and 2-aminoimidazoles **4a-k**, **n**: as pure compounds. The products **3n**[19] and **4a-e**,**h-i** [18]are known and their characterization data resulted in agreement with those reported in literature. Spectroscopic data for 2-aminopyrimidin-4-one derivatives **3a-e**, **g-m** and 2-aminoimidazoles **4f-g**, **j-k** are unknown and are reported below.

1,6-Diphenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3a): pale yellow solid(366 mg, 72%); m.p. 166–168 °C.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.11(broad s, 1 H, NH, exchange with D_2O), 6.63 (s, 1 H, CHC=O), 7.13 (t, *J* = 7.3 Hz , 1 H,Ar), 7.34 (t, *J* = 7.4 Hz , 2 H, Ar), 7.41-7.46 (m, 7 H, Ar), 7.54-7.66 (m, 3 H, Ar), 7.99-8.0 (m, 2 H, Ar) ppm.^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 101.0, 121.4, 124.5, 127.0, 128.6 (2C), 128.8, 130.3, 130.4, 130.9, 134.1, 136.8, 137.3, 150.4, 161.1, 163.4 ppm. FT-IR ($CHCl_3$):v = 3416 (NH), 3066, 3010, 1671, 1568, 1475, 1240 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 339 (95) [M]$^+$, 338 (100), 247 (28), 207 (15), 145 (49), 77 (40).HRMS (ESI): calcd. for $C_{22}H_{18}N_3O$ [M+H]$^+$ 340.1451; found 340.1454.

6-(4-Chlorophenyl)-1-phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3b): pale yellow solid (380 mg, 68%);m.p. 156–158 °C.^{1}H NMR (400.13 MHz, $CDCl_3$): δ =6.12 (broad s, 1 H, NH, exchange with D_2O), 6.59 (s, 1 H, CHC=O), 7.14 (t, *J* = 7.1 Hz , 1 H,Ar), 7.34 (t, *J* = 7.4 Hz , 2 H,Ar), 7.41-7.45 (m, 6 H, Ar), 7.57-7.67 (m, 3 H, Ar), 7.92 (d, *J* = 7.6 Hz ,2 H,Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ =100.9, 121.6, 124.7, 127.2, 128.3, 128.6, 128.8, 130.4, 130.9, 133.9, 135.3, 136.5, 137.1, 150.6, 159.9, 163.2 ppm. FT-IR ($CHCl_3$):v = 3417 (NH), 3066, 3015, 1670, 1597,

1569, 1370, 1290 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 375 (29), 374 (50), 373 (95) $[M]^+$,372 (100), 281 (28), 145 (74), 77 (37). HRMS (ESI): calcd. for $C_{22}H_{17}ClN_3O$ $[M+H]^+$ 374.1061; found 374.1063.

6-(4-Methoxyphenyl)-1-phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3c): yellow oil (338 mg, 61%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.11 (broad s, 1 H, NH, exchange with D_2O), 6.56 (s, 1 H, CHC=O), 6.98 (d, *J* = 8.9 Hz , 2 H,Ar), 7.13 (t, *J* = 7.4 Hz , 1 H,Ar), 7.32-7.49 (m, 6 H, Ar), 7.56-7.66 (m, 3 H, Ar), 7.97 (d, *J* = 8.9 Hz ,2 H,Ar) ppm.^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 55.3, 99.4, 113.9, 121.4, 124.3, 128.5, 128.7 (2C), 129.2, 130.2, 130.8, 134.1, 137.4, 150.2, 160.5, 161.5, 163.3 ppm. FT-IR ($CHCl_3$):v = 3416 (NH), 3064, 3013, 1671, 1593, 1567, 1378, 1294, 1250cm^{-1}.GC/MS (70 eV): *m/z* (%) = 369 (100) $[M]^+$, 368 (87), 277 (20), 145 (53), 77 (30). HRMS (ESI): calcd. for $C_{23}H_{20}N_3O_2$ $[M+H]^+$ 370.1556; found 370.1553.

