KF/Al_2O_3 as a highly efficient reagent for the synthesis of *N*-aryl derivatives of pyrimidine and purine nucleobases

Abdolkarim Zare,*[a] Alireza Hasaninejad,*[b] Ahmad Reza Moosavi-Zare,[a] Mohammad Hassan Beyzavi,[c] Ali Khalafi-Nezhad,[c] Nasrin Pishahang,[a] Zahra Parsaee,[a] Parvin Mahdavinasab,[a] and Nahid Hayati[a]

[a]*Department of Chemistry, College of Sciences, Payame Noor University (PNU), Bushehr 1698, Iran*
[b]*Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran*
[c]*Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran*
E-mail: abdolkarimzare@yahoo.com , ahassaninejad@yahoo.com

Abstract

KF/Al_2O_3 acts as a highly efficient reagent for the synthesis of N-aryl derivatives of pyrimidine and purine nucleobases as biologically interesting compounds via N-arylation reaction under microwave as well as conventional heating conditions. Using this method, the title compounds are produced in good to excellent yields and relatively short reaction times.

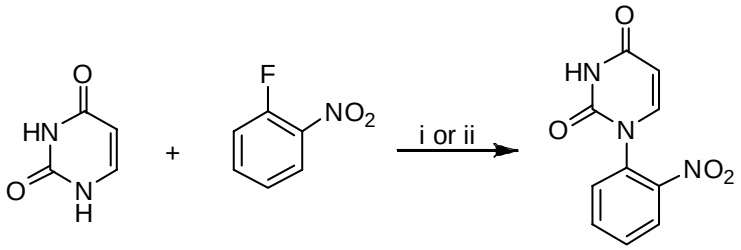
Keywords: KF/Al_2O_3, N-aryl nucleobase, pyrimidine, purine, N-arylation, microwave

Introduction

Recently, solid-supported reagents have proved to be useful to chemists in the laboratory and industry due to the good activation of adsorbed compounds, reaction rate enhancement, selectivity and easier workup.[1,2] Alumina-supported KF is one of the most interesting of these reagents because it has surface properties that suggest that very rich organic reactions may occur there.[2] KF/Al_2O_3 is an inexpensive and commercially available reagent which has been used in several organic transformations, such as acetylation of amines, alcohols and phenol,[2a] preparation of amides from nitriles,[2b] cycloaddition of azomethine ylides,[2c] and hydrothilation of alkynes,[2d] etc.[2e-2k] The coupling of microwave irradiation with the use of mineral-supported reagents provides chemical processes with special attributes, such as enhanced reaction rates, higher yields, better selectivity and improved ease of manipulation.[3] Consequently, the combination of solid-supported reagents with the use microwave irradiation represents a suitable way toward the so-called ideal synthesis.

N-Aryl nucleobases have been frequently used as antitumor,[4a,b] antimicrobial,[4c,d] and plant growth stimulating agents.[4e] Furthermore, they have been applied as agonist or antagonist for various receptors,[5a-c] and enzymes.[5d-i] Therefore, there is a great deal of interest in the synthesis of this class of compounds. The methods have been established for the preparation of N-aryl derivatives of nucleobase are multi-step reactions[6] and N-arylation of nucleobases via cross-coupling reactions,[7] as well as nucleophilic aromatic substitution (SN_{Ar}).[8] It is worth noting that the reported methods have one or more of the following drawbacks: (i) long reaction time, (ii) unsatisfactory yield, (iii) low selectivity, (iv) the use of expensive reagent, (v) application of the method for the synthesis of only N-aryl pyrimidines or only N-aryl purines, and (vi) tedious experimental procedure. Moreover, N-arylation of nucleobases via SN_{Ar} reaction has been scarcely studied so far. Thus, it seems highly desirable to find an efficient, general, rapid, simple and inexpensive protocol for the synthesis of this class of nucleosides.

