Insights into the *N*,*N*-diacylation reaction of 2-aminopyrimidines and deactivated anilines: an alternative *N*-monoacylation reaction

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Abstract

During the *N*-benzoylation reaction for the synthesis of *N*-substituted aminopyrimidines, an undesired *N*,*N*-diacylation reaction took place. The extension of this *N*-acylation reaction to a series of several 2-aminopyrimidines, aminopyrazines and highly deactivated anilines produced analogous results. The possible mechanism responsible for that behavior is investigated and an advantageous alternative procedure for the clean formation of the desired amides is suggested.

Keywords: *N*,*N*-Diacylation, *N*-monoacylation, 2-aminopyrimidine, aminopyrazine, deactivated anilines, Imatinib analogues

Introduction

Since the discovery of Imatinib or Glivec, a tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia,[1-4] the design of small organic molecules as kinase inhibitors is a matter of high potential therapeutic interest and numerous studies on the synthesis of Imatinib analogues have been carried out. Compounds containing the 2-aminopyrimidine as a common structural moiety are useful intermediate derivatives for the synthesis of important pharmaceuticals[5-8] that show a broad spectrum of biological activities, including inhibitory activity against specific kinases.

With the aim of designing and evaluating new Imatinib analogues, we modified the Imatinib scaffold at the A, C and D rings (Figure 1) and prepared a series of of *N*-substituted 2-aminopyrimidines.[9] Our analogues generally showed greater activity against the family of PDGF receptors and poorer activity against Abl, providing a platform for further drug development against the therapeutically important PDGF receptor family. Recently, we have also prepared a new series of analogues,[10] replacing the NH group of the 2-aminopyrimidine ring (general structure **I**, compound **I**, Figure 1) with the alternative binding group NHCO (general structure **II**, compounds **ii-vi**, Figure 1), in order to improve their activities against protein kinases.

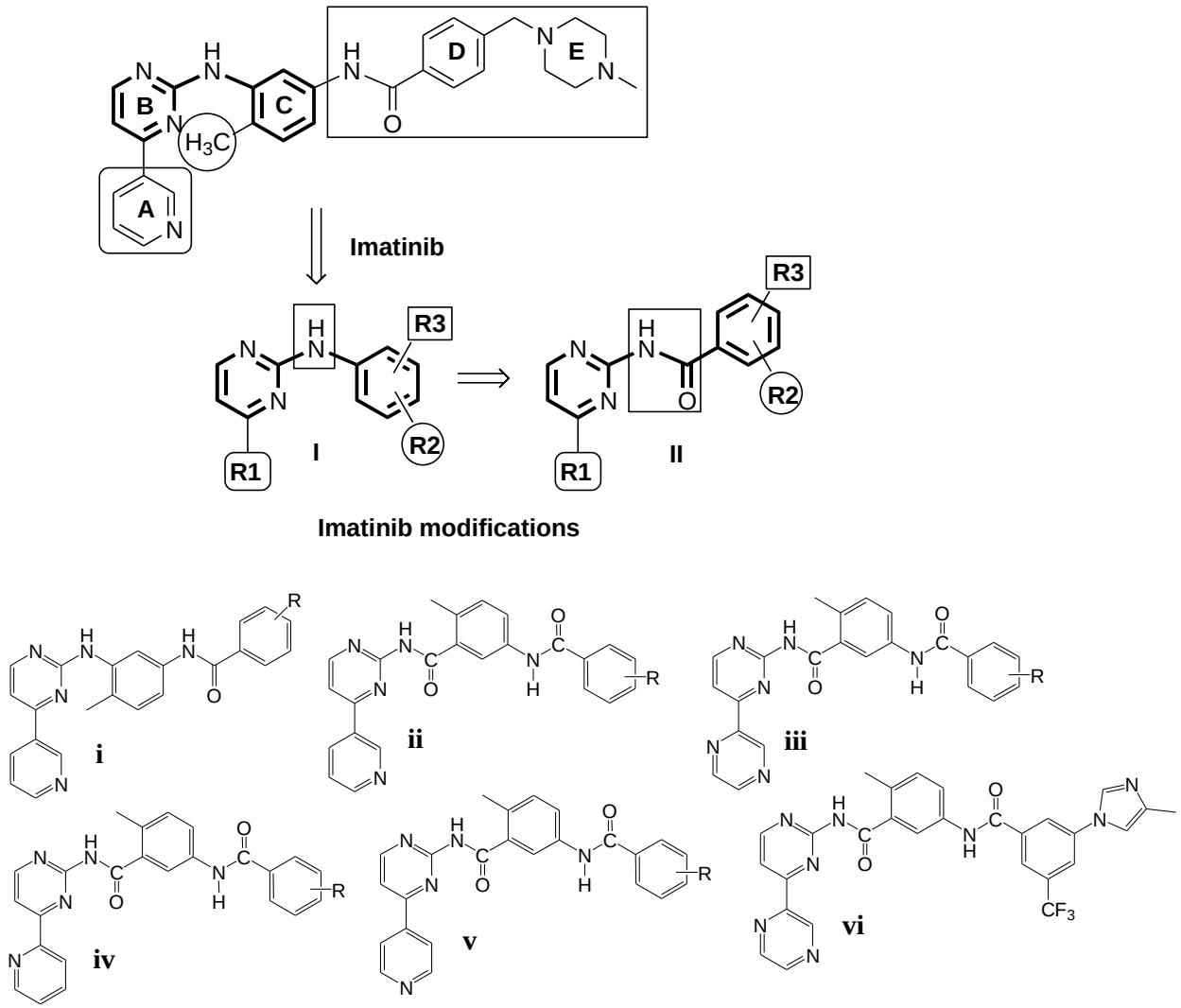
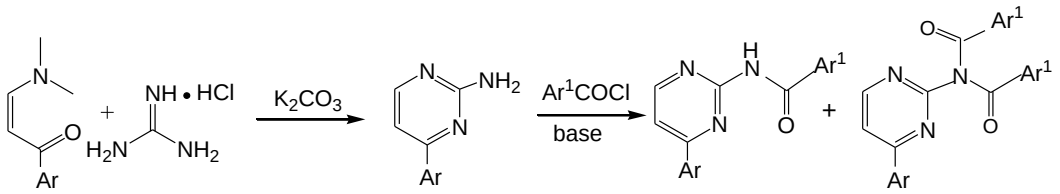


