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Greener and Versatile Synthesis of Bioactive 2-Nitroimidazoles Using Microwave Irradiation

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ABSTRACT

The utilization of green chemistry techniques is dramatically reducing chemicalwaste and reaction times as has recently been proven in several organic syntheses and chemicaltransformations. To illustrate these advantages in the synthesis of bioactive heterocycles, we have studied various environmentally benign protocols that involve greener alternatives. Herein we are reporting a greener and general methodology for the synthesis of a small library of 2-nitroimidazoles including azomycin and its differently substituted analogs. The present protocol involves the reaction of 2-aminoimdazoles with $NaNO_2$ in dry condition, catalysed by a natural clay, which is preanalyzed to be an iron rich kaolinite clay, under microwave condition. Use of solid acid clay catalyst instead of strong mineral acids under solvent-free condition along with simple work up is a major significance of this method.

Key words: 2-aminoimidazoles,2-nitroimidazoles,sodium nitrite, natural kaolinite clay, microwave-assisted reactions.

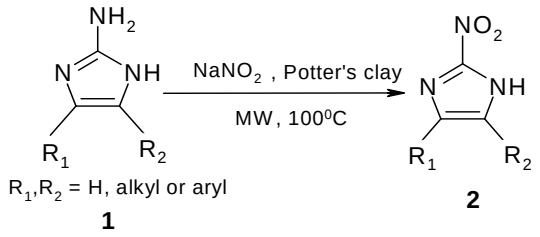
INTRODUCTION

Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs[1]. 2-Nitroimidazoles play a major role as bioreductive markers for tumour hypoxia, as radiosensitizers[2-4], and some also demonstrate antiprotozoal activity[5]. Some dinitro and mono nitroimidazole derivatives have been predicted as notable radiosensitizers, antiprotozoal and antibacterial or antiepileptic agents[6]. The antibiotic azomycin, a 2-nitroimidazole, isolated from a streptomycete, was the first active nitroimidazole to be discovered[7], which acted as the main impetus for the systematic search for drugs with activity against anaerobic protozoa. One of the first reports to note the

antimycobacterial activity of 2-nitroimidazoles compounds were a series of compounds synthesized with a variety of substituents at the 1- and 5 positions[8]. The 2-nitroimidazoles have been studied extensively for their use as radiosensitizers, hypoxic cytotoxins, and molecular markers of hypoxic regions in solid tumours[9-11]. Their selective hypoxic cytotoxicity and use as imaging agents for hypoxia are dependent on the bio-reduction of these compounds to reactive intermediates and the binding of these reductive species to intracellular macromolecules. Bio-reduction occurs only under extremely low oxygen tensions and, therefore, is selective for hypoxic regions[12]. In contrast, the use of 2-nitroimidazoles as radiosensitizers requires the intact compound to act as an oxygen mimic and potentiate the lethal effects of ionizing radiation in hypoxic but not aerobic cells[13].

