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Microwave assisted synthesis and characterization of pharmaceutical important imidazole acetamides

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ABSTRACT

*A series of imidazole acetamides were synthesized by reaction of substituted N-chloroacetyl aryl amines with imidazole in presence of anhydrous potassium carbonate in microwave oven. The corresponding N'-(substitutedphenyl)-2-(1H-imidazol-1-yl)acetamides**(2a-g)** were obtained in good yields. All the synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectral data.*

Keywords: aryl amines, chloroacetyl chloride, alkylation, anhydrous potassium carbonate.

INTRODUCTION

Many natural products and bioactive compounds such as proteins, peptide and enzymes are amide derivatives [1,2]. Carboxamides and its derivatives are well known bioactive compounds, drugs such as penicillin, pyrazineamide possess specific activity due to presence of amide linkage in their structures[3].Heterocycliccompounds with –NHCO group possess broad spectrum of pharmacological activities such as antimicrobial [4,5], analgesic [6], anticonvulsant [7,8] and antidepressant [9]. Numbers of reports are present which showed the potential of amides as cytotoxic agents [10,11]. Among various antimicrobial agents, azoles are best known for their antifungal activity [12,13,14]. The antifungal activity of azoles has become one of the most important areas in antifungal drug development. Several drugs have been used in practice such as itraconazole, fluconazole, posaconazole, voriconazole and clotrimazole [15]. Imidazole derivatives found to have number of favorable properties such as excellent permeability, bioavailability with good safety profile [16].

The present study is the continuation of our work to develop green route for the synthesis of biological important heterocyclic compounds, reporting here the synthesis of various imidazole acetamides by microwave irradiation within fewminutes with good yields.

MATERIALS AND METHODS

All chemicals used are of analytical grade and solvents were distilled prior to use. Melting point were measured by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu 8400 spectrometer. The ^{1}H NMR spectra were recorded onBruker 300 MHz, NMR spectrometer while Mass spectra were obtained with LC-MS,Shimadzu 2020 spectrometer. The progress of was monitored by TLC. The spectral data are in agreement with the proposed structure of all synthesized compounds.

General Procedure:

Synthesis of N-chloroacetyl aryl amines (1a-g)

The various aryl substituted N-chloroacetyl aryl amines were prepared by reported procedure [17]. To a stirred solution of chloroacetylchloride (0.02mol, 1.6ml) and TEA (0.01mol) in dry toluene (10ml) various substituted

aromatic amines (0.02mol) dissolved in dry toluene were added in drop wise and the resulting reaction mixture were refluxed on water bath for 2h. The reaction was allowed to cool, filtered and recrystallized from ethanol.

Synthesis of 2-(1H-imidazol-1-yl)-N-(substituted phenyl) acetamides(2a-g)
The various N-chloroacetyl aryl amines**(1a-g)**(0.01mol), imidazole (0.01mol, 0.68g) and catalyst anhydrous potassium carbonate (0.005mol, 0.690g) were taken in Borosil conical flask. The flask plugged with loose cotton and irradiated in microwave oven for 30-90 sec. at 180 power. The reaction mixture was allowed to cool to rt, neutralized with dil. HCl and residue obtained crystallized from ethanol.

2-(1H-imidazol-1-yl)-N-phenyl acetamide(2a)
Colorless crystals, 76% yield, mp. 217-220 ^{0}C; IR: cm^{-1} 3242 (NH), 1657 (CO), 749, 695 (mono sub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 9.64 (s, 1H, NH), 7.42-6.84(m, 8H, Ar-H), 5.12 (s, 2H, CH_2); MS m/z: 200.16 (M^+-1).

2-(1H-imidazol-1-yl)-N-(2-methylphenyl) acetamide(2b)
Reddish crystals, 68% yield, mp. 168-170 ^{0}C; IR: cm^{-1} 3267 (NH), 1656 (CO), 752 (orthodisub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 10.22(s, 1H, NH), 7.33-6.90(m, 7H, Ar-H), 5.27(s, 2H, CH_2), 2.32 (s, 3H, Ar-H); MS m/z: 215.14 (M^+).

2-(1H-imidazol-1-yl)-N-(4-methylphenyl) acetamide(2c)
Colorless crystals, 72 % yield, mp. 145-147^{0}C; IR: cm^{-1} 3210 (NH), 1667 (CO), 817 (paradisub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 9.43 (s, 1H, NH), 7.27-6.82(m, 7H, Ar-H), 4.90 (s, 2H, CH_2), 2.45 (s, 3H, Ar-H); MS m/z: 214.10 (M^+-1).

2-(1H-imidazol-1-yl)-N-(4-hydroxyphenyl) acetamides(2d)
Colorless crystals, 74% yield, mp. 224-226^{0}C; IR: cm^{-1} 3416, 3358 (OH), 1676 (CO), 828 (paradisub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 9.76 (br, 1H, NH), 6.23 (s, 1H, OH), 7.65-6.90 (m, 7H, Ar-H), 5.17 (s, 2H, CH_2); MS m/z: 215.32 (M^+-2).