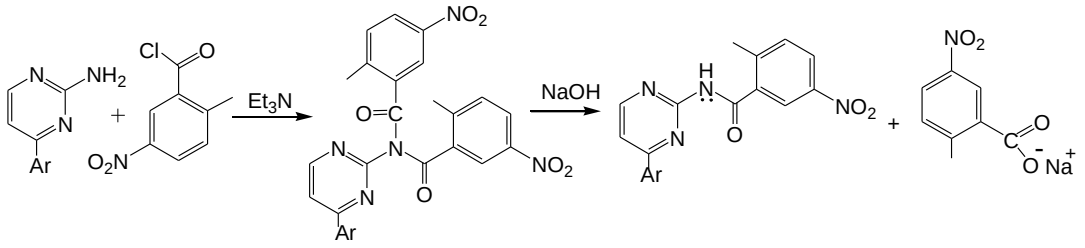
Figure 1. Representative modified Imatinib analogues.

The methodology for the synthesis of *N*-substituted aminopyrimidines was based on the construction of the heterocycle by condensation of moieties containing the required substituents.[9,10] 2-Aminopyrimidines, achieved by condensation of guanidine hydrochloride and dimethylamino-derivatives of the suitable enones, were benzoylated by benzoyl chlorides (Ar^1COCl, Scheme 1) in order to obtain the *N*-benzoyl derivatives.[10] Despite the seeming simplicity of that transformation, some problems arised during their synthesis. Surprisingly, direct treatment of 2-aminopyrimidines with substituted benzoyl chlorides, in the presence of triethylamine, resulted in *N*,*N*-dibenzoyl derivatives and unreacted amine.



Scheme 1. Formation and *N*-acylation of substituted 2-aminopyrimidines.

Carboxyl activating conditions with the aid of typical coupling reagents, such as HBTU, EDC, DCC, and PyBrOP, resulted in no product formation. The reaction was repeated under more forcing conditions with similar results. As the desired mono-acyl products were inaccessible by those methods, they have been obtained by the cautious alkaline hydrolysis of the *N*,*N*-diacyl derivatives with one equivalent of NaOH (Scheme 2).



Scheme 2. Formation and selective alkaline hydrolysis of the diacyl derivative by the reaction of substituted 2-amino-pyrimidines with 2-methyl-4-nitro-benzoyl chloride using Et_3N (Ar=pyrazinyl or pyridin-3-yl).