Chiral 2-nitroimidazole derivatives containing a 2-aminomethylene-4-cyclopentene-1,3- dione moiety were designed and synthesized as antiangiogenic hypoxic cell radiosensitizers[14]. All of these bifunctional derivatives proved to have activity as antiangiogenic hypoxic cell radiosensitizing agents and protein tyrosine kinase (PTK) inhibitory activities. TX-2036 was the most promising candidate for further development as an antiangiogenic hypoxic cell radiosensitizer. Despite of these wide applicability and importance there only a very few synthetic methodologies for 2-nitroimidazoles are available in the literature. The classical and probably the most popular method involves the treatment of sulphate or hydrochloride salt of the corresponding 2-amonoimidazole with an alkali metal nitrate. Use of H_2SO_4 in large amounts for strict maintenance of pH is a major disadvantage of this method in terms of green chemical context[15]. Later on the work by Dwight P. et.al.for substituted 2-nitroimidazoles necessitates the use of hazardous organic solvents like tetrahydrofuran and involves tedious work up procedure including protections and deprotections[16]. Moreover their work could not give satisfactory yields. They were to be satisfied only at a maximum of 40% yield. The synthetic chemical community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in short periods of time, and the best option to accelerate these synthetic processes is to use microwave (MW) technology. The efficiency of MW flash-heating has resulted in dramatic reductions in reaction times (reduced from days and hours to minutes and seconds). The time saved by using the MW heating approach is potentially important in traditional organic synthesis and assembly of heterocyclic systems[17]. In particular, the clay catalysts make the reaction process more convenient, economical, environmentally benign, and act as both Bronsted and Lewis acids in their natural and ion-exchanged forms, enabling them to function as efficient catalysts for various transformations[18]. Our present aim is to make it convenient to use locally available traditional potter's clay of Assam, India as catalysts in organic synthesis. Recently, in one of our works, characterization of this potter's clay using XRD, SEM-EDXRA, thermal analysis, FT-IR spectra and elemental analysis revealed it to be an iron rich clay with kaolinite as the major component[19]. The potent catalytic activity of this clay is already eatablished by the synthesis of a diverse set of imidazolinones and pyrimidinones using this natural clay[19].

We now wish to present an ameliorated, rapid, high yielding and convenient one-pot single-step protocol for the synthesis of a considerable number of 2-nitro-1H-imidazoles**2** (Scheme 1), starting from the corresponding 2-aminoimdazoles and sodium nitrite, applying microwave irradiation supported by the traditional potter's clay without using any solvent.



Scheme 1. Microwave-assisted synthesis of 2-nitroimidazoles

EXPERIMENTAL SECTION

To optimize the reaction conditions, we began our investigation by carrying out the synthesis of simple unsubstituted 2-nitroimidazole, azomycin.Keeping in mind the strong acidic behaviour of clays, we have tried to replace H_2SO_4 used in the conventional methodologies by the iron rich kaolinite natural clay. Initially the reaction was done by irradiating a mixture of 1mmol of 2-aminoimidazole (R_1, R_2 = H in **1,** Scheme1), 1mmol of $NaNO_2$ and 0.5g of the clay in a Microwave reactor. However, only a trace amount of 2-nitroimidazole was obtained in the reaction under 60^0C ceiling temperature in 25 minutes (Table 1, entry 2). A further experiment performed at 80^0C improved substantially the yield of 2-nitro-1H-imidazole and the reaction was completed within 15 min (monitored by TLC). Finally the optimum amount of the product (82%) was obtained using 1.5mmol of $NaNO_2$ at a ceiling temperature of 100^0C, increasing the amount of clay to 1g (entry 4, table1). Necessity of the clay support is revealed by the fact that no yield was obtained when the reaction was carried out without using the clay (entry 1, table 1). No considerable increase in in the amount of product was observed with further increase in the amount of clay, temperature or reaction time (entries 5, 6, table 1).The recyclability of the clay was investigated by reusing it for three subsequent cycles and its activity was almost intact (**Table 1**).

Table1. Optimization of 2-nitration of 2-aminoimidazoles under microwave irradiation conditions[a]

Entry	Amount of clay used(g)	Temp. (^{0}C)	Time(min)	Yield(%)[b]		
				1st cycle	2nd cycle	3rd cycle
1	0.0	60	15	0.0	-	-
2	0.5	60	25	trace	-	-
3	0.5	80	15	53	53	52
4	1.0	100	15	82	82	81
5	1.0	120	20	81	81.5	81
6	1.5	120	20	82	82	81

*[a]All reactions were carried out on a 1 mmol scale of 2-aminoimidazole (R_1, R_2 = H, in substrate **1**) with 1.5 mmol of sodium nitrite without solvent.*
[b]Isolated yield after recrystallization from ethanol

General Procedures

All chemical reagents were obtained from either Aldrich or Merck and were used without further purification. Melting points were determined using an Electrothermal 9200 digital melting point apparatus and are uncorrected. The microwave-assisted reactions were performed using a CEM Mars X microwave oven equipped with an EST-300 plus temperature probe as sensor. Ramp time was 5 min for all the reactions. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or iodine chamber. Flash column chromatograph was performed with silica (Merck, 70–230 mesh). ^{1}H and ^{13}C NMR spectra were measured at 298 K on either a Bruker AMX500 or a Bruker ACF 300 Fourier transform spectrometer and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet),

q (quartet), m (multiplet). The number of protons (*n*) for a given resonance was indicated as *n*H. Mass spectra were performed on Finnigan MAT 95/XL-T spectrometer under electron impact (EI).