1-Phenyl-2-(phenylamino)-6-(*p*-tolyl)pyrimidin-4(1*H*)-one (3d): yellow solid(392 mg, 74%);m.p. 110–112°C.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3) 6.09 (broad s, 1 H, NH, exchange with D_2O), 6.60 (s, 1 H, CHC=O), 7.11 (t, *J* = 7.3 Hz , 1 H,Ar), 7.26(d, *J* = 7.6 Hz , 2 H,Ar), 7.32 (t, *J* = 7.4 Hz , 2 H,Ar), 7.41 (d, *J* = 7.6 Hz , 2 H,Ar), 7.47 (d, *J* = 7.6 Hz , 2 H,Ar), 7.55-7.64 (m, 3 H, Ar), 7.89 (d, *J* = 7.5 Hz , 2 H,Ar) ppm.^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.4, 100.4, 121.3, 124.4, 126.9, 128.7, 128.8, 129.3, 130.2, 130.9, 134.1, 134.2, 137.4, 140.7, 150.3, 161.1, 163.4 ppm. FT-IR ($CHCl_3$):v = 3418 (NH), 3065, 3013, 2960, 2930, 2850, 1674, 1497, 1448, 1405, 1370, 1240 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 353 (100) $[M]^+$,352 (98), 261 (25), 207 (10), 145 (51), 77 (30).HRMS (ESI): calcd. for $C_{23}H_{20}N_3O[M+H]^+$354.1607; found 354.1607.

6-(4-Fluorophenyl)-1-phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3e): yellow oil(369 mg, 69%); ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.12 (broad s, 1 H, NH, exchange with D_2O), 6.56 (s, 1 H, CHC=O), 7.11-7.15 (m, 3 H, Ar), 7.34 (t, *J* = 7.2 Hz , 2 H,Ar), 7.43 (t, *J* = 8.7 Hz , 4 H,Ar), 7.57-7.67 (m, 3 H, Ar), 7.96-7.99 (m, 2 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 100.5, 115.6 (d, *J* = 21.6 Hz , 2C, F–C–*C*), 121.5, 124.6, 128.6, 128.8, 128.9, 129.0, 130.3, 130.9, 134.0, 137.2, 150.5, 160.0, 163.2, 164.3 (d, *J* = 250.6 Hz , 1C, F–*C*–C) ppm. FT-IR ($CHCl_3$):v = 3417 (NH), 3065, 3020, 1670, 1621, 1406, 1369, 1345, 1290 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 357 (100) $[M]^+$, 356 (95), 265 (28), 145 (55), 77 (31).HRMS (ESI): calcd. for $C_{22}H_{17}FN_3O[M+H]^+$358.1356; found 358.1359.

5-(2-Bromophenyl)-*N*,1-diphenyl-1*H*-imidazol-2-amine (4f): dark yellow oil (216 mg, 37%); ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 6.04 (broad s, 1 H, NH, exchange with D_2O), 6.92 (t, *J* = 7.2 Hz , 1 H,Ar), 7.07 (t, *J* = 7.6 Hz , 1 H,Ar), 7.27 (t, *J* = 7.6 Hz , 2 H,Ar), 7.38 (t, *J* = 7.5 Hz , 1 H,Ar), 7.42-7.55 (m, 7 H, Ar), 7.61 (d, *J* = 8.0 Hz , 1 H,Ar), 7.71 (s, 1 H, N–CH), 8.25 (d, *J* = 7.9 Hz , 1 H,Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 116.4, 116.5, 120.2, 121.1, 125.5, 127.4, 127.5, 128.5, 129.1, 130.2 (2C), 133.7, 134.3, 135.6, 136.3, 140.9, 142.8 ppm. FT-IR ($CHCl_3$):v = 3422 (NH), 3066, 3030, 2968, 2868, 1673, 1539, 1315 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 391 (97), 389 (100) $[M]^+$, 207 (51), 155 (27), 77 (52). HRMS (ESI): calcd. for $C_{21}H_{17}BrN_3$ $[M+H]^+$ 390.0607; found 390.0605.