Previous reports related to this type of transformations have appeared in the literature, but they have been only briefly investigated.[6, 11-25]

Activation methods have found the reagents to be resistant to amide formation of 2-aminopyrimidines with low or moderate yields.[11-14] By the addition of the appropriate benzoyl chloride to 2-amino-4-(3-pyridinyl)pyrimidine in refluxing pyridine,[6] a group of *N*-mono- and *N*,*N*-dibenzoyl derivatives has been prepared in low yield. The same mixture of *N*-monobenzoyl- and *N*,*N*-dibenzoyl-2-aminopyrimidines has been obtained (15% and 45%, respectively) by reaction of the 2-aminopyrimidine scaffold with benzoyl chloride in refluxing dichloromethane[15] and excess pyridine for 48 h. Peracylation of a 2,4-diaminopyrimidine-derivative has also been obtained with excess of benzoyl chloride in pyridine at room temperature for 18 hours,[16,17] while *N*,*N*-dibenzoyl-deoxycytidine has been formed as a by-product in the *N*-benzoylation of deoxycytidine[18] and 2-aminopyridines.[19] Finally, 2-*N*-pyrimidinyl acrylamide has been prepared under forcing conditions (NaH/THF) from acryloyl chloride in modest yield.[20]

Acetylation of 2-amino-phenylpyrimidines with acetic anhydride has given both the mono- and di-acetylated products,[21-25] which were easily converted into *N*-monoacylated by treatment in basic medium.

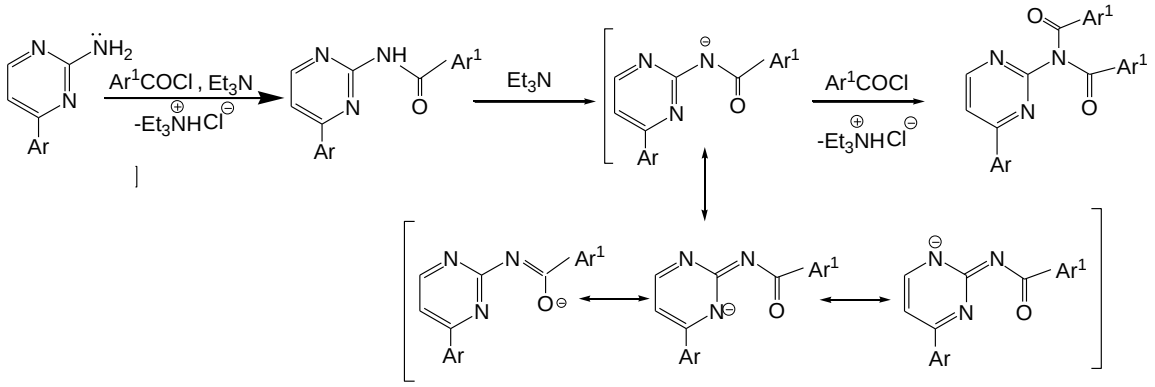
The acylation of 2-aminopyrimidines or 2-amino-*N*-heterocycles has, in some cases, been accompanied by the cyclocondensation of the resulting acyl derivatives,[21, 26] as a result of the interaction between the peripheral group and one of the nitrogen atoms of the ring. Reacting with aldehydes 2-aminopyrimidine scaffold plays a dual role by providing a nucleophilic amino group to form a Schiff base and/or a ring nitrogen to form adducts.[27, 28]

Results and Discussion

In this paper, we report our findings on the preparation of the title compounds, in continuation of our on-going efforts on the design and synthesis of *N*-substituted 2-amino-phenylpyrimidine derivatives, structurally related to Imatinib, with enhanced yield. We were interested in understanding and further exploring the reaction mechanism, with respect to the properties of 2-aminopyrimidine. The inability to provide direct conversion to the desired amide intrigued us to study again the reaction conditions and broaden the scope of the *N*-acylation of deactivated anilines with several acid chlorides and acetic anhydride.

2-Aminopyrimidine, a cyclic amidine that exists in tautomeric forms, is a very poor nucleophilic reagent, a highly deactivated aniline with acidic properties.[29-31] The acidity of 2-aminopyrimidine is increased by the aza substitution, compared with aniline and aminopyridines, due to the electronic effects exerted by the ring nitrogen atoms.

We consider that initial nucleophilic attack of the amino group on the carbonyl of the acid chloride first affords the expected amide. This amide is more acidic than 2-aminopyrimidine and, as soon as it is formed, loses its amide proton by the relatively strong base triethylamine (pKb=3.25), to form a further stabilized anion. The later reacts rapidly with a second molecule of the acid chloride to form the diacyl product (Scheme 3).

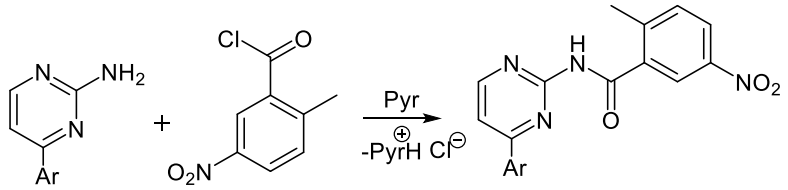


Scheme 3. 2-Aminopyrimidine *N*,*N*-diacylation using triethylamine and proposed plausible reaction pathway.