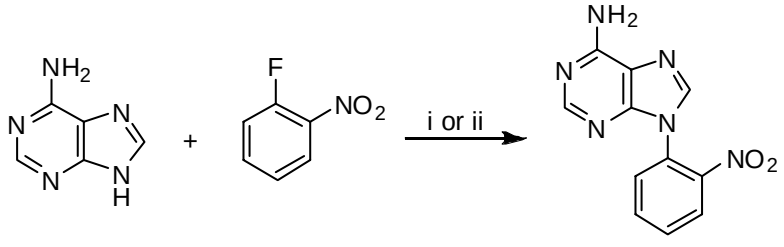
Having the above facts in mind, and also in extension of our previous researches on nucleosides chemistry,[8a,9] we report here a highly efficient method for the preparation of *N*-aryl derivatives of pyrimidine and purine nucleobases via SN_{Ar} in the presence of KF/Al_2O_3 under microwave and thermal conditions (Scheme 1). Interestingly, this method has none of the above-mentioned disadvantages at all.



1a

i = KF/Al_2O_3, DMF, MW, 300 W, 130 °C, 18 min, 91%

ii = KF/Al_2O_3, DMF, Conventional heating, 130 °C, 240 min, 93%



2a

i = KF/Al_2O_3, DMF, MW, 300 W, 130 °C, 27 min, 83%

ii = KF/Al_2O_3, DMF, Conventional heating, 130 °C, 480 min, 80%

Scheme 1. N-Arylation of pyrimidine and purine nucleobases.

Results and Discussion

As previously mentioned KF/Al_2O_3 has been applied as a highly efficient reagent for different organic transformations.[2] This subject encouraged us to use it for the synthesis of N-aryl nucleobases as one of the most interesting derivatives of nucleosides via N-arylation of nucleobases with activated aryl halides. Therefore, firstly we examined N-arylation reaction of uracil (1 mmol) with 1-fluoro-2-nitrobenzene (1.1 mmol) in DMF (1 mL) in the presence KF/Al_2O_3 (1 mmol) under microwave irradiation (300 W, max. 130 ºC) (Scheme 1). In these conditions, the desired product **1a** was produced in 91% within 18 min. The reaction was also tested at different microwave powers (100-600 W, max. 130 ºC); however, the reasonable results were observed at 300 W. Moreover, the reaction of uracil with 1-fluoro-2-nitrobenzene was efficiently achieved using conventional heating (130 ºC) (Scheme 1). This optimized reaction conditions was also extended to N-arylation of adenine as a purine nucleobase in which the product **2a** was obtained in high yield under both microwave and thermal conditions (Scheme 1).

To recognize the efficiency of KF/Al_2O_3, the reaction of uracil with 1-fluoro-2-nitrobenzene was examined in the presence of KF as well as Al_2O_3 separately in both microwave and thermal conditions. The results are summarized in Table 1. As Table 1 indicates, the reaction yields decreased when KF and Al_2O_3 were separately applied in the reaction. Thus, it is necessary to support KF on Al_2O_3.

Table 1. N-Arylation of uracil with 1-fluoro-2-nitrobenzene using KF and Al_2O_3 separately in DMF under microwave irradiation (300 W, max. 130 ºC) and conventional heating (130 ºC)

Entry	Reagent	MW Conditions		Conventional Heating	
		Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
1	KF/Al_2O_3	18	91	240	93
2	KF	25	64	360	60
3	Al_2O_3	25	53	360	46

[a]Isolated yield.

To select the appropriate solvent for the N-arylation reaction, the model reaction was tested in different solvents under both microwave and thermal conditions (Table 2). As it can be seen from Table 2, the best results were obtained when DMF was used. The reaction was also checked under solvent-free conditions; however, these conditions were not efficient (Table 2).

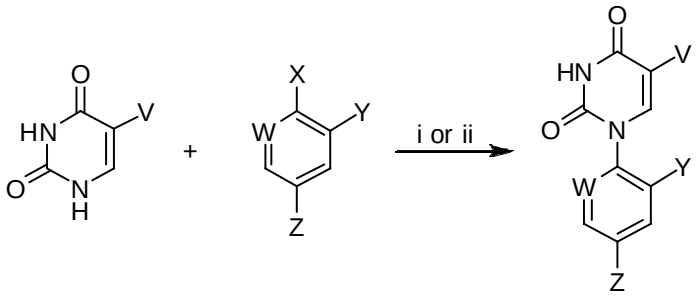
To assess the efficiency and scope of our method, different pyrimidine and purine nucleobases were N-arylated with structurally diverse aryl halides. The results are displayed in Tables 3 and 4. As Tables 3 and 4 indicate, all reactions proceeded efficiently and the desired N-aryl nucleobases were produced in good to excellent yields in both microwave and thermal conditions. Moreover, the reaction yields in both conditions were relatively similar.

