

A Highly Efficient Protocol for the Synthesis of *N*-Aryl Nucleobases Using Zinc Oxide in Ionic Liquids

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A highly efficient and simple method for the synthesis of *N*-aryl derivatives of pyrimidine and purine nucleobases *via N*-arylation of nucleobases using zinc oxide in 1-butyl-3-methylimidazolium bromide ([bmim]Br) under microwave as well as thermal conditions is described. In both conditions, the title compounds were produced in high to excellent yields and in short reaction times.

Keywords: *N*-Aryl nucleobase, Zinc oxide, Ionic liquid, *N*-Arylation, Microwave

INTRODUCTION

Nucleoside derivatives have attracted much interest because of possessing various biological activities [1-3]. Among them, *N*-aryl nucleobases have been used as antimicrobial [2a] and antitumor agents [2b,c]. Moreover, they have been applied as agonist or antagonist for various receptors [3a-c] and enzymes [3d-g]. Therefore, the synthesis of this class of compounds is significant. The synthetic routes toward *N*-aryl nucleobases include *N*-arylation of nucleobases *via* nucleophilic aromatic substitution (S_NAr) [4] and cross-coupling reactions [5] as well as multi-step reactions [6]. It is noteworthy that the reported methods for the synthesis of this class of nucleosides are associated with one or more of the following drawbacks: (i) long reaction time, (ii) unsatisfactory yield, (iii) low selectivity, (iv) expensive reagents, (v)

applicability of the method for the synthesis of only *N*-aryl pyrimidines or only *N*-aryl purines, and (vi) tedious experimental procedure. Furthermore, there are only very few reports of *N*-arylation of nucleobases *via* S_NAr in the literature. Moreover, these methods are difficult to generalize. Not long ago, we developed a new method for *N*-arylation of nucleobases using KF/Al₂O₃ in DMF [4c]. However, this method has some disadvantages including: (i) lack of high generality (for example, the *N*-arylation reaction would not occur efficiently when 1-fluoro-4-nitrobenzene is used), (ii) relatively long reaction time in the case of thermal conditions, and (iii) the use of toxic DMF. Therefore, development of an efficient, general, and simple procedure for the synthesis of *N*-aryl nucleobases is warranted.

Zinc oxide is an inexpensive, commercially available, moisture-stable and environmentally benign reagent which has been used in several organic transformations such as Michael addition reactions [7a,b], ring opening of epoxides with amines [7c], the condensation of indoles with carbonyl

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compounds [7d], Friedel-Crafts acylation [7e], Beckmann rearrangements [7f], benzylic oxidations [7g], synthesis of *N*-sulfonyl imines [7h], and acylation of alcohols [7i].

The exploitation of ionic liquids as solvents in organic transformations has been reported extensively during the past decade [8]. The most useful properties of ionic liquids are the ability to dissolve a wide range of substances, very low vapor pressure, high thermal stability, recyclability, non-flammability, and the fact that they can be stored for long periods without decomposition [8]. Moreover, it is often possible to run reactions in ionic liquids that otherwise would proceed with great difficulty, or even would not occur at all [8]. Substitution of common solvents along with microwave irradiation have been applied as powerful tools to decrease reaction times and to enhance reaction rates [9].

To overcome the above-mentioned drawbacks in the synthesis of *N*-aryl derivatives of nucleobases, and also in continuation of our previous studies on nucleoside chemistry [4a-c,7a,10], we report here a highly efficient method for the synthesis of *N*-aryl nucleobases by *N*-arylation of nucleobases via $\text{S}_{\text{N}}\text{Ar}$ in the presence of zinc oxide in [bmim]Br under microwave and thermal conditions (Schemes 1 and 2). By adopting this method, the synthesis of *N*-aryl nucleobases has been drastically improved.

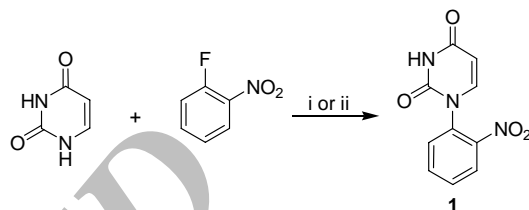
EXPERIMENTAL

Chemicals and Apparatus

All chemicals were purchased from Merck or Fluka Chemical Companies. All reactions occurred using laboratory microwave oven, MicroSYNTH, MILESTONE Company, Italy. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^1H 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. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for the Synthesis of *N*-Aryl Nucleobases and Recycling of [Bmim]Br