The use of other bases with about the same basicity as that of triethylamine, e.g. K_2CO_3

(pK_b=3.66), is expected to lead to the same diacyl derivative. On the other hand, in a low basicity medium this anion could not be sufficiently produced and the diacylation reaction should not take place.

This idea was supported by an experiment using pyridine (Pyr) as the base, or excess of the week base aminopyrimidine ($ArNH_2$) ($pK_b \geq 10$). Indeed, the very weak tertiary base Pyr (pK_b=8.77) could not abstract the amide proton to form the anion and the reaction affords in most cases only the desired monoacyl derivative (Scheme 4).



Scheme 4. Acylation of 2-aminopyrimidine with 2-methyl-4-nitro-benzoyl chloride using pyridine (Ar= pyrazinyl or pyridin-3-yl).

Obviously, highly inactivated anilines with acidic properties, in the presence of a strong base, are expected to undergo diacylation much faster than monoacylation, especially with activated acid halides. For this reason, this acylation reaction was extended to a series of deactivated anilines (as 2-aminopyrimidine, aminopyrazine, nitroanilines, aminopyridines, etc., Table 1).

The experimental results, shown in Table 1, strongly support all our suggestions about the role of the base and, subsequently, the proposed reaction mechanism, and help to better understand the above transformations. The nature and the strength of the base, as well as the efficacy of the acid chlorides, appear to be important.

Not surprisingly, in almost all cases, the expected *N*-monoacylated amides were attained by the use of pyridine (or in excess of the very weak aromatic amine $ArNH_2$) at room temperature. With triethylamine, the only or the main product was the *N*,*N*-diacylated compound, while the *N*-monoacylated was formed in traces. Importantly, through a reduction in the acidity of the deactivated anilines, and the analogous reduction of the monoacyl derivative's acidity, the amount of the diacyl derivative decreases (compounds **2c**, **2g**, **2k**, **2n**, entries 7, 16, 23 and 28, respectively, Table 1), while aniline affords only the monoacyl product (**1l**). It should also be noticed that electronic effects on the reaction of substituted acid halides were observed. Aromatic acid halides bearing electron withdrawing groups are more reactive than those with electron donating groups, or aliphatic acylating agents (compounds **2e**, **2f**, **2g**, entries 11, 13 and 16, respectively, Table 1). In particular, acetylations with acetyl chloride by the use of Et_3N afforded mainly the diacetylated compounds (Table 1, compounds **1d** and **1h**, entries 9 and 18). Acetylation in refluxing acetic anhydride was also examined, with analogous behavior.

All the amides were prepared under mild conditions and the obtained products, N-mono- and/or *N*,*N*-diamides, were easily purified by column chromatography on silica gel. The identity of the final products was determined by ^{1}H NMR and IR spectroscopy and mass spectrometry. In

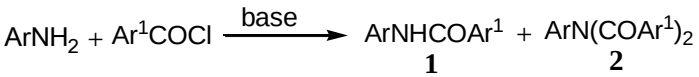
the case of the *N*,*N*-diacyl-compounds, it is clear that both acyl groups are equivalent, attached to the same exocyclic nitrogen, as deduced from the integral and the chemical shift of each set of peaks of the ^{1}H NMR spectra of the pure products. There is no acylation on the ring nitrogen. It should be noted that the diacyl products, during their purification by column chromatography on silica, were gradually partially decomposed to afford amounts of the corresponding monoamides and acids. In addition, compounds **1o** and **1p**, prepared by the use of Pyr, were identical with these obtained by alkaline hydrolysis of the diacyl products (**2o** and **2p**, respectively).[10]

Conclusions

In conclusion, we have reported herein a new method for the conversion of several 2-aminopyrimidines to the corresponding *N*-acyl derivatives with benzoyl chlorides. In the presence of a relatively strong base (Et_3N, K_2CO_3), an undesired *N*,*N*-diacylation product is formed, while when a weak base is used (Pyr, aminopyrimidine-$ArNH_2$), the *N*,*N*-diacylation is avoided and almost clean monoamides are achieved. The probable pathway seems to proceed through nucleophilic attack of the amino group at the carbonyl of the acid chloride and formation of the desired amide. Rapid deprotonation of this acidic amide by the strong base and subsequent attack of this anion at the acyl donor yields the final diacyl product. A weak base cannot deprotonate the acidic amide.