Table 2. Effect of solvents on the reaction of uracil with 1-fluoro-2-nitrobenzene under microwave (300 W, max. 130 ºC) and thermal conditions (130 ºC)

Entry	Solvent	MW Conditions		Conventional Heating	
		Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
1	DMF	18	91	240	93
2	DMSO	18	83	240	86
3	HMPTA	18	73	240	72
4	-	30	17	360	21

[a]Isolated yield.

Table 3. Synthesis of N-aryl derivatives of pyrimidine nucleobases



i = KF/Al_2O_3, DMF, MW, 130 °C **1a-k**
ii = KF/Al_2O_3, DMF, Conventional heating, 130 °C

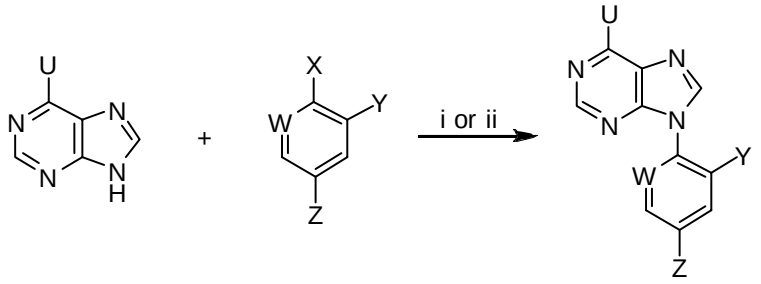
V	W	X	Y	Z	Product	MW Power (W)	MW Conditions		Conventional Heating	
							Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
H	CH	F	NO_2	H	**1a**	300	18	91	240	93
Me	CH	F	NO_2	H	**1b**	300	22	87	300	86
H	CH	Cl	NO_2	NO_2	**1c**	200	15	93	70	94
Me	CH	Cl	NO_2	NO_2	**1d**	200	18	88	90	89
Br	CH	Cl	NO_2	NO_2	**1e**	200	15	87	70	85
Cl	CH	Cl	NO_2	NO_2	**1f**	200	15	90	70	91
F	CH	Cl	NO_2	NO_2	**1g**	200	15	89	70	91

Table 3. Continued

V	W	X	Y	Z	Product	MW Power (W)	MW Conditions		Conventional Heating	
							Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
H	CH	Cl	NO_2	Cl	**1h**	300	28	86	360	81
H	CH	F	H	NO_2	**1i**	500	25	77	600	70
F	CH	F	H	NO_2	**1j**	500	25	73	600	67
H	N	Cl	NO_2	H	**1k**	200	25	87	240	83

[a]Isolated yield.

Table 4. Synthesis of N-aryl derivatives of purine nucleobases



i = KF/Al_2O_3, DMF, MW, 130 °C **2a-d**

ii = KF/Al_2O_3, DMF, Conventional heating, 130 °C

U	W	X	Y	Z	Product	MW Power (W)	MW Conditions		Conventional Heating	
							Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)
NH_2	CH	F	NO_2	H	**2a**	300	27	83	480	80
NH_2	CH	Cl	NO_2	NO_2	**2b**	200	18	92	90	91
Cl	CH	Cl	NO_2	NO_2	**2c**	200	18	92	90	93
OH	N	Cl	NO_2	H	**2d**	300	20	82	360	76

[a]Isolated yield.

In our method pyrimidine and purine nucleobases were regioselectively arylated at N1 and N9 positions respectively. The sites of N-arylation in both pyrimidine and purine nucleobases were indicated and confirmed by ^{1}H and ^{13}C NMR spectra analysis.

The efficiency and capacity of the presented method was compared with the reported methods for N-arylation of nucleobases via SN_{Ar} (Table 5). For this purpose, we have tabulated the results of the reported methods for the preparation of compounds **1a**, **1c**, **1h**, **1k**, **2a**, **2c** and **2d**. As Table 5 demonstrates, our method has significantly improved N-arylation of nucleobases via SN_{Ar}.

