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Research Article

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Facile synthesis of some new maleamic acid and maleimide derivatives of 1,3-thiazoles

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ABSTRACT

*Some new maleamic acid derivatives of thiazoles (**2a-e**) and their maleimide derivatives (**3a-e**) were efficiently synthesized. The maleimide derivatives were synthesized using both the conventional method and microwave irradiation technique where it has been found that the microwave supported syntheses is more efficient than the conventional heating method. The precursor's substituted aminothiazoles (**1a-e**) were prepared by employing the solvent free conditions. The structures of all the compounds were ascertained by spectral and analytical data.*

Keywords: Maleimides, maleamic acid, thiazole derivatives, microwave irradiation.

INTRODUCTION

2 –Aminothiazole is a heterocyclic amine with a wide spectrum of pharmaceutical applications. It is a fundamental scaffold in many biologically active compounds, including sulfur drugs, biocides, fungicides, dyes, and chemical reaction accelerators. 2–Aminothiazoles can be used as a thyroid inhibitor in the treatment of hyperthyroidism, and has antibacterial activity and also used as an acid tartrate. Recent studies on prion-infected neuroblastoma cell lines suggested aminothiazoles can also be used as a therapeutic drug for diseases caused by prions [1].

Cyclic imides are an important class of compounds having bis-amide linkages with common nitrogen. They are useful building blocks in the synthesis of natural products [2] and other heterocycles [3] as well. Their ability to pass through biological membranes in *vivo*, due to their hydrophobicity is well established [4]. Maleimides are the important class of compounds among cyclic amides.

Maleimides are an important class of compounds known for biological, pharmacological and chemical applications. Their derivatives have been extensively used in industry as antibacterial agents[5-7]pharmaceutical intermediates [8,9] cross linking reagents for natural rubbers[10,11],encapsulation resins of integrated circuit (IC) dyes[12] and structural adhesives for fiber-reinforcedcomposites in the aerospace industry. Among these compounds, N-aryl maleimides have recently gained special interest because of their use as the modifiers for the engineering plastics[13] and the modified plastics show excellent heat resistance[14,15]. Also N-substituted maleimides constitute a promising class of potent and selective monoglyceride lipase (MGL) inhibitors[16].Different synthetic approaches have been reported for the synthesis of N-aryl maleimide by utilizing either amine and maleic anhydride or primary alcohol and maleimide [17, 18]. In view of these fascinating results and in continuation of our work on biologically active nitrogen and sulfur heterocycles, we have efficiently synthesized some maleamic acid and maleimide derivatives of thiazoles**(Scheme 1-3).**In present work N-heteroarylmaleimides are synthesized by using heterocyclic amine and maleic anhydride.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Shimadzu FT IR – 8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on Bruker400 MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard.

General procedure for synthesis of 4-(4-substituted-phenyl)-1, 3-thiazole 2-amine (**1a-e**):

A mixture of substituted acetophenone (0.01mol), thiourea (0.02mol) and iodine (0.02mol) was taken in round bottom flask and heated for 3 hrs. Reaction mixture was then cooled; solid part is washed with diethyl ether followed by sodium thiosulphate and water. Solid was precipitated with liquid ammonia. The solid was filtered, dried and recrystallised from ethanol: water mixture (70:30).

General procedure for synthesis 4-{4-(4-substituted phenyl)-1,3-thiazol-2-yl]amino}-4-oxobut-2-enoic acid (**2a-e**): 4-(4-substituted) phenyl 1,3-thiazole 2 - amine derivatives (0.005mol) were dissolved in dioxane, tothis solution maleic anhydride (0.005mol) was dissolved in methanol ordiethyl ether was added drop wise with constant stirring. The mixture was stirred at 0-5°C for 2hrs. The precipitate was filtered off and washed with diethyl ether.Crystals are collected and recrystallized from dioxane.

4-[(4-phenyl-1,3-thiazol-2-yl)amino]-4-oxobut-2-enoic acid(2a): Yield 75%, m.p. 220-222°C;IR cm^{-1} : 3448, 3203, 3019, 1701, 1589, 1496; ^{1}H NMR (400MHz, DMSO) δ: 4.91(s, 2H, CH=CH), 6.96-7.34(m, 5H, Ar-H), 9.53(s, 1H, N-H), 10.06(s, 1H, COOH).

4-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]amino}-4-oxobut-2-enoic acid (2b): Yield 69%, m.p. 228-230°C; IR cm^{-1}: 3489, 3164, 2990, 1717, 1578, 1500; ^{1}H NMR (400MHz, DMSO) δ: 4.71(s, 2H, CH=CH), 6.90-7.30(m, 4H, Ar-H), 9.59(s, 1H, N-H), 10.04(s, 1H, COOH).