The synthetic utility of the present work is that it provides a very simple novel *N*-acylation methodology of inactivated anilines, under mild conditions and good yield, including the transformation of versatile synthetic intermediates, precursors to useful compounds of pharmaceutical and biological interest.

Table 1. Acylation reaction of the deactivated amines $ArNH_2$



Entry	Aniline (ArNH2)	Acylating agent	Base	Amide (1:2)[a] (yield %-main product)		
				Mono-**1**	Di-**2**[a]	
1	2-aminopyrimidine	PhCOCl	Et_3N	**1a**	**2a** (10:90)	65 (**2a**)
2		PhCOCl	Pyr	**1a**	—[b]	76 (**1a**)
3		4-chloro-3-nitrobenzoyl chloride	Et_3N	**1b**	**2b** (5:95)	69 (**2b**)
4		4-chloro-3-nitrobenzoyl chloride	Pyr	**1b**	—[b]	75 (**1b**)
5		4-chloro-3-nitrobenzoyl chloride	K_2CO_3	—[b]	**2b**	nd[c]
6		4-chloro-3-nitrobenzoyl chloride	$ArNH_2$	**1b**	—[b]	nd[c]
7		4-nitrobenzoyl chloride	Et_3N	—[b]	**2c**	73 (**2c**)
8		4-nitrobenzoyl chloride	Pyr	**1c**	—[b]	69 (**1c**)
9		acetyl chloride	Et_3N	**1d**	**2d** (15:85)	nd[c]
10		Ac_2O	Et_3N	**1d**	**2d** (10:90)	nd[c]
11	aminopyrazine	PhCOCl	Et_3N	**1e**	**2e** (15:85)	60 (**2e**)
12		PhCOCl	Pyr	**1e**	—[b]	69 (**1e**)
13		4-chloro-3-nitrobenzoyl chloride	Et_3N	**1f**	**2f** (10:90)	65 (**2f**)
14		4-chloro-3-nitrobenzoyl chloride	Pyr	**1f**	—[b]	72 (**1f**)
15		4-chloro-3-nitrobenzoyl chloride	$ArNH_2$	**1f**	—[b]	nd[c]
16		4-nitrobenzoyl chloride	Et_3N	**1g**	**2g** (5:95)	71 (**2g**)
17		4-nitrobenzoyl chloride	Pyr	**1g**	**2g** (90:10)	70 (**1g**)
18		acetyl chloride	Et_3N	**1h**	**2h** (35:65)	45 (**2h**)
19		Ac_2O	Et_3N	**1h**	**2h** (60:40)	nd[c]
20		Ac_2O	Pyr	**1h**	**2h** (85:15)	nd[c]
21	4-aminopyridine	4-nitrobenzoyl chloride	Et_3N	**1i**	**2i** (35:65)	nd[c]
22		4-nitrobenzoyl chloride	Pyr	**1i**	**2i** (95:5)	70 (**1i**)
23	2-aminopyridine	4-nitrobenzoyl chloride	Et_3N	**1k**	**2k** (30:70)	54 (**2k**)
24		4-nitrobenzoyl chloride	Pyr	**1k**	**2k** (90:10)	68 (**1k**)
25	aniline	4-nitrobenzoyl chloride	Et_3N	**1l**	—[b]	nd[c]
26	2-nitroaniline	4-nitrobenzoyl chloride	Et_3N	**1m**	**2m** (40:60)	50 (**2m**)

Table 1. Continued

Entry	Aniline (ArNH2)	Acylating agent	base	Amide (1:2)[a] (yield %-main product)		
				Mono-**1**	Di-**2**[a]	
27	2-amino-4-(3-pyridinyl)-pyrimidine	4-nitrobenzoyl chloride	Pyr	**1m**	—[b]	76 (**1m**)
28	2-methyl-4-nitroaniline	4-nitrobenzoyl chloride	Et_3N	**1n**	**2n** (55:45)	nd[c]
29		4-nitrobenzoyl chloride	Pyr	**1n**	—[b]	nd[c]
30		2-methyl-5-nitrobenzoyl chloride	Et_3N	-	**2o**	67 (**2o**)
31		2-methyl-5-nitrobenzoyl chloride	Pyr	**1o**	—[b]	70 (**1o**)
32	2-amino-4-(pyrazinyl)-pyrimidine	2-methyl-5-nitrobenzoyl chloride	Et_3N	-	**2p**	74 (**2p**)
33		2-methyl-5-nitrobenzoyl chloride	Pyr	**1p**	—[b]	68 (**1p**)

[a] The ratio (**1:2**) is estimated approximately, because of a minor decomposition of the diacyl products during the column purification. The relative amounts of the mono- and di-acyl products in the reaction mixtures were estimated by thin layer chromatography, which was representative and informative.
[b] Not formed or formed in traces. [c] Not measured.