Microwave Experiments

A multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems) was used in the standard configuration as delivered, including proprietary software. Reaction temperatures were monitored by an IR sensor on the outside wall of the reaction vial and a fiber optic sensor inside the reaction vial. All experiments were carried out in sealed microwave process vials (15, 50 mL). After completion of the reaction, the vial was cooled to 25 °C via air jet cooling before opening.

General Procedure for the Synthesis of 2-Amino-1*H*-imidazoles, 2a-2s

1mmol of 2-amino-1H-imidazole, **1**, 1.5mmol of $NaNO_2$, were mixed thoroughly with 1g of the clay in a glass mortar. The mixture was transferred to a 20 mL microwave vial and was degassed by passing nitrogen gas through it properly by shaking for 2-3 min. The vial was sealed and exposed to microwave irradiation in Milestone MicroSYNTH multi-mode microwave reactor at 150 W maximum power and a ceiling temperature 100°C for the appropriate time required (TLC monitored). After the mixture was cooled with an air flow for 15 min, it was diluted with H_2O (50 mL), extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel using 15-20% MeOH-DCM as the eluent.

Spectral data of some of the synthesized compounds

2-Nitro-1H-imidazole, 2a

Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product **2a** (117 mg, 82%) as a light yellow solid, mp.287^{0}C

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.26 (br, 1H), 6.97 (d, 1H), 6.78 (d, 1H), 5.33 (br, 2H). ^{13}C NMR (300 MHz, DMSO-*d*6): δ = 150.7, 134.8, 134.1, 110.8. DEPT-135 NMR (75 MHz, DMSO-d_6) δ 110.8.

2-Nitro-4-Phenyl-1*H*-imidazol, 2o

Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product **2o** (72 mg, 75%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.46 (br, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H). ^{13}C NMR (300 MHz, DMSO-*d*6): δ = 150.7, 134.8, 134.1, 128.7 (×2), 125.4, 123.7 (×2), 110.8. DEPT-135 NMR (75 MHz, DMSO-d_6) δ 128.7 (×2), 125.4, 123.7 (×2), 110.8.

2-Nitro-5-(4-Methoxyphenyl)-1*H*-imidazol, 2d

Purification by column chromatography [silica gel, 20% MeOH-DCM] afforded the product **2d** (0.75 g, 79%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.27 (br, 1H), 7.50 (br, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.83 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.4, 150.5, 128.0, 124.9 (×2), 114.1, 55.3.

2-Nitro-4-(4-Chlorophenyl)-1*H*-imidazol, 2f

Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product **2f** (0.85 g, 88%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.29 (br, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.04 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.8, 134.0, 129.5, 128.6 (×2), 125.3 (×2), 110.6.

2-Nitro-4-(4-Bromophenyl)-1*H*-imidazol, 2e

Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product **2e** (1.04 g, 87%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.56 (br, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.06 (s, 1H), 5.40 (br 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.8, 134.3, 133.5, 131.5 (×2), 125.7 (×2), 117.8, 110.7. HRMS (EI): $C_9H_8BrN_3$calcd 236.9902, found 236.9911.

2-Nitro-4-(*p*-Tolyl)-1*H*-imidazol, 2k

Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product **2k** (0.69 g, 80%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.14 (br, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.6, 134.2, 134.1, 129.2 (×2), 123.7 (×2), 110.2, 21.1.

