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ONE-POT MICROWAVE-ASSISTED DRY SYNTHESIS OF MISONIDAZOLE AND ITS O-PHENYL ANALOGUE

Kandarpa Phukan*

Department of Chemistry, Handique Girls' College, Guwahati-781 001, Assam, India.

***Corresponding Author: Kandarpa Phukan**

Department of Chemistry, Handique Girls' College, Guwahati-781 001, Assam, India.

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ABSTRACT

A short, efficient, environmental benign synthesis for 1-(2-nitro-1-imidazolyl)-3-methoxy propanol, misonidazole (MISO) and 1-(2-nitro-1-imidazolyl)-3-phenoxy propanol starting from 2-aminoimidazole and sodium nitrite using microwave irradiation supported by a natural iron rich kaolinite clay is described. This method helps to avoid conc. H_2SO_4 in the synthesis of these bioactive 2-nitroimidazole derivatives.

KEYWORDS: 2-aminoimidazole, sodium nitrite, 2-nitroimidazole, 1,2-epoxy-3-phenoxy/methoxypropane, misonidazole, natural kaolinite clay, microwave-assisted reactions.

INTRODUCTION

2-Nitroimidazoles play a major role as bioreductive markers for tumour hypoxia, as radiosensitizers,[1-4] and some also demonstrate antiprotozoal activity.[5-7] The 2-nitroimidazoles have been studied extensively for their use as radiosensitizers, hypoxic cytotoxins, and molecular markers of hypoxic regions in solid tumours.[8-12] Moreover, a series of investigations at Hoffmann-La Roche resulted in the discovery of very active 1-substituted 2-nitroimidazoles such as misonidazole, 1-(2-nitro-1-imidazolyl)-3-methoxy propanol, which exhibited the best activity against *Trichonomasvaginalis* in mice.[13,14]

Despite of their wide applicability and importance there only a very few synthetic methodologies for 2-nitroimidazoles are available in the literature.[15-20] 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] 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.[21] The potent catalytic activity of this clay is already eatablished by the synthesis of a diverse set of imidazole derivatives using this natural clay.[21]

A two step methodology by Chi-Ching Yang uses corrosive concentrated H_2SO_4 and suffers from very poor yield.We therefore investigated the use of microwave irradiation supported by the kaolinite natural clay to promote and activate this synthetic strategy and as a result, we now wish to present an ameliorated, rapid, high yielding and convenient one-pot single-step protocol for the synthesis of misonidazole c (Scheme 1), via the nitration of 2-aminoimidazole with sodium nitrite followed by the alkylation at N-1 position of 2-nitroimidazole with 1,2-epoxy-3-methoxypropane, applying microwaveirradiation supported by a traditional potter's clay without using any solvent.

MATERIALS AND METHODS

The required 1,2-epoxy-3-methoxypropane or 1,2-epoxy-3-phenoxypropane was obtained from Aldrich-Sigma or can be freshly prepared by the treatment of 1-methoxy-2-hydroxy-3-chloropropane with 1.5 equvalent of sodium hydroxide in diethyl ether at room temperature for eight hours.[23] All other 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 were 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 a 400 MHz Bruker AMX500 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.

Preparation of 2-nitro-1*H*-imidazole, azomycin (for two step synthesis of misonidazole)

132.2mg, 1mmol of 2-amino-1H-imidazolesulphate and 1.46g, 20mmol 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.(137 mg, 96%).

Preparation of 1-(2-nitro-1-imidazolyl)-3-methoxy propanol, Misonidazole(one pot method)