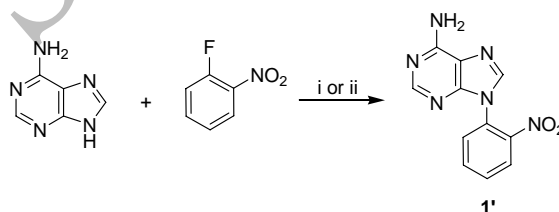
To a mixture of nucleobase (2 mmol), aryl halide (2.1 mmol), and well-ground ZnO (2.4 mmol, 0.195 g) in a



i = ZnO, [Bmim]Br, MW, 380 W, 130 °C, 7 min, Yield = 92%

ii = ZnO, [Bmim]Br, Thermal Conditions, 130 °C, 80 min, Yield = 94%

Scheme 1



i = ZnO, [Bmim]Br, MW, 400 W, 130 °C, 6 min, Yield = 86%

ii = ZnO, [Bmim]Br, Thermal Conditions, 130 °C, 120 min, Yield = 83%

Scheme 2

microwave vessel was added [bmim]Br (1 g) and mixed carefully with a small rod. The resulting mixture was irradiated in a microwave oven for the powers and the times reported in Tables 2 and 3. The microwave was programmed to give a maximum internal temperature of 130 °C. Then, the reaction mixture was cooled to room temperature and suspended in warm MeOH (5 ml), filtered to separate the ZnO residues and the filtrate was added to ice-water (20 ml). The resulting solids (crude products) were filtered and the filtrate was extracted with Et₂O (4 × 50 ml). The organic layer was separated and dried over MgSO₄. Then, the solvent was evaporated and the resulting residue was combined with the solids (crude product). The resulting solid mixture was purified by column chromatography on silica gel eluting with EtOAc/*n*-hexane or EtOAc to give pure product. The solvent of the aqueous layer resulting from the last step was evaporated under reduced pressure to regenerate the ionic liquid. The recycled [bmim]Br was re-used for the next run under similar reaction conditions. In the case of thermal conditions, the starting materials were stirred in an oil-bath (130 °C) for the appropriate times (Tables 2 and 3). The other steps of the thermal conditions were similar to the microwave procedure.

Selected Physical and Spectral Data of the Products

1-(2-Nitro-phenyl)-1*H*-pyrimidine-2,4-dione (1).

Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **1** as a pale yellow solid; m.p.: 233-235 °C (Lit. [4a] 234-236 °C); IR (KBr): 3439, 3055, 1694, 1647, 1607, 1290 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 5.79 (d, *J* = 7.9 Hz, 1H, H-5 of uracil), 7.69-7.77 (m, 2H, H-4 and H-6 of the aromatic ring), 7.82-7.94 (m, 2H, H-3 and H-5 of the aromatic ring), 8.01 (d, *J* = 7.9 Hz, 1H, H-6 of uracil), 11.62 (s, 1H, NH); ¹³C 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*⁺).

1-(2-Nitro-phenyl)-5-methyl-1*H*-pyrimidine-2,4-dione (2). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **2** as a pale yellow solid; m.p.: 277-279 °C (Lit. [4a] 278-280 °C).

1-(4-Nitro-phenyl)-1*H*-pyrimidine-2,4-dione (3). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **3** as a yellow solid; m.p.: 193-196 °C (Lit. [4a] 186-189 °C).

1-(4-Nitro-phenyl)-5-fluoro-1*H*-pyrimidine-2,4-dione (4). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **4** as a yellow solid; m.p.: 239-241 °C (Lit. [4c] 239-241 °C).

1-(2,4-Dinitro-phenyl)-1*H*-pyrimidine-2,4-dione (5). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **5** as a pale yellow solid; m.p.: 225-227 °C (Lit. [4d] 221-222 °C).

1-(2,4-Dinitro-phenyl)-5-methyl-1*H*-pyrimidine-2,4-dione (6). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **6** as a pale yellow solid; m.p.: 230-232 °C (Lit. [4b] 228-230 °C).

1-(2,4-Dinitro-phenyl)-5-fluoro-1*H*-pyrimidine-2,4-dione (7). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **7** as a pale yellow solid; m.p.: 245-247 °C (Lit. [4d] 248-249 °C).

1-(2,4-Dinitro-phenyl)-5-chloro-1*H*-pyrimidine-2,4-dione (8). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **8** as a pale yellow solid; m.p.: 242-242 °C (Lit. [4d] 243-244 °C).

1-(2,4-Dinitro-phenyl)-5-bromo-1*H*-pyrimidine-2,4-dione (9). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/1) gave **9** as a pale yellow solid; m.p.: 265-267 °C (Lit. [4d] 270-271 °C).

1-(4-Chloro-2-nitro-phenyl)-1*H*-pyrimidine-2,4-dione (10).