Table 5. Comparative synthesis of nucleoside derivatives **1a**, **1c**, **1h**, **1k**, **2a**, **2c** and **2d** using the reported methods versus the presented method

Compound	Gondela et al. [8a]		Khalafi-Nezhad et al. [8a]		Our method [a]		Our Method [b]	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1a	-	-	3	74	18	91	240	93
1c	60	62	2	84	15	93	70	94
1h	-	-	3	77	28	86	360	81
1k	-	-	3	82	25	87	240	83
2a	-	-	2	76	27	83	480	80
2c	-	-	1.5	85	18	92	90	93
2d	-	-	2.5	75	20	82	360	76

[a] Microwave conditions. [b] Thermal conditions.

Conclusions

In summary, we have developed a highly efficient method for N-arylation of nucleobases via S_{NAr}. This new strategy for the synthesis of *N*-aryl nucleobases has several advantages, such as generality, high yield, high selectivity, short reaction time, low cost, and simple experimental as well as straightforward isolation.

Experimental Section

General Procedures. All chemicals were purchased from Merck or Fluka Chemical Companies. All compounds were identified by comparison of their melting points and spectral data with those in the authentic samples. All reactions were carried out using laboratory microwave oven (MicroSYNTH, MILESTONE Company, Italy). IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker

Avance DPX-250, FT-NMR spectrometer (δ in ppm). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Preparation of KF/Al_2O_3. A mixture of KF (0.291 g, 5 mmol) and Al_2O_3 (0.510, 5 mmol) was ground vigorously in a mortar to give the KF/Al_2O_3 reagent as a white powder (0.801 g).

General procedure for the synthesis of *N*-aryl nucleobases

To a well-ground mixture of nucleobase (1 mmol), aryl halide (1.1 mmol)[10] and KF/Al_2O_3 (0.16 g) in a microwave vessel was added DMF (1 mL) and mixed carefully with a small rod. The resulting mixture was irradiated and stirred in a microwave oven for the powers and the times reported in Tables 3 and 4. The microwave was programmed to give a maximum internal temperature of 130 °C. Afterward, the reaction mixture was cooled to room temperature and was poured in ice-water (10 mL), the solids was filtered and the filtrate was extracted with ethyl acetate (2×50 mL). The solvent was evaporated and the the residue was combined with the solids. This mixture was purified by column chromatography on silica gel eluting with EtOAc-*n*-hexane.

1-(2-Nitro-phenyl)-1*H*-pyrimidine-2,4-dione (1a). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 232-234 ˚C (Lit.[8a] mp 234-236 ˚C); IR (KBr): ν_{max} 3439, 3055, 1694, 1647, 1607, 1290 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 5.79 (1H, d, *J* = 7.9 Hz, H-5 of uracil), 7.69-7.77 (2H, m, H-4 and H-6 of the aromatic ring), 7.82-7.94 (2H, m, H-3 and H-5 of the aromatic ring), 8.01 (1H, d, *J* = 7.9 Hz, H-6 of uracil), 11.62 (1H, s, NH); ^{13}C NMR (DMSO-d_6): δ 103.7, 123.4, 128.8, 131.6, 133.9, 136.5, 143.1, 146.1, 149.9, 163.6; MS (*m/z*): 233 (M^+); Anal. calcd. for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.32; H, 2.83; N. 17.86.

1-(2-Nitro-phenyl)-5-methyl-1*H*-pyrimidine-2,4-dione (1b). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 277-279 ˚C (Lit.[8a] mp 278-280 ˚C); ^{1}H NMR (DMSO-d_6): δ 1.82 (3H, s, CH_3), 7.67-7.75 (3H, complex, H-4 and H-6 of the aromatic ring as well as H-6 of thymine), 7.94 (1H, dd, *J* = 4.3, 8.2 Hz, H-5 of the aromatic ring), 8.13 (1H, d, *J* = 8.6 Hz, H-3 of the aromatic ring), 11.61 (1H, s, NH).