Experimental Section

General. ^{1}H NMR spectra were recorded on a 250 MHz (Bruker AMX 250 spectrometer) spectrometer at ambient temperature using tetramethylsilane (TMS) as an internal standard. The high resolution ESI mass spectra were obtained using a Thermo Fischer Scientific Orbitrap XL spectrometer. Melting points were measured on an Büchi 510 apparatus. IR spectra were obtained in KBr discs on a Shimadzu FTIR-84005 spectrophotometer. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC was purchased from E. Merck Co. All chemicals were used as purchased (Aldrich, Fluka and Merck companies) without further purification. The acyl chlorides were prepared following literature procedures.

General experimental procedure

***N*-Acylation.** A solution of the suitable freshly prepared benzoyl chloride (1.2 mmol) in dichloromethane (5 mL) was added to a stirring mixture of pyridine (3 mmol) in dry

dichloromethane (2 mL) at 0 °C under argon. The mixture was stirred for 5 min before a solution of 2-aminopyrimidine (1 mmol) or the deactivated amine in dichloromethane (2 mL) was added over 10 min. The mixture was inspected by TLC (CH_2Cl_2-MeOH, 9:1). After being stirred for a further 3-6 h at room temperature, it was concentrated to dryness. The residue was diluted with CH_2Cl_2 and extracted with H_2O, then with solution of $NaHCO_3$, H_2O and finally with solution of $KHSO_4$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2-MeOH, 9:1) to afford the desired compounds (overall yield 67-76%). Their identity was confirmed by NMR and IR spectroscopy and MS spectrometry.

***N,N*-Diacylation.** The above described procedure, using triethylamine instead of pyridine, afforded *N,N*-diacyl-compounds, or mixtures of mono- and diacyl-compounds (Table 1), which were isolated and identified as well.

4-Chloro-3-nitro-*N*-(2-pyrimidinyl)benzamide (1b). White solid (75%, 0.208 g), mp 188-190 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.18 (t, 1H, *J* 4.75 Hz, ArH), 7.76 (d, 1H, *J* 8.50 Hz, ArH), 8.19 (d, 1H, *J* 8.50 Hz, ArH), 8.55 (s, 1H, ArH), 8.73 (d, 2H, *J* 4.75 Hz, ArH), 9.35 (s, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 117.54, 125.21, 131.05, 132.27, 132.45, 134.16, 147.83, 157.51, 158.56, 163.03 ppm; IR (KBr, ν_{max} cm^{-1}): 3290, 1682, 1525, 1344; HRMS (ESI): *m/z* (M+Na$^+$) calcd for $C_{11}H_7ClN_4O_3Na^+$ 301.0099; Found: 301.0086. Anal. Calcd for $C_{11}H_7ClN_4O_3$: C, 47.41; H, 2.53; N, 20.21%. Found: C, 47.49; H, 2.61; N, 20.37%.

***N,N*-Bis(4-chloro-3-nitrobenzoyl)-2-aminopyrimidine (2b).** White solid (69%, 0.32 g), mp 159-160 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (t, 1H, *J* 4.75 Hz, ArH), 7.68 (d, 2H, *J* 8.50 Hz, ArH), 7.95 (dd, 2H, *J* 1.25 and 8.50 Hz, ArH), 8.32 (d, 2H, *J* 1.25 Hz, ArH), 8.75 (d, 2H, *J* 4.75 Hz, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 117.57, 124.14, 124.16, 128.82, 128.84, 139.80, 150.17, 157.40, 158.68, 163.26 ppm; IR (KBr, ν_{max} cm^{-1}): 1722, 1699, 1531, 1298; HRMS (ESI): *m/z* (M+Na$^+$) calcd for $C_{18}H_9Cl_2N_5O_6Na^+$ 483.9822; Found: 483.9802. Anal. Calcd for $C_{18}H_9Cl_2N_5O_6$: C, 46.77; H, 1.96; N, 15.15%. Found: C, 46.69; H, 2.07; N, 15.37%.