Column chromatography on silica gel eluting with EtOAc/*n*-hexane (2/1) gave **10** as a pale yellow solid; m.p.: 247-249 °C (Lit. [4c] 246-248 °C); IR (KBr): 3432, 3071, 1692, 1648, 1605, 1303 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 5.80 (d, *J* = 7.9 Hz, 1H, H-5 of uracil), 7.74-7.82 (m, 2H, H-5 and H-6 of the aromatic ring), 7.99 (d, *J* = 7.9 Hz, 1H, H-6 of uracil), 8.28 (s, 1H, H-3 of the aromatic ring), 11.68 (s, 1H, NH); ¹³C NMR (DMSO-*d*₆): δ 102.5, 125.1, 130.3, 131.6, 134.1, 134.8, 144.3, 145.6, 149.9, 163.4; MS (*m/z*): 267 (*M*⁺).

1-(3-Nitro-pyridin-2-yl)-1*H*-pyrimidine-2,4-dione (11). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (2/1) gave **11** as a pale yellow solid; m.p.: 225-227 °C (Lit. [4c] 225-227 °C).

9-(2-Nitro-phenyl)-9*H*-purin-6-ylamine (1'). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (3/1) gave **1'** as a yellow solid; m.p.: 267-269 °C (Lit. [4b] 268-270 °C); IR (KBr): 3318, 3141, 1658, 1585, 1293 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.52 (s, 2H, NH₂), 7.75-7.86 (m, 2H, H-4 and H-6 of the aromatic ring), 7.92 (dd, *J* = 4.5, 7.8 Hz, 1H, H-5 of the aromatic ring), 8.09 (s, 1H, H-2 of adenine), 8.23 (d, *J* = 8.3 Hz, 1H, H-3 of the aromatic ring), 8.48 (s, 1H, H-8 of adenine); ¹³C 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*⁺).

9-(2,4-Dinitro-phenyl)-9*H*-purin-6-ylamine (2'). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (3/1) gave **2'** as a yellowish brown solid; m.p.: 284-286 °C (Lit. [4a] 286-288 °C).

9-(3-Nitropyridin-2-yl)-9*H*-purin-6-one (3'). Column chromatography on silica gel eluting with EtOAc gave **3'** as a yellow solid; m.p.: 252-254 °C (Lit. [4a] 253-255 °C).

6-Chloro-9-(2,4-dinitro-phenyl)-9*H*-purine (4'). Column chromatography on silica gel eluting with EtOAc/*n*-hexane (1/3) gave **4'** as a pale red solid; m.p.: 167-169 °C (Lit. [4b] 167-169 °C).

RESULTS AND DISCUSSION

At first, as a model *N*-arylation of uracil (2 mmol) with 1-fluoro-2-nitrobenzene (2.1 mmol) was examined in some conventional solvents (2 ml) in the presence of zinc oxide (2.4 mmol) under microwave irradiation (380 W, max. 130 °C) to

produce compound **1** (Scheme 1 and Table 1). However, these conditions were not efficient and the desired product was produced in only a trace amount despite increasing the reaction time, the microwave power or the temperature (Table 1). The same results were obtained when the reaction proceeded under thermal conditions. Likewise, the *N*-arylation reaction did not proceed under solvent-free conditions using both microwave irradiation and conventional heating (Table 1, entry 4). Interestingly, the model reaction took place efficiently under both microwave and thermal conditions when ionic liquid [bmim]Br was used as the solvent (Table 1, entry 5). The reaction was also examined in ionic liquids [bmim]Cl and [bmim]I; nevertheless, higher yield of the product was only obtained in [bmim]Br (Table 1). These optimized

reaction conditions were extended to *N*-arylation of adenine as a purine nucleobase in which the desired product was obtained in 86% and 83% in microwave and thermal conditions, respectively (Scheme 2). In another study, the reaction between uracil and 1-fluoro-2-nitrobenzene was examined in the absence of zinc oxide in [bmim]Br. These conditions afforded the product in 26% and 17% using microwave irradiation and conventional heating, correspondingly (Table 1, entry 6). Thus, to cause the *N*-arylation reaction, it is necessary to use zinc oxide beside an ionic liquid.

