AN EFFICIENT ONE POT SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW THIAZOLE SUBSTITUTED PYRAZOLE DERIVATIVES

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ABSTRACT

New thiazole substituted pyrazole derivatives 4a-e and 5a-e were synthesized by one pot method. The synthesis was carried out by two ways, one by conventional method in which pyrazole aldehyde, thiosemicarbazide and ethyl 4-chloro-3-oxobutanoate or ethyl 2-chloro-3-oxobutanoate were refluxed in ethanol and second way in which the reaction mixture was grinded at room tempterature. Rate of the reaction, yield and purity of the products were compared for both the methods. Structure of all the synthesized compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. All synthesized compounds were tested for their antimicrobial activity against S. Aureus, B. subtilis, E. coli, P. aeruginos, A. Niger and C. Albicans.

KEYWORDS: Thiazole substituted pyrazole**,** one pot, ethyl 4-chloro-3-oxobutanoate, ethyl 2-chloro- 3-oxobutanoate, antimicrobial activity.

INTRODUCTION

Pyrazole and thiazole heterocycles show wide-range antimicrobial activities and therefore the compounds containing thiazole and pyrazole derivatives are of significant curiosity for drug discovery and have made them nice-looking targets for synthesis. Thiazole and pyrazoles are an important class of five member heterocyclic compounds, which have been the subject of great interest because of its wide range of biological activities. Thiazole ring is an important pharmacophore[1] and its coupling with other rings could furnish new biologically active compounds. Thiazole and its derivatives exhibited a broad range of biological activities such as anti cancer[2], anti-tumor[3], antibiotic[4-7], anti-inflammatory[8-9], anti tubercular[10], antibacterial, antifungal[11-12] anti liver cancer[13], antimalerial[14] and anticancer[15] activities. pyrazole derivatives also possesses versatile biological activities like anti-microbial[16], anti-histaminic[17], anti depressant[18], insecticides[19], anti-inflammatory[20], antifungal[21], antitumor[22-24] . Literature survey also showed that pyrazole and thiazole nuclei in combination showed good microbial activities[25-27]. On the basis of these observations, we planned to design and synthesize new derivatives which combines pyrazole and thiazole nucleus in one molecular framework in anticipation that such compounds would show enhanced biological activity.

EXPERIMENTAL PROCEDURE

GENERAL PROCEDURE FOR THE SYNTHESIS OF PHENYL HYDRAZONE DERIVATIVES (2a-e):

A mixture of substituted acetophenone 1a-e (0.04 mol), phenyl hydrazine (0.04 mol) and acetic acid (3-4 drops) in ethanol (15-20 ml) was refluxed for 30-45 minutes. After the completion (monitored on TLC), the reaction mixture was cooled and poured in crushed ice to obtain precipitate. The product was filtered, washed with water and re- crystallized from ethanol.

GENERAL PROCEDURE FOR THE SYNTHESIS OF 1-PHENYL-3-(SUBSTITUTED -PHENYL)-1H-PYRAZOLE-4-CARBALDEHYDE (3a-e):

To a well stirred and cooled (0^oC) DMF (0.2 mole), $POCl_3$ (0.14 mole) was added drop wise during 1h. After complete addition of $POCl_3$, the reaction mixture was further stirred at 0^oC for 1h. To this well stirred and cooled reaction mixture a solution of 2a (0.02mol) in anhydrous DMF (10 mL) was added drop wise during one hour, after complete addition, reaction mixture was stirred at room temperature for 24 hrs. The reaction mixture was then poured into crushed ice to obtain solid mass (3a). The product was filtered, washed with water and re-crystallized from ethanol. Same procedure was followed for synthesis of 3b-e.