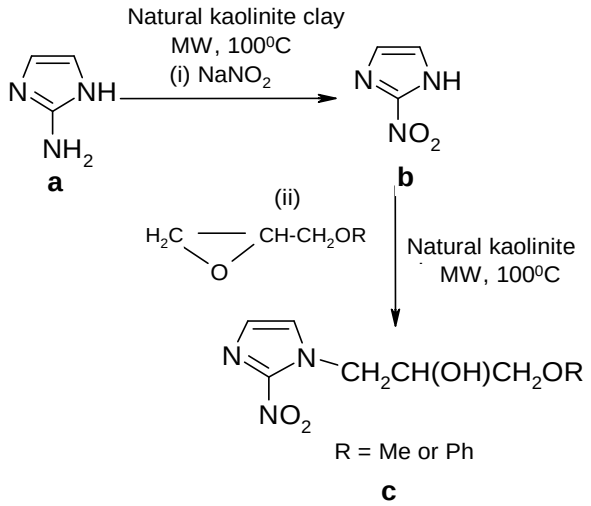
132.2mg, 1mmol of 2-amino-1H-imidazole sulfate, 1.46g, 20mmol of $NaNO_2$ and 0.28g (0.28ml), 3mmol of 1, 2-epoxy-3-methoxypropane were mixed thoroughly with 1g of the clay in a glass mortar. The mixture was transferred to a 20 mL microwave vial and was degassed by passing nitrogen gas through it properly 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 10 minutes (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 volatile material was removed by rotary evaporator and gave a brown solid crude product. This crude product was purified by recrystallization in ethanol at 0^0C and TLC (ethyl acetate/methanol, 9/1, R_f = 0.6) and gave 168 mg of pure misonidazole (84% yield).

Preparation of 1-(2-nitro-1-imidazolyl)-3-phenoxy propanol

It was prepared using the same procedure for misonidazole, using 0.45g (0.45ml), 3mmol of 1,2-epoxy-3-phenoxypropane inplace of 1,2-epoxy-3-methoxypropane.

RESULTS AND DISCUSSION

For optimization purposes, we began ourinvestigation by carrying out the synthesis of misonidazole using the conventional procedure described by Chi-Ching Yang*et.al.*[22], wherein they have synthesized MISO via nitration of 2-aminoimidazole with $NaNO_2$, $CuSO_4$, and H_2SO_4 followed by 1-N-alkylation of the resulting 2-nitroimidazole with 1,2-epoxy-3-methoxypropane catalysed by K_2CO_3 in a two step way. Keeping in mind the strong acidic behaviour of clays, we have tried to replace H_2SO_4 used in the first step by the mentioned natural clay in this conventional method. Satisfactory results were obtained resulting a good amount of 2-nitroimidazole (96%). Search for simple version of the protocol led us to investigate the methodology in a one-pot manner. We tried the conversion in the same pot used in the first step simply by adding the alkylating agent 1,2-epoxy-3-methoxypropane or1,2-epoxy-3-phenoxypropane (3 equivalent) in the reaction mixture of the first step without further separation of the 2-nitroimidazole, continuing irradiation and without using K_2CO_3. Amounts of the clay and $NaNO_2$are the key factors for this nitration reaction.Initially the reaction was done by mixing 1equiv. of 2-aminoimidazole,5 equiv.of $NaNO_2$ and 0.5g of the clay at 50^0C but only a trace amount of the final product was obtained (Table 1, entry 2). So the reaction was repeated by irradiating the reaction mixture at 80^0C ceiling temperature taking an increased amount of $NaNO_2$ (10 equiv.).It improved the yield as monitored by TLC (Table 1, entry 3). A further experiment performed at 90^0C using 20 equiv. of $NaNO_2$ improved substantially the yield of 1-(2-nitro-1-imidazolyl)-3-methoxy propanoland the reaction was completed within 10 min. Finally the optimum amount of the product (84%) was obtained when the temperature was increased to 100^0C increasing the amount of clay to 1g (entry 5, 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 6, 7, table 1).The recyclability of the clay was investigated by reusing it for three subsequent cyclesand its activity was almost intact (Table 1) The optimized methodology also worked well for 1-(2-nitro-1-imidazolyl)-3-phenoxy propanol, using 3 equiv. of 1,2-epoxy-3-phenoxypropane, however with comparatively low yield (72%) in longer reaction time (15 min) (entry 8, table 1).



Scheme 1: Microwave-assisted synthesis of 2-nitroimidazole derivatives.

R= Me, **c** =1-(2-nitro-1-imidazolyl)-3-methoxy propanol, misonidazole.
R = Ph, **c** =1-(2-nitro-1-imidazolyl)-3-phenoxy propanol.