2-Nitro-4-(4-Nitrophenyl)-1*H*-imidazol, 2g

Purification by column chromatography [silica gel, 20% MeOH-DCM] afforded the product **2g** (0.92 g, 90%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.80 (br, 1H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.37 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 151.9, 144.2, 142.0, 133.2 (br), 124.4 (x2), 123.8 (x2), 115.4 (br).

2-Nitro-5-(4-Chlorophenyl)-4-phenyl-1*H*-imidazol, 2n

Purification by column chromatography [silica gel, 5% MeOH-DCM] afforded the product **2n** (92 mg, 68%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.95 (br, 1H), 8.16 (m, 1H), 7.65–7.13 (m, 8H), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.5, 150.8, 133.3, 131.0, 130.5, 129.0, 128.8 (×2), 128.6 (×2), 127.4 (×2), 127.2 (×2), 126.7.

2-Nitro-4-(4-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazol, 2p

Purification by column chromatography [silica gel, 5% MeOH-DCM] afforded the product **2p** (120 mg, 83%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.18 (br, 1H), 7.75–7.02 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.5, 161.3, 161.1, 151.2, 138.2, 131.6, 130.7, 129.6 (×4), 129.1 (×2), 128.9 (×2), 112.3, 111.9, 109.3, 109.0, 104.6, 101.7, 101.3, 101.0.

2-Nitro-4-(4-Chlorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-imidazol, 2q

Purification by column chromatography [silica gel, 10% MeOH-DCM] afforded the product **2q** (160 mg, 95%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-*d*6): δ = 11.08 (br, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.40 (br, 4H). ^{13}C NMR (75 MHz, DMSO-*d*6): δ = 151.4, 137.4 (×2), 129.3 (×2), 128.9 (×2), 127.1 (×2), 126.5, 126.1, 125.6, 123.0, 104.6.

2-Nitro-5-(4-Chlorophenyl)-4-*p*-tolyl-1*H*-imidazol, 2r

Purification by column chromatography [silica gel, 10% MeOH-DCM] afforded the product **2r**(133 mg, 94%) as an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.01 (br, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.4, 136.2, 133.5, 130.5 (×2), 129.5 (×2), 129.3, 128.7, 128.5 (×2), 127.5, 127.4, 21.2.

2-Nitro-5-(4-Methoxyphenyl)-4-phenyl-1*H*-imidazol, 2s

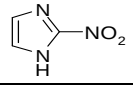
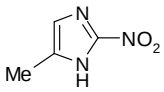
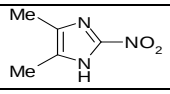
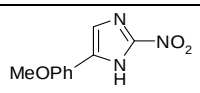
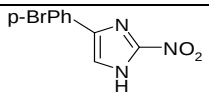
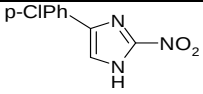
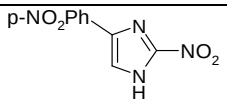
Purification by column chromatography [silica gel, 10% MeOH-DCM] afforded the product **2s** (110 mg, 83%) as an amorphous solid.

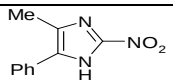
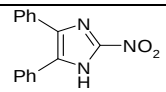
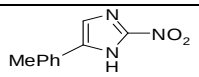
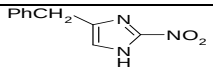
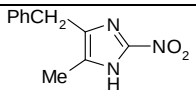
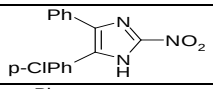
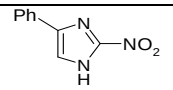
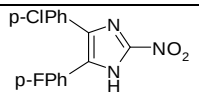
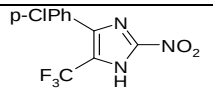
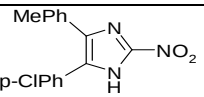
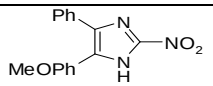
^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.77 (br, 1H), 7.91–6.86 (m, 9H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.5, 158.2, 150.2, 129.9, 129.0 (×2), 128.8 (×2), 128.6 (×2), 126.8, 126.0, 115.3, 114.1 (×2), 55.4.