4-Chloro-3-nitro-*N*-pyrazinylbenzamide (1f). White solid (72%, 0.20 g), mp 208-210 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* 8.50 Hz, ArH), 8.18 (dd, 1H, *J* 2.00 and 8.50 Hz, ArH), 8.40 (d, 1H, *J* 2.00 Hz, ArH, 8.53 (d, 1H, *J* 2.25 Hz, ArH), 8.55 (d, 1H, *J* 2.25 Hz, ArH), 8.63 (s, 1H, ArH), 9.75 (s, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 124.79, 131.67, 131.73, 132.93, 133.15, 137.31, 141.20, 142.26, 147.69, 148.12, 162.22 ppm; IR (KBr, ν_{max} cm^{-1}): 3388, 1682, 1536, 1304; HRMS (ESI): *m/z* (M+H$^+$) calcd for $C_{11}H_7ClN_4O_3H^+$ 279.0279; Found: 279.0281. Anal. Calcd for $C_{11}H_7ClN_4O_3$: C, 47.41; H, 2.53; N, 20.21%. Found: C, 47.53; H, 2.36; N, 20.32%.

***N,N*-Bis(4-chloro-3-nitrobenzoyl)aminopyrazine (2f).** White solid (65%, 0.30 g), mp 146-147 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J* 8.50 Hz, ArH), 7.90 (d, 2H, *J* 1.00 and 8.50 Hz, ArH), 8.30 (d, 2H, *J* 1.00 Hz, ArH), 8.47 (dd, 1H, *J* 1.00 and 2.25 Hz, ArH), 8.64 (d, 1H, *J* 2.25 Hz, ArH), 8.75 (d, 1H, *J* 1.00 Hz, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 126.43, 132.31, 132.91, 132.93, 132.95, 143.26, 143.78, 143.82, 148.02, 149.02, 169.34 ppm; IR (KBr, ν_{max} cm^{-}

[1]): 1713, 1696, 1537, 1298; HRMS (ESI): *m/z* (M+H$^+$) calcd for $C_{18}H_9Cl_2N_5O_6H^+$ 461.0003; Found: 462.9988. Anal. Calcd for $C_{18}H_9Cl_2N_5O_6$: C, 46.77; H, 1.96; N, 15.15%. Found: C, 46.65; H, 2.04; N, 15.33%.

4-Nitro-*N*-(2-nitrophenyl)benzamide (1m). White solid (76%, 0.218 g), mp 221-222 °C (mp lit.[32] 223 ºC); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40 (d, 1H, *J* 8.25 Hz, ArH), 7.85 (t, 2H, *J* 8.25 Hz, ArH), 8.25 (d, 2H, *J* 8.75 Hz, ArH), 8.41 (d, 1H, *J* 8.25 Hz ArH), 8.49 (d, 2H, *J* 8.75 Hz, ArH), 9.06 (s, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 122.20, 124.22, 124.33, 126.15, 128.63, 134.66, 136.51, 136.68, 139.50, 163.68, 171.12 ppm; IR (KBr, ν_{max} cm^{-1}): 3336, 1676, 1508, 1274. Anal. Calcd for $C_{13}H_9N_3O_5$: C, 54.36; H, 3.16; N, 14.63%. Found: C, 54.53; H, 3.02; N, 14.82%.

***N,N*-Bis(4-nitrobenzoyl)-2-nitroaniline (2m).** White solid (50%, 0.22 g), mp 175-176 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.20 (d, 1H, *J* 8.25 Hz, ArH), 7.65 (m, 2H, ArH), 8.02 (d, 4H, *J* 8.75 Hz, ArH), 8.27-8.36 (m, 5H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 123.95, 124.14, 126.53, 126.87, 129.98, 130.25, 131.14, 134.94, 139.22, 150.06, 170.21 ppm; IR (KBr, ν_{max} cm^{-1}): 1705, 1689, 1526, 1310. Anal. Calcd for $C_{20}H_{12}N_4O_8$: C, 55.05; H, 2.77; N, 12.84%. Found: C, 55.21; H, 2.60; N, 12.99%.

2-Methyl-5-nitro-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzamide (1o). White solid (70%, 0.234 g), mp 190-192 °C (lit.[33] does not provide mp); ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.53 (m, 1H, ArH), 7.61 (d, *J* 5.25 Hz, 1H, ArH), 7.89 (d, *J* 5.25 Hz, 1H, ArH), 8.28 (m, 3H, ArH), 8.71 (dd, *J* 4.75 Hz, 1.75 Hz, 1H, ArH), 8.80 (d, *J* 5.25 Hz, 1H, ArH), 9.15 (d, *J* 1.75 Hz, 1H, ArH), 11.44 (s, 1H, NH) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.03, 113.35, 122.72, 124.41, 124.71, 131.83, 132.51, 135.01, 138.57, 144.19, 145.94, 148.85, 152.49, 158.34, 160.43, 162.53, 167.09 ppm; IR (KBr, ν_{max} cm^{-1}): 3203, 1676, 1515, 1326; HRMS (ESI): *m/z* (M+H$^+$) calcd for $C_{17}H_{13}N_5O_3H^+$ 336.1091; Found: 336.1077. Anal. Calcd for $C_{17}H_{13}N_5O_3$: C, 60.89; H, 3.91; N, 20.89%. Found: C, 60.63; H, 3.79; N, 21.05%.