With these results in hand, we developed an efficient, onepot, microwave-assisted protocol for the synthesis of misonidazole along with its O-phenyl analogue. 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.

Table 1: Optimization of one pot synthesis of misonidazole under microwave irradiation[a].

Entry	Amount of $NaNO_2$ used(equiv.)	Amount of clay used(g)	Temp. (^{0}C)	Time(min)	Yield(%)[b]		
					1st cycle	2nd cycle	3rd cycle
1	10	0.0	80	15	0	-	-
2	5	0.5	50	10	trace	-	-
3	10	0.5	80	10	65	65	64
4	20	0.5	90	10	77	76	77
5	20	1.0	100	10	84	84	83
6	20	1.5	100	15	84	83	84
7	20	1.5	120	10	84	84	84
*8	20	1.5	100	15	72	72	71

[a]All reactions were carried out using 1 equiv. of 2-aminoimidazole and 3 equiv. of 1,2-epoxy-3-methoxypropane (or 1,2-epoxy-3-phenoxypropane) without solvent.
[b]Isolated yield after recrystallization from ethanol
*Done for 1-(2-nitro-1-imidazolyl)-3-phenoxy propanol, using 3 equiv. of 1,2-epoxy-3-phenoxypropane

Physical data of the synthesized compounds

2-Nitro-1H-imidazole, azomycin: Purification by column chromatography [silica gel, 15% MeOH-DCM] afforded the product (137 mg, 96%) 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.

1-(2-nitro-1-imidazolyl)-3-methoxy propanol, Misonidazole: Light yellow crystals, ^{1}H NMR (400MHz, $CDCl_3$), δ = 3.35 (s, -CH_2-O$C\underline{H}_3$, 3H), δ = 3.64 (t, J = 5.0 Hz, -N$C\underline{H}_2$CH(OH)-, 2H), δ = 4.04 (m, -$NCH_2C\underline{H}$(OH)-, 1H), δ = 3.64 (dd, J = 13.8 Hz, J = 8.18 Hz, -CH(OH)$C\underline{H}_2$-OCH_3, 1H), δ = 4.68 (dd, J = 13.8 Hz, J = 3.74 Hz, -CH(OH)$C\underline{H}_2$-OCH_3, 1H), δ = 4.87 (s, -$NCH_2CH(O\underline{H})$, 1H), δ= 7.10 (d, J = 1 Hz, -$CH_2NC\underline{H}CHN$-, 1H), δ = 7.41 (d, J =1.0 Hz, -$CH_2NCHC\underline{H}N$-, 1H). 1-(2-nitro-1-imidazolyl)-3-phenoxy propanol: ^{1}H NMR (400MHz, $CDCl_3$), δ = 7.58 (d, -CH_2-O$C_6\underline{H}_5$, *J* = 7.5 Hz, 2H), 7.26 (t, -CH_2-O$C_6\underline{H}_5$, *J* = 7.4 Hz, 2H), 7.08 (t, -CH_2-O$C_6\underline{H}_5$, *J* = 7.5 Hz, 1H), δ = 3.64 (t, J = 5.0 Hz, -N$C\underline{H}_2$CH(OH)-, 2H), δ = 4.04 (m, -$NCH_2C\underline{H}$(OH)-, 1H), δ = 3.64 (dd, J = 13.8 Hz, J = 8.18 Hz, -CH(OH)$C\underline{H}_2$-OCH_3, 1H), δ = 4.62 (dd, J = 13.8 Hz, J = 3.71 Hz, -CH(OH)$C\underline{H}_2$-OCH_3, 1H), δ = 4.79 (s, -$NCH_2CH(O\underline{H})$, 1H), δ = 7.01 (d, J = 1 Hz, -$CH_2NC\underline{H}CHN$-, 1H), δ = 7.44 (d, J =1.0 Hz, -$CH_2NCHC\underline{H}N$-, 1H).

CONCLUSION

In conclusion, we have investigated the 2-nitration of 2-aminoimidazoles with sodium nitrite followed by N-alkylation of the resulting 2-nitroimidazole with 1,2-epoxy-3-methoxypropane or 1,2-epoxy-3-phenoxypropane 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 misonidazole.

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