1-(2,4-Dinitro-phenyl)-1*H*-pyrimidine-2,4-dione (1c). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 225-227 ˚C (Lit.[8b] mp 221-222 ˚C); ^{1}H NMR (DMSO-d_6): δ 5.87 (1H, d, *J* = 7.9 Hz, H-5 of uracil), 7.89 (1H, d, *J* = 7.9 Hz, H-6 of uracil), 8.02 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.71 (1H, d, *J* = 8.7 Hz, H-5 of the aromatic ring), 8.83 (1H, s, H-3 of the aromatic ring), 11.78 (1H, s, NH).

1-(2,4-Dinitro-phenyl)-5-methyl-1*H*-pyrimidine-2,4-dione (1d). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 231-233 ˚C (Lit.[8a] mp 228-230 ˚C); ^{1}H NMR (DMSO-d_6): δ 2.00 (3H, s, CH_3), 7.98 (1H, s, H-6 of thymine), 8.15 (1H,

d, *J* = 8.8 Hz, H-6 of the aromatic ring), 8.83 (1H, d, *J* = 8.8 Hz, H-5 of the aromatic ring), 8.97 (1H, s, H-3 of the aromatic ring), 11.93 (1H, s, NH).

1-(2,4-Dinitro-phenyl)-5-bromo-1*H*-pyrimidine-2,4-dione (1e). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 266-268 ˚C (Lit.[8b] mp 270-271 ˚C); ^{1}H NMR (DMSO-d_6): δ 8.05 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.52 (1H, s, H-6 of 5-bromouracil), 8.76 (1H, d, *J* = 8.7 Hz, H-5 of the aromatic ring), 8.79 (1H, s, H-3 of the aromatic ring), 12.35 (1H, s, NH).

1-(2,4-Dinitro-phenyl)-5-chloro-1*H*-pyrimidine-2,4-dione (1f). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 241-243 ˚C (Lit.[8b] mp 243-244 ˚C); ^{1}H NMR (DMSO-d_6): δ 8.10 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.54 (1H, s, H-6 of 5-chlorouracil), 8.73 (1H, d, *J* = 8.7 Hz, H-5 of the aromatic ring), 8.82 (1H, s, H-3 of the aromatic ring), 12.32 (1H, s, NH).

1-(2,4-Dinitro-phenyl)-5-fluoro-1*H*-pyrimidine-2,4-dione (1g). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave pale yellow solid; mp 245-247 ˚C (Lit.[8b] mp 248-249 ˚C); ^{1}H NMR (DMSO-d_6): δ 8.03 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.47 (1H, d, *J* = 6.6 Hz, H-6 of 5-fluorouracil), 8.74 (1H, d, *J* = 8.7 Hz, H-5 the of aromatic ring), 8.84 (1H, s, H-3 of the aromatic ring), 12.34 (1H, s, NH).

1-(4-Chloro-2-nitro-phenyl)-1*H*-pyrimidine-2,4-dione (1h). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (2:1) gave pale yellow solid; mp 246-248 ˚C (Lit.[8a] mp 245-247 ˚C); ^{1}H NMR (DMSO-d_6): δ 5.80 (1H, d, *J* = 7.9 Hz, H-5 of uracil), 7.74-7.82 (2H, m, H-5 and H-6 of the aromatic ring), 7.99 (1H, d, *J* = 7.9 Hz, H-6 of uracil), 8.28 (1H, s, H-3 of the aromatic ring), 11.68 (1H, s, NH).

1-(4-Nitro-phenyl)-1*H*-pyrimidine-2,4-dione (1i). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave yellow solid; mp 192-195 ˚C (Lit.[8a] mp 186-189 ˚C); ^{1}H NMR (DMSO-d_6): δ 5.77 (1H, d, *J* = 7.9 Hz, H-5 of uracil), 7.72-7.85 (3H, m, H-2 and H-6 of the aromatic ring as well as H-6 of uracil), 8.21 (2H, d, *J* = 7.8 Hz, H-3 and H-5 of the aromatic ring), 11.56 (1H, s, NH).