6-Phenyl-1-(*o*-tolyl)-2-(*o*-tolylamino)pyrimidin-4(1*H*)-one (3g): dark yellow oil (308 mg, 56%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ =1.90 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 5.96 (broad s, 1 H, NH, exchange with D_2O), 6.65 (s, 1 H, CHC=O), 7.06-7.16 (m, 2 H, Ar), 7.26-7.30 (m, 1 H, Ar), 7.36 -7.38 (m 1 H, Ar), 7.44-7.51 (m, 6 H, Ar), 7.96-7.98 (m, 2 H, Ar), 8.07 (d, *J* = 8.1 Hz , 1 H,Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.3, 17.4, 100.6, 123.1, 125.0, 126.7, 127.0, 128.5, 128.6, 129.3, 130.4, 130.6, 132.4, 133.2, 135.7, 136.7, 136.8, 150.5, 161.3, 162.9, 169.1 ppm.FT-IR ($CHCl_3$):v = 3415 (NH), 3065, 2955, 2920, 2848, 1670, 1596, 1406, 1344 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 367 (80) $[M]^+$, 352 (100), 261 (41), 116 (40), 91 (5). HRMS (ESI): calcd. for $C_{24}H_{22}N_3O$ $[M+H]^+$ 368.1764; found 368.1761.

5-Phenyl-*N*,1-di-*o*-tolyl-1*H*-imidazol-2-amine (4g): yellow oil (127 mg, 25%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 5.63 (broad s, 1 H, NH, exchange with D_2O), 6.85 (t, *J* = 7.8 Hz , 1 H,Ar), 7.04-7.06 (m, 2 H, Ar and N–CH), 7.22-7.25 (m, 2 H, Ar), 7.33-7.44 (m, 6 H, Ar), 7.86 (d, *J* = 7.2 Hz , 2 H, Ar), 8.34 (d, *J* = 8.0 Hz , 1 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 17.6, 111.6, 116.4, 120.9, 123.4, 124.5, 126.5, 127.2, 127.4, 127.9, 128.5, 129.7, 130.0, 131.7, 134.3, 134,8, 136.2, 138.3, 139.0, 144.4 ppm.FT-IR ($CHCl_3$):v = 3419 (NH), 3066, 2029, 2965, 2868, 1675, 1540, 1418, 1315 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 339 (85) $[M]^+$, 233 (100), 206 (10), 18 (11), 91 (19). HRMS (ESI): calcd. for $C_{23}H_{22}N_3[M+H]^+$ 340.1814; found 340.1816.

6-Methyl-1-phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3h): pale yellow oil (299 mg, 72%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 5.98-6.0 (m, 2 H, NH and CHC=O), 7.08 (t, *J* = 7.3 Hz , 1 H, Ar), 7.28 (t, *J* = 7.9 Hz , 2 H, Ar), 7.35-7.41 (m, 4 H, Ar), 7.55-7.65 (m, 3 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 24.2, 104.1, 121.0, 124.3, 128.7, 128.8, 130.2, 130.8, 134.1, 137.3, 150.0, 162.7, 164.4 ppm. FT-IR ($CHCl_3$):v = 3417 (NH), 3065, 3008, 2965, 2924, 2850, 1675, 1525, 1497, 1420, 1344 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 277 (81) $[M]^+$, 276 (100), 185 (81), 145 (39), 77 (33).HRMS (ESI): calcd. for $C_{17}H_{16}N_3O[M+H]^+$ 278.1294; found 278.1297.

6-(*Tert*-butyl)-1-phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3i): yellow solid(364 mg, 76%);m.p. 122–124°C.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 6.00 (broad s, 1 H, NH, exchange with D_2O), 6.14 (s, 1 H, CHC=O), 7.06 (t, *J* = 7.3 Hz , 1 H,Ar), 7.28 (t, *J* = 7.8 Hz , 2 H,Ar), 7.37 (d, *J* = 7.4 Hz , 2 H,Ar), 7.43 (d, *J* = 7.6 Hz , 2 H,Ar), 7.55-7.65 (m, 3 H, Ar) ppm.^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 28.8, 37.4, 100.6, 120.5, 123.8, 128.5, 128.7, 130.2, 130.8, 134.2, 137.7, 149.4, 163.5, 175.0 ppm. FT-IR ($CHCl_3$):v = 3416 (NH), 3065, 3008, 2964, 2925, 2850, 1674, 1602, 1498, 1450, 1344, 1245cm^{-1}.GC/MS (70 eV): *m/z* (%) = 319 (100) $[M]^+$, 318 (88), 304 (72), 277 (91), 195 (21), 77 (32).HRMS (ESI): calcd. for $C_{20}H_{22}N_3O$ $[M+H]^+$ 320.1764; found 320.1761