4-{[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]amino}-4-oxobut-2-enoic acid(2c): Yield 78%, m.p. 234-236°C; IR cm^{-1}: 3459, 3212, 2998, 1719, 1580, 1509; ^{1}H NMR (400MHz, DMSO) δ: 3.72(s, 3H, -OCH_3), 4.78(s, 2H, CH=CH), 6.99-7.38(m, 4H, Ar-H), 9.62(s, 1H, N-H), 10.11(s, 1H, COOH).

4-{[4-(4-hydroxy-phenyl)-1,3-thiazol-2-yl]amino}-4-oxobut-2-enoic acid(2d): Yield 66%, m.p. 244-246°C; IR cm^{-1}: 3485, 3430, 3171, 3007, 1711, 1589, 1492; ^{1}H NMR (400MHz, DMSO) δ: 4.65(s, 2H, CH=CH), 4.86(s, 1H, O-H), 6.95-7.24(m, 4H, Ar- H), 9.71(s, 1H, N-H), 10.08(s, 1H, COOH).

4-{[4-(4-nitro-phenyl)-1,3-thiazol-2-yl]amino}-4-oxobut-2-enoic acid(2e): Yield 73%, m.p. 230-232°C; IR cm^{-1}: 3479, 3202, 2963, 1712, 1592, 1497; ^{1}H NMR (400MHz, DMSO) δ: 4.54(s, 2H, CH=CH), 7.24-7.42 (m, 4H, ArH), 9.68 (s, 1H, NH), 10.07(s, 1H, COOH).

General procedure for synthesis of 1-[4-(4-substituted phenyl)-1,3-thiazol-2-yl]-1H-pyrrole-2,5-dione (**3a-e**):

Method A: The derivatives of maleamic acid (**2a-e**) was dissolved in acetic anhydride and 8% of anhydrous sodium acetate, the mixture was refluxed for 2 hrs on water bath until the color was changed, then cooled thesolution and poured in ice bath with vigorously stirred. Then filtered and washed with sodium bicarbonate solution, dried and recrystallized from ethanol.

Method B: The derivatives of maleamic acid were dissolved in acetic anhydride and 8% of anhydrous sodium acetate, the mixture was microwaved for 15-17 minutes. Then the same work up was followed as for the *method A* to get the derivatives **3a-e**.

1-[(4-phenyl)-1,3-thiazol-2-yl]-1H-pyrrole-2,5-dione(3a): Yield 71% (MWI) and 62% (classical heating method), m.p. 260-262°C; IR cm^{-1}: 3019, 2908, 1704, 1650, 1568; ^{1}H NMR (400MHz, DMSO) δ: 5.26(s, 2H, CH=CH), 7.27-7.33 (m, 3H, ArH), 7.38 (d, 2H, Ar-H).

1-[4-(4-chloro-phenyl)-1,3-thiazol-2-yl]-1H-pyrrole-2,5-dione(3b): Yield 70% (MWI) and 62% (classical heating method), m.p. 256-258°C; IR cm^{-1}: 3068, 2908, 1667, 1612, 1566; ^{1}H NMR (400MHz, DMSO) δ: 5.31(s, 2H, CH=CH), 6.81 (s, 1H, CH), 7.05-7.32 (m, 4H, ArH).

1-[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-1H-pyrrole -2,5-dione(3c): Yield 68% (MWI) and 59% (classical heating method), m.p. 266-268°C; IR cm^{-1}: 3031, 2910, 1668, 1603, 1534; ^{1}H NMR (400MHz, DMSO) δ: 3.68(s, 3H, OCH_3), 5.32(s, 2H, CH=CH), 6.88 (s, 1H, CH), 7.22 (d, 2H, J = 9.14 Hz, ArH), 7.34(d, 2H, J = 9.16 Hz, Ar-H).

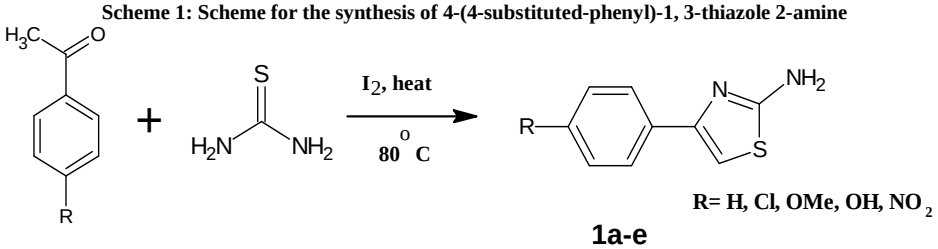
1-[4-(4-hydroxy-phenyl)-1,3-thiazol-2-yl]-1H-pyrrole-2,5-dione(3d): Yield 68% (MWI) and 60% (classical heating method), m.p. 267-269°C; IR cm^{-1}: 3433, 2992, 1674, 1589, 1554; ^{1}H NMR (400MHz, DMSO) δ: 4.81(s, 1H, O-H), 5.29(s, 2H, CH=CH), 6.85 (s, 1H, CH), 7.12-7.31 (m, 4H, ArH).