***N,N*-Bis(2-methyl-5-nitrobenzoyl)-4-(pyridin-3-yl)pyrimidin-2-amine (2o).** White solid (67%, 0.334 g), mp 146-148 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.56 (s, 6H, CH_3), 7.51 (m, 3H, ArH), 8.11 (d, *J* 5.25 Hz, 1H, ArH), 8.19 (d, *J* 2.5 Hz, 1H, ArH), 8.22 (d, *J* 2.5 Hz, 1H, ArH), 8.37 (m, 3H, ArH), 8.75 (dd, *J* 4.75 Hz, 1.5 Hz, 1H, ArH), 8.94 (d, *J* 5.25 Hz, 1H, ArH), 9.16 (s, 1H, ArH) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.40, 115.28, 122.52, 124.10, 125.76, 130.91, 132.57, 134.96, 135.74, 145.87, 146.08, 148.18, 152.29, 159.31, 160.10, 164.02, 170.10 ppm; IR (KBr, ν_{max} cm^{-1}): 1749, 1678, 1525, 1276; HRMS (ESI): *m/z* (M+H$^+$) calcd for $C_{25}H_{18}N_6O_6H^+$ 499.1361; Found: 499.1342. Anal. Calcd for $C_{25}H_{18}N_6O_6$: C, 60.24; H, 3.64; N, 16.86%. Found: C, 60.51; H, 3.48; N, 17.07%.

2-Methyl-5-nitro-*N*-(4-(pyrazinyl)pyrimidin-2-yl)benzamide (1p). White solid (68%, 0.228 g), mp 201-202 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.73 (s, 3H, CH_3), 7.62 (d, *J* 5.25 Hz, 1H, ArH), 8.16 (d, *J* 3.25 Hz, 1H, ArH), 8.37 (dd, *J* 5.25 Hz, *J* 1.50 Hz, 1H, ArH), 8.75 (d, *J* 1.50 Hz, 1H, ArH), 8.75 (m, 2H, ArH), 8.86 (s, 1H, ArH), 8.90 (d, *J* 3.25 Hz, 1H, ArH), 9,28 (s, 1H, NH) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.23, 113.54, 122.02, 124.88, 132.20, 137.40, 143.46, 144.20, 144.50, 146.06, 146.56, 148.36, 157.25, 160.08, 162.63, 166.90 ppm; IR (KBr, ν_{max} cm^{-}

^{1}): 3202, 1674, 1518, 1338; HRMS (ESI): *m/z* (M+K$^+$) calcd for $C_{16}H_{12}N_6O_3K^+$ 375.0593; Found: 375.0602. Anal. Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H, 3.60; N, 24.99%. Found: C, 57.38; H, 3.49; N, 25.17%.

***N,N*-Bis(2-methyl-5-nitrobenzoyl)-4-(pyrazinyl)pyrimidin-2-amine (2p).** White solid (74%, 0.37 g), mp 152-154 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.81 (d, 6H, CH_3), 7.51 (d, *J* 8.50 Hz, 2H, ArH), 8.23 (m, 3H, ArH), 8.55 (d, *J* 2.00 Hz, 2H, ArH), 8.76 (m, 2H, ArH), 8.88 (d, *J* 5.25 Hz, 1H, ArH), 9.41 (d, *J* 1.25 Hz, 1H, ArH) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.45, 116.311 122.53, 125.80, 132.58, 135.69, 143.46, 144.30, 145.90, 146.11, 147.06, 147.48 158.93, 160.56, 163.63, 170.10 ppm; IR (KBr, ν_{max} cm^{-1}): 1720, 1655, 1538, 1350; HRMS (ESI): *m/z* (M+K$^+$) calcd for $C_{24}H_{17}N_7O_6K^+$ 538.0872; Found: 538.0865. Anal. Calcd for $C_{24}H_{17}N_7O_6$: C, 57.72; H, 3.43; N, 19.63%. Found: C, 57.89; H, 3.27; N, 19.90%.

Acknowledgements

This research project has been co-financed by the European Union (European Regional Development Fund- ERDF) and Greek national funds through the Operational Program "THESSALY- MAINLAND GREECE AND EPIRUS-2007-2013" of the National Strategic Reference Framework (NSRF 2007-2013). We thank the NMR Center and the Mass Spectrometry Unit of the University of Ioannina for taking the ^{1}H NMR and HRMS spectra.

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