To probe the efficiency and the scope of our method, different nucleobases were reacted with structurally diverse activated aryl halides. The results are summarized in Table 2. As can be seen from Table 2, a wide range of pyrimidine and

Table 1. Effect of Solvents on the Reaction of Uracil with 1-Fluoro-2-nitrobenzene under Microwave (380 W, max. 130 °C) and Thermal Conditions (130 °C)

Entry	Solvent	MW Conditions		Thermal conditions	
		Time (min)	Yield (%) ^a	Time (min)	Yield (%) ^a
1	DMF	15	Trace	360	Trace
2	DMSO	15	Trace	360	Trace
3	HMPTA	15	Trace	360	Trace
4	Solvent-free	15	Trace	360	Trace
5	[Bmim]Br	7	92	80	94
6 ^b	[Bmim]Br	15	26	240	17
7	[Bmim]Cl	7	81	80	82
8	[Bmim]I	7	72	80	75

^aIsolated yield. ^bThis reaction was performed in the absence of zinc oxide.

Table 2. Synthesis of *N*-Aryl Derivatives of Pyrimidine and Purine Nucleobases via *N*-Arylation of Nucleobases with Aryl Halides


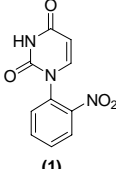
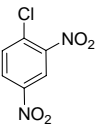
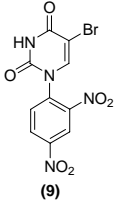
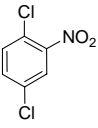
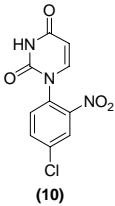

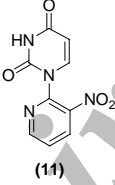

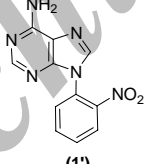
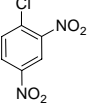
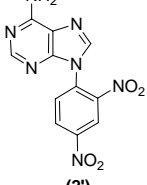

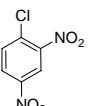
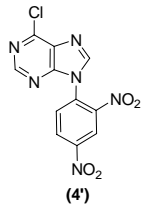
Aryl halide	Product ^a	MW Power (W)	MW Conditions		Thermal conditions	
			Time (min)	Yield (%) ^b	Time (min)	Yield (%) ^b
	 (1)	380	7	92	80	94

Table 2. Continued

		380	8	87	100	86
		500	6	87	120	86
		500	6	86	120	84
		250	6	94	30	95
		250	7	90	40	92
		250	6	95	30	95
		250	6	92	30	91

Table 2. Continued

	 (9)	250	6	91	30	92
	 (10)	400	8	87	130	84
	 (11)	270	7	91	60	89
	 (1')	400	6	86	120	83
	 (2')	250	8	89	40	91
	 (3')	300	6	85	90	82
	 (4')	250	5	91	30	94

^aAll compounds were identified by comparison of their melting points and spectral data with those in the authentic samples. ^bIsolated yield.

Table 3. The *N*-Arylation of Uracil with 1-Fluoro-2-nitrobenzene using Zinc Oxide in Recycled [Bmim]Br under Microwave Irradiation and Conventional Heating

Entry	Cycle	MW Conditions		Thermal conditions	
		Time (min)	Yield (%) ^a	Time (min)	Yield (%) ^a
1	1 st run	7	92	80	94
2	2 nd run	7	91	80	92
3	3 rd run	8	88	90	90
4	4 th run	10	86	100	87

^aIsolated yield.

purine nucleobases were efficiently *N*-arylated with different aryl halides, including 1-fluoro-2-nitrobenzene, 1-fluoro-4-nitrobenzene, 1-chloro-2,4-dinitrobenzene, 1,4-dichloro-2-nitrobenzene and 2-chloro-3-nitropyridine under both microwave and thermal conditions. Therefore, the method enjoys generality and in addition, the reaction yields in both conditions were almost similar.

The regioselectivity of our method was also high. Pyrimidine nucleobases were regioselectively arylated at the *N*1 positions. In these cases, *N*1,*N*3-diarylated pyrimidines were obtained in trace yields. Purine nucleobases were arylated exclusively at the *N*9 positions. The sites of *N*-arylation were confirmed by comparison of ¹H and ¹³C NMR spectra of the products with those in the authentic samples.

Ease of recycling of ionic liquids is one of the advantages of these green solvents. For the reaction of uracil with 1-fluoro-2-nitrobenzene no significant loss of the product yield was observed when [bmim]Br was re-used even after three times of recycling (see Table 3).

CONCLUSIONS

In summary, we have developed a new method for *N*-arylation of nucleobases *via* S_NAr. The distinguishing characteristics of the presented methodology are efficiency, generality, high yield, short reaction time, cleaner reaction profile, ease of product isolation, simplicity, potential for recycling of the solvent, and low cost all of which make it a useful and attractive process for the synthesis of *N*-aryl nucleobases as biologically interesting compounds.

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Highly Efficient Protocol for the Synthesis of *N*-Aryl Nucleobases

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