1-[4-(4-nitro-phenyl)-1,3-thiazol-2-yl]-1H-pyrrole-2,5-dione(3e): Yield 65% (MWI) and 58% (classical heating method), m.p. 253-255°C; IR cm^{-1}: 3013, 1654, 1599, 1548; ^{1}H NMR (400MHz, DMSO) δ: 5.33(s, 2H, CH=CH), 6.87 (s, 1H, CH), 7.00 (d, 2H, J = 9.16 Hz, ArH), 7.12 (d, 2H, J = 9.13 Hz, ArH).

RESULTS AND DISCUSSION

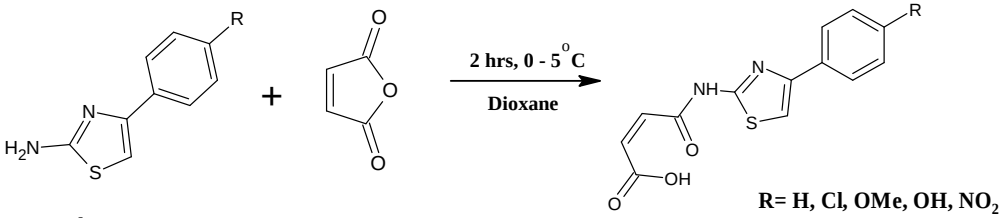
Maleimide derivatives of1, 3 thiazoles (**3a-e**)were synthesized from substituted 2-amino 1, 3 thiazoles (**1a-e**) via maleamic acid derivatives (**2a-e**) [17, 18]. Maleamic acid derivatives (**2a-e**) of thiazoles were synthesized by reacting aminothiazoles (**1a-e**) with maleic anhydride in dioxane at 0-5^{0}C (**Scheme 2**). The precursors (**1a-e**) in turn prepared by employing the solvent free conditions (**Scheme 1**).We employed microwave irradiation method for the synthesis of maleimide derivatives of thiazoles (**3a-e**) (**Scheme 3**).The microwave irradiation provided a remarkable rate of acceleration for the reaction, and the reaction time decreased significantly. All the compounds are characterized by using IR and NMR spectroscopy.

Scheme 1: Scheme for the synthesis of 4-(4-substituted-phenyl)-1, 3-thiazole 2-amine



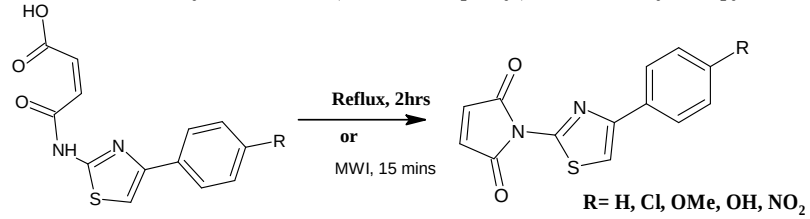
1a-e

Scheme 2: Scheme for the synthesis of 4-[4-(4-substituted phenyl)-1, 3-thiazol-2-yl] amino]-4-oxobut-2-enoic acid



1a-e **2a-e**

Scheme 3: Scheme for the synthesis of 1-[4-(4-substituted phenyl)-1, 3-thiazol-2-yl]-1H-pyrrole-2,5-dione



2a-e **3a-e**

Infrared spectrum of maleamic acid derivatives shows peak carboxylic acid at about 3400-3460cm^{-1}, whereas for keto group of amide and secondary amineshows peaks at about 1690-1720 cm^{-1} and 3100-3250cm^{-1}respectively. For maleimide derivatives characteristic peaks are observed at 1655-1670cm^{-1} for the carbonyl of imide linkage, which confirms the formation of ring with imide linkage.

In case of ^{1}H NMR spectral analysis, maleamic acid derivatives are confirmed by the signals present in the region of 10.02-10.10 δ and 4.00-4.75δ for acid and amine protons respectively, but both of these peaks are absent in case of maleimide derivatives.

CONCLUSION

In the current research, we are reportingsome facile and eco-friendly methods for the synthesis of different thiazole derivatives. Maleimide derivatives of thiazoles were synthesized efficiently using microwave irradiation technique where we found good improvement in yields of the product as well as the reaction time was reduced. We herein report a comparative study of these syntheses under microwave and by conventional method whereit has been found that the microwave supported syntheses is more efficient than the conventional heating method.

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