6-Methyl-1-(*o*-tolyl)-2-(*o*-tolylamino)pyrimidin-4(1*H*)-one (3j):pale yellow oil (270 mg, 59%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.85 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 5.85 (broad s, 1 H, NH, exchange with D_2O), 5.99 (s, 1 H, CHC=O), 7.04 (t, *J* = 7.4 Hz , 1 H, Ar), 7.11 (d, *J* = 7.2 Hz , 1 H, Ar), 7.22 (t, *J* = 7.5 Hz , 1 H, Ar), 7.29-7.31 (m, 1 H, Ar), 7.43-7.48 (m, 3 H, Ar), 8.00 (d, *J* = 8.1 Hz , 1 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.2, 17.3, 24.3, 103.8, 122.7, 124.8, 126.7, 128.4, 128.5, 129.0, 130.4, 130.5, 132.3, 133.3, 135.7, 136.8, 150.1, 162.3, 164.9 ppm. FT-IR ($CHCl_3$):v = 3417 (NH), 3065, 3007, 2970, 2930, 2850, 1674, 1495, 1420, 1344 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 305 (88) $[M]^+$, 290 (100), 199 (55), 116 (20), 91 (22).HRMS (ESI): calcd for $C_{19}H_{20}N_3O$ $[M+H]^+$ 306.1607; found 306.1604.

5-Methyl-*N*,1-di-*o*-tolyl-1*H*-imidazol-2-amine (4j):pale yellow oil (91 mg 22%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ= 1.93 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 5.56 (broad s, 1 H, NH, exchange with D_2O), 6.45 (s, 1 H ,N–CH), 6.81 (t, *J* = 7.4 Hz , 1 H, Ar), 7.01 (d, *J* = 7.4 Hz , 1 H, Ar), 7.16 (t, *J* = 7.7 Hz , 1 H, Ar), 7.24-7.35 (m, 4 H, Ar), 7.93 (d, *J* = 8.1 Hz , 1 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ= 14.0, 17.1, 17.6, 112.4, 116.7, 121.0, 124.0, 127.1, 127.2, 127.8, 129.3, 130.1, 131.5, 134.6, 135.2, 136.1, 139.3, 143.8 ppm. FT-IR ($CHCl_3$):v = 3420 (NH), 3065, 3032, 2967, 2870, 1676, 1540, 1420, 1313 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 277 (81) $[M]^+$, 171 (100), 118 (18), 91 (22). HRMS (ESI): calcd. for $C_{18}H_{20}N_3[M+H]^+$ 278.1658; found 278.1662.

6-(*Tert*-butyl)-1-(*o*-tolyl)-2-(*o*-tolylamino)pyrimidin-4(1*H*)-one(3k): pale yellow oil (328 mg, 63%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ= 1.30 [s, 9 H, $C(CH_3)_3$], 1.80 (s, 3 H, PhCH_3), 2.25 (s, 3 H, PhCH_3), 5.92 (broad s, 1 H, NH, exchange with D_2O), 6.17 (s, 1 H, CHC=O), 7.00-7.48 (m, 7 H, Ar), 8.20 (d, *J* = 8.1 Hz , 1 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ= 17.0, 17.3, 28.8, 37.4, 100.2, 121.6, 124.0, 126.6, 127.8, 128.3, 128.4, 130.2, 130.4, 132.2, 133.3, 136.1, 136.7, 149.4, 163.2, 175.5 ppm. FT-IR ($CHCl_3$):v = 3416 (NH), 3066, 3010, 2965, 2925, 2850, 1670, 1532, 1496, 1405cm^{-1}.GC/MS (70 eV): *m/z* (%) = 347 (82) $[M]^+$, 346 (25), 332 (100), 305 (25), 241 (35), 106 (23). HRMS (ESI): calcd. for $C_{22}H_{26}N_3O$ $[M+H]^+$ 348.2077; found 348.2074.