1-(4-Nitro-phenyl)- 5-fluoro-1*H*-pyrimidine-2,4-dione (1j). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:1) gave yellow solid; mp 239-241 ˚C (Lit.[8b] mp 244-245 ˚C); ^{1}H NMR (DMSO-d_6): δ 7.80 (2H, d, *J* = 8.0 Hz, H-2 and H-6 of the aromatic ring), 8.39 (1H, d, *J* = 6.7 Hz, H-6 of 5-fluorouracil), 8.31 (2H, d, *J* = 7.9 Hz, H-3 and H-5 of the aromatic ring), 12.03 (1H, s, NH).

1-(3-Nitro-pyridin-2-yl)-1*H*-pyrimidine-2,4-dione (1k). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (2:1) gave pale yellow solid; mp 225-227 ˚C (Lit.[8a] mp 223-225 ˚C); ^{1}H NMR (DMSO-d6): δ 5.88 (1H, d, *J* = 8.0 Hz, H-5 of uracil), 7.81 (1H, dd, *J* = 4.8, 8.0 Hz, H-5 of pyridine), 8.06 (1H, d, *J* = 8.0 Hz, H-6 of uracil), 8.63 (1H, d, *J* = 8.0 Hz, H-4 of pyridine), 8.86 (1H, d, *J* = 4.8 Hz, H-6 of pyridine), 11.78 (1H, s, NH).

9-(2-Nitro-phenyl)-9*H*-purin-6-ylamine (2a). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (3:1) gave yellow solid; mp 267-269 ˚C (Lit.[8a] mp 268-270 ˚C); IR (KBr): ν_{max} 3318, 3141, 1658, 1585, 1293 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.52 (2H, s, NH_2), 7.75-7.86

(2H, m, H-4 and H-6 of the aromatic ring), 7.92 (1H, dd, *J* = 4.5, 7.8 Hz, H-5 of the aromatic ring), 8.09 (1H, s, H-2 of adenine), 8.23 (1H, d, *J* = 8.3 Hz, H-3 of the aromatic ring), 8.48 (1H, s, H-8 of adenine); ^{13}C NMR (DMSO-d_6): δ 118.4, 125.7, 127.4, 129.6, 130.2, 134.8, 139.7, 144.4, 149.8, 153.2, 156.2; MS (*m/z*): 256 (M^+); Anal. calcd. for $C_{11}H_8N_6O_2$: C, 51.56; H, 3.15; N, 32.80. Found: C, 51.74; H, 2.92; N. 32.96.

9-(2,4-Dinitro-phenyl)-9*H*-purin-6-ylamine (2b). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (3:1) gave yellowish brown solid; mp 285-287 ˚C (Lit.[8a] mp 286-288 ˚C); ^{1}H NMR (DMSO-d_6): δ 7.55 (2H, s, NH_2), 8.08 (1H, s, H-2 of adenine), 8.19 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.57 (1H, s, H-8 of adenine), 8.74 (1H, d, *J* = 8.7 Hz, H-5 of the aromatic ring), 8.93 (1H, s, H-3 of the aromatic ring).

6-Chloro-9-(2,4-dinitro-phenyl)-9*H*-purine (2c). Column chromatography on silica gel eluting with EtOAc-*n*-hexane (1:3) gave pale red solid; mp 169-171 ˚C (Lit.[8a] mp 167-169 ˚C); ^{1}H NMR (DMSO-d_6): δ 8.21 (1H, d, *J* = 8.7 Hz, H-6 of the aromatic ring), 8.62 (1H, s, H-8 of 6-chloropurine), 8.73 (1H, d, *J* = 8.7 Hz, H-5 of the aromatic ring), 8.92 (1H, s, H-3 of aromatic ring), 9.01 (1H, s, H-2 of 6-chloropurine).

9-(3-Nitropyridin-2-yl)-9*H*-purin-6-one (2d). Column chromatography on silica gel eluting with EtOAc gave yellow solid; mp 252-254 ˚C (Lit.[8a] mp 253-255 ˚C); ^{1}H NMR (DMSO-d_6): δ 7.88 (1H, dd, *J* = 4.8, 8.1 Hz, H-5 of pyridine), 8.06 (1H, s, H-2 of hypoxanthin), 8.59 (1H, s, H-8 of hypoxanthin), 8.71 (1H, d, *J* = 8.2 Hz, H-4 of pyridine), 8.95 (1H, d, *J* = 4.8 Hz, H-6 of pyridine), 12.76 (1H, br, NH).

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