GENERAL PROCEDURE FOR THE SYNTHESIS OF 2,4-DISUBSTITUTDE THIAZOLE DERIVATIVES(4a-e and 5a-e):

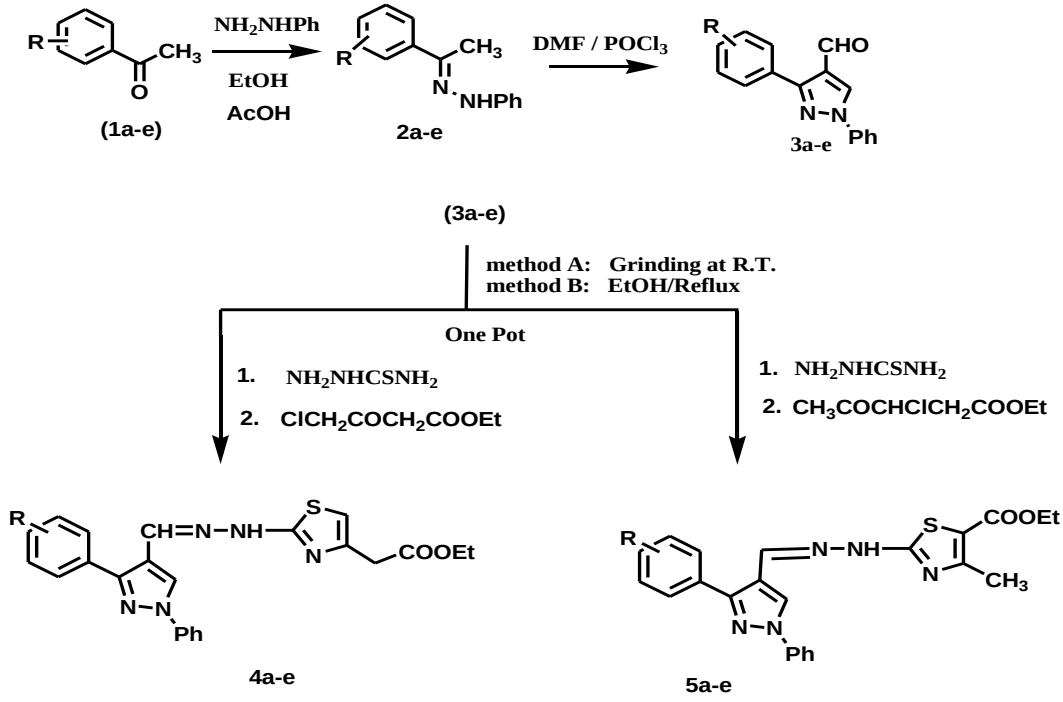
METHOD A:

A mixture of pyrazole aldehyde (0.003mol), thiosemicarbazide (0.003mol) and ethyl 4-chloro-3-oxobutanoate or ethyl 2-chloro-3-oxobutanoate (0.003mol) was grinded thoroughly by pestle in mortar at room temperature for 20-30 minutes. The progress of reaction was monitored by TLC (Ethyl acetate, hexane 6:4). After completion of reaction, the mixture was washed with water and re-crystallized from ethanol to afford the pure product (5a-e).

METHOD B:

A mixture of pyrazole aldehyde (0.003mol), thiosemicarbazide (0.003mol) and ethyl 4-chloro-3-oxobutanoate or ethyl 2-chloro-3-oxobutanoate (0.003mol) in ethanol was refluxed for 3-4hr. The reaction mixture was cooled at room temperature and poured into crushed ice. The separated solid was filtered, washed with ice cold water and recrystallized from ethanol to afford the pure product (5a-e).