5-(*Tert*-butyl)-*N*,1-di-*o*-tolyl-1*H*-imidazol-2-amine (4k):dark yellow oil (134 mg, 28%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 1.91 (s, 3 H, PhCH_3), 2.11 (s, 3 H, PhCH_3), 5.57 (broad s, 1 H, NH, exchange with D_2O), 6.42 (s, 1 H, N–CH), 6.76 (t,*J* = 7.4 Hz , 1 H, Ar), 6.97 (d,*J* = 7.4 Hz , 1 H, Ar), 7.12 (t,*J* = 7.9 Hz , 1 H, Ar), 7.23-7.25 (m, 2 H, Ar), 7.29-7.33(m, 2 H, Ar), 7.94 (d,*J* = 7.9 Hz , 1 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 17.5, 30.0, 31.8, 109.6, 115.6, 120.3, 123.2, 126.9, 127.0, 127.7, 129.0, 129.8, 131.3, 135.4, 135.8, 140.0, 143.0, 149.0 ppm. FT-IR ($CHCl_3$):v = 3420 (NH), 3066, 3030, 2967, 2870, 1675, 1540, 1420, 1314 cm^{-1}.GC/MS (70 eV): *m/z* (%) = 319 (78) $[M]^+$, 304 (76), 262 (8), 213 (100), 118 (15), 91 (28).HRMS (ESI): calcd. for $C_{21}H_{26}N_3$[M+H]$^+$ 320.2127; found 320.2129.

1-Phenyl-2-(phenylamino)-5,6,7,8-tetrahydroquinazolin-4(1*H*)-one (3l): white solid (309 mg, 65%);m.p. 188–190 °C.^{1}H NMR (400.13 MHz, $CDCl_3$): δ =1.77-1.80 (m, 4 H, CH_2CH_2CH_2CH_2), 2.49-2.61 (m, 4 H, CH_2CH_2CH_2CH_2), 5.85 (broad s, 1 H, NH, exchange with D_2O), 7.05-7.61 (m, 10 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 22.2 (2C), 22.4, 32.1 112.9, 120.5, 123.8, 128.7, 128.8, 130.0, 130.7, 134.5, 137.8, 147.5, 160.5, 162.8 ppm. FT-IR ($CHCl_3$):v = 3420 (NH), 3066, 3009, 2965, 2928, 2850, 1675, 1602, 1525, 1498, 1420, 1344, 1250cm^{-1}.GC/MS (70 eV): *m/z* (%) = 317 (85) $[M]^+$, 316 (100), 288 (17), 225 (16), 77 (28).HRMS (ESI): calcd. for $C_{20}H_{20}N_3O$[M+H]$^+$ 318.1607; found 318.1605.

6-Phenyl-2-(phenylamino)pyrimidin-4(1*H*)-one (3m): pale yellow oil(134 mg, 34%);^{1}H NMR (400.13 MHz, $CDCl_3$): δ =4.86 (broad s, 2 H, NH, exchange with D_2O), 6.49 (s, 1 H, CHC=O), 7.35-7.45 (m, 5 H, Ar), 7.51-7.62 (m, 3 H, Ar), 7.92-7.94 (m, 2 H, Ar) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 100.2, 125.3, 126.9, 128.2, 129.0, 130.3, 130.6, 134.9, 137.8, 154.4, 162.1, 163.2 ppm. FT-IR ($CHCl_3$):v = 3430 (broad NH), 3060, 3015, 1660, 1605, 1475, 1360, 1279cm^{-1}.GC/MS (70 eV): *m/z* (%) = 263 (100) $[M]^+$, 262 (35), 235 (35), 132 (46), 77 (49). HRMS (ESI): calcd. for $C_{16}H_{14}N_3O$[M+H]$^+$ 264.1138; found 264.1135.

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Keywords: α-chloroketones • guanidines • Pd-carbonylation • pyrimidin-4-ones • isocytosine

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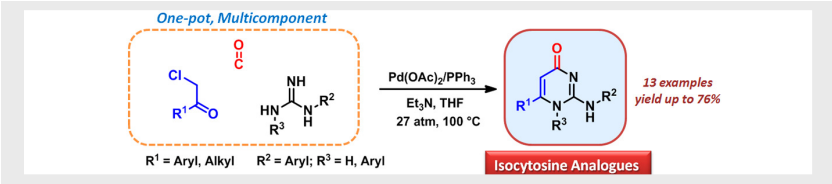

A Pd-catalyzed carbonylative coupling, involving α-chloroketones and guanidines, has been developed for the assembly of 2-aminopyrimidin-4-one core. A range of differently di- and tri-substituted derivatives have been synthesized in a satisfactory yield and selectivity. The products obtained, namely isocytosines, belong to the valuable family of unnatural nucleobases.

Pd-carbonylation

Martina Capua, Serena Perrone, Fabio Bona, Antonio Salomone and Luigino Troisi**

Page No. – Page No.

A Direct Synthesis of Isocytosine Analogues by Carbonylative Coupling of α-Chloroketones and Guanidines