RESULTS AND DISCUSSION

On achieving this encouraging result the methodology was extended to investigate its general nature. A set of reactions were performed taking differently substituted 2-amino-1H-imidazoles, sometimes with difficulties to furnish substituted *2-nitro-1H-imidazoles* in yields ranging from low to satisfactory, 35-82% (**Table 2**). All reactions were carried out on a 1 mmol scale of 2-aminoimidazole (R_1, R_2 = H, in substrate 1) with 1.5 mmol of sodium nitrite without solvent at a ceiling temperature of 100^0C, applying microwave irradiation at 150W maximum power (**Table 2**). Most of the reactions proceeded smoothly with a very low amount of the starting material left and the products 2a–s were purified by column chromatography using 15-20% MeOH in CH_2Cl_2 as the eluent. The reaction times varied from 10 to 25 min depending on the nature of substituent R_1 and R_2 in the substrate **1** (**Table 2).** It was found that substrates bearing electron donating substituents, for example, p-methoxyphenyl and p-tolyl (Table 2, entries 2d and 2k), require up to 25 min to drive the reaction to completion. On the contrary, the cyclization of the substrates bearing electron withdrawing substituents was completed within 10 min (Table 2, entries 2e, 2f, and 2g). Importantly, the nitro function remained intact upon irradiation for the product 2-nitro-4-(4-Nitrophenyl)-1H-imidazol (Table 2, entry 2g) and we have not observed any trace of by-products.

Table 2: Microwave-assisted synthesis of 2-nitro-1H-imidazoles[a]

Entry	R_1	R_2	Product(s), **2**	Time(min)	Yield(%)[b]
2a	H	H		10	82
2b	H	Me		15	76
2c	Me	Me		20	75
2d	H	p-MeOPh		25	75
2e	p-BrPh	H		7	80
2f	p-ClPh	H		10	72
2g	p-NO_2Ph	H		9	67

2h	Me	Ph		25	57
2j	Ph	Ph		18	50
2k	H	p-MePh		25	80
2l	CH_2Ph	H		10	55
2m	CH_2Ph	Me		20	52
2n	Ph	p-ClPh		15	68
2o	Ph	H		20	75
2p	p-ClPh	p-FPh		22	35
2q	p-ClPh	F_3C		25	48
2r	MePh	p-ClPh		15	75
2s	Ph	MeOPh		15	65

[a]*All reactions were carried out on a 1 mmol scale of 2-aminoimidazole (R_1, R_2 = H, in substrate **1**) with 1.5 mmol of sodium nitrite*
All the microwave experiments were performed at a ceiling temperature of 100^0C and 150W maximum power.
[b]*All yields are isolated yields.*

With these results in hand, we developed an elegant onepot, single-step, microwave-assisted protocol for the synthesis of unsubstituted 2-nitroimidazole, azomycin, along with 4-, 5-, and 4,5-substituted 2-nitroimidazoles. Upon completion, the reaction mixture was diluted with water and extracted with dichloromethane. Side products could easily be removed by washing the organic phase with water, resulting in nearly pure compounds. The residual clay was washed twice with acetone and distilled water and recycled to use in the subsequent reactions.

CONCLUSION

In conclusion, we have developed a simple and practical procedure for the preparation of 2-nitroimidazole and its differentky substituted homologs. We have investigated the 2-nitration of 2-aminoimidazoles with sodium nitrite and found microwave irradiation supported by a natural kaolinite clay to be very effective in this regard.The merits of this method are that (a) it is a very simple, one-pot, rapid, high yielding process, (b) natural potter's clay is cheap and available as compared to other catalysts, (c) the method is environmentally benign as it does not require any solvent. Because of its simplicity, generality, efficacy, cost-effectiveness, environment friendly nature and recyclability of the clay, this method is expected to an effective alternative of the conventional synthetic methods for 2-nitroimidazoles.

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