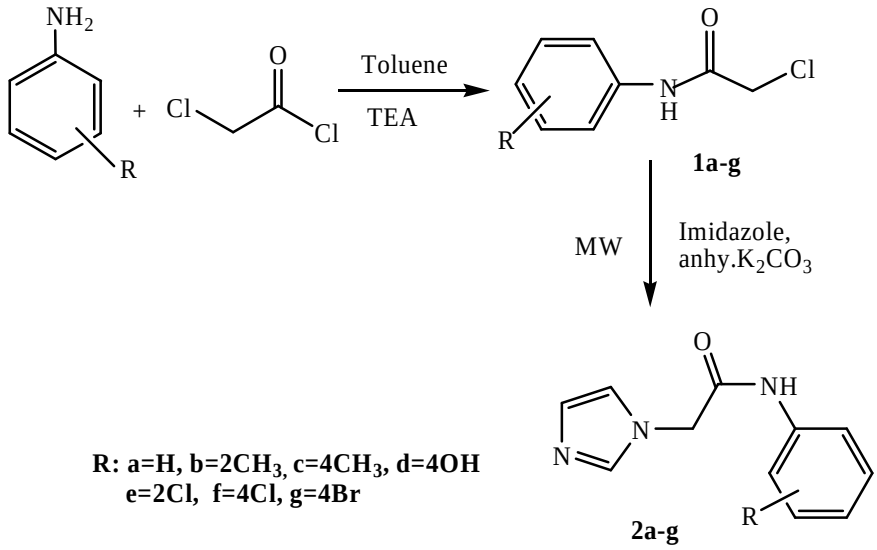
2-(1H-imidazol-1-yl)-N-(2-chlorophenyl) acetamide (2e)
Colorless crystals, 59 % yield, mp. 241-243^{0}C; IR: cm^{-1} 3325 (NH), 1629 (CO), 759 (orthodisub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 6.95 (s, 1H, NH), 7.49-7.00(m, 7H, Ar-H), 5.23 (s, 2H, CH_2); MS m/z: 234.46 (M^+-1).

2-(1H-imidazol-1-yl)-N-(4-chlorophenyl) acetamide (2f)
Colorless crystals, 57 % yield, mp. 236-238^{0}C; IR: cm^{-1} 3276 (NH), 1669 (CO), 830 (paradisub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 10.53 (s, 1H, NH), 7.62-7.19 (m, 7H, Ar-H), 5.08 (s, 2H, CH_2); MS m/z: 234.77 (M^+-1).

2-(1H-imidazol-1-yl)-N-(4-bromophenyl) acetamide(2g)
Colorless crystals, 70% yield, mp. 162-164^{0}C; IR: cm^{-1} 3263 (NH), 1685 (CO), 824 (para disub ring); ^{1}H NMR (DMSO-d6, 300MHz): δ 10.12 (s, 1H, NH), 7.46-7.04 (m, 7H, Ar-H), 5.28 (s, 2H, CH_2); MS m/z: 279.92 (M^+).

RESULTS AND DISCUSSION

Microwave assisted synthesis are well routed and are considered as green reactions. The present study reports clean and efficient synthesis of imidazole acetamides. The various substituted N-chloroacetyl aryl amines in presence of base, potassium carbonate in a couple of minutes gave target amides in good yields. The IR spectra of compound **2a**, showed a peak at 3242 cm^{-1} corresponding to the NH stretching of amide group. The amide carbonyl frequency appear at 1657 cm^{-1} as a strong peak while the two peaks at 749 and 695 indicates presence of mono substituted phenyl ring in the compound. The ^{1}H NMR spectra displayed the sharp singlet at δ 9.64 and 5.12 accounts for the presence of NH proton and methylene proton respectively. The aromatic proton of imidazole and phenyl ring appears in the range δ 7.42-6.84. The downfield shift of the aromatic protons seen in hydroxyl and halogen substituted phenyl ring in the compounds **2d, 2e** and **2f**. The methyl group in the compound **2b, 2c** well appears as singlet in the range δ 2.3-2.5. The mass spectra of compound **2a**showed peak at m/z 200.16 corresponding to molecular formula $C_{11}H_{11}N_3O$. Similar spectral pattern observed in rest of the compounds, confirmed the structure of synthesized compounds. (Scheme)



R: a=H, b=2CH$_3$, c=4CH$_3$, d=4OH
e=2Cl, f=4Cl, g=4Br

Scheme: Synthesis of imidazole acetamides

CONCLUSION

The present study highlights the use of microwave as a clean and efficient source of energy for the synthesis of biological potential heterocyclic compounds within short reaction time. The procedure adapted for the synthesis of target compounds was simple, convenient and versatile.

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