SYYNTHETIC ROUT FOR SYNTHESIS OF NEW THIAZOLE SUBSTITUTED PYRAZOLE DERIVATIVES:



RESULTS AND DISCUSSION

Structures of all the synthesized compounds 4a-e and 5a-e, were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrometry. The grinding of aldehyde with thiosemicarbazide and ethyl 4-chloro-3-oxobutanoate or ethyl 2-chloro-3-oxobutanoate was carried out at room temperature to obtain the corresponding 2,4-disubstituted thiazole derivatives in high yield (60-70%). In this procedure, pyrazole aldehyde reacts with thiosemicarbazide and ethyl 4-chloro-3- oxobutanoate or ethyl 2-chloro-3-oxobutanoate to afford good yields of 2,4- disubstituted thiazoles after 30-40 minutes of grinding. To optimize the reaction conditions, the reaction between 3- (3, 5-bis (trifluoromethyl) phenyl 1)-1-phenyl-1H-pyrazole-4-carbaldehyde thiosemicarbazide and 2-chloro-3-oxobutanoate was chosen as a model reaction. The reaction completed after grinding for 30 minutes and afforded 2,4 disubstituted thiazole derivative with 70% yield. We also carried out the reaction of different pyrazole 4-caradehydes following same method. We found that all the reactions work smoothly and completed in 30-40 min by grinding without use of catalyst or solvent at room temperature. However highly efficient grinding was required for the success of these reactions. When the same reactions were carried out using solvent like ethanol under reflux condition, it was observed that for the reaction completion more time was required more time ie 1-2 hrs.(shown in table 1). From these observations we came to know that the above cyclization reactions occur effectively in absence of any catalyst as well as without use of solvent which is rapid and ecofriendly.

Table 1: Table showing difference between conventional and solvent free method.

Compound	Time	
	Conventional (hrs.)	Solvent free (min)
4a	4.0	25-27
4b	4.3	30-32
4c	4.4	25-28
4d	3.4	28-30
4e	3.2	26-30
5a	3.4	30-33
5b	4.0	27-30
5c	3.1	30-35
5d	3.2	29-32
5e	4.0	28-31

SPECTRAL DATA:

1-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(thiazol-4-yl)acetate) hydrazine(4a)

IR data:1730(C=O, ester), 3420-3480(NH), 1560 (C=C), 1130(C-O), 3100, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.7(bs, 1H, NH), 8.2(s, 1H, pyrazolyl-H), 8.0 (s,1H, thiazolyl-H), 8.3 (s, 1H, CH=N), 7.0-7.6(m, 10H, Ar-H), 2.2 (s, 2H, CH_2), 3.5(q, 2H, CH_2), 1.3(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 170,167, 158, 151.5, 143,140, 131.5, 131, 130, 129.3, 127.6, 129.4, 128.8, 118.5, 115, 112, 60, 41.3, 15. MS (EI, 70 eV) : m/z (%) = 431(M^+, 100).

1-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-Ethyl-2-(thiazol-4-yl)acetate)hydrazine (4b):

IR data:1735 (C=O, ester), 3450-3500 (NH), 1540, 1345 (NO_2), 1110 (C-O), 3100, (Ar-H). ^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.8(bs, 1H, NH), 8.2(s, 1H, pyrazolyl-H), 8.4 (s,1H, thiazolyl-H), 8.3 (s, 1H, CH=N), 8.1(d, J = 8.0 Hz, 2H), 8.5(d, J = 8.0 Hz, 2H), 7.1-7.6(m, 5H, Ar-H), 2.3 (s, 2H, CH_2), 3.3(q, 2H, CH_2), 1.4(t, 3H, CH_3).,^{13}C NMR (75 MHz, $CDCl_3$-d_6): 170,168, 158.2, 150.3, 145.3, 142.2,

141, 139.5, 132.2, 131.6, 130.5, 129.5, 123, 119.5, 114.3, 112.5, 61.4, 39.3, 14.1. MS (EI, 70 eV) : m/z (%) = 476 (M^+, 100).

1-((3-(3,5,bis trifluorohenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(thiazol-4-yl)acetate) hydrazine(4c)

IR data:1730(C=O, ester), 3400-3500(NH), 1110(C-O), 2900, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.9(bs, 1H, NH), 8.3(s, 1H, pyrazolyl-H), 8.4 (s,1H, thiazolyl-H), 8.2 (s, 1H, CH=N), 7.8(s, 2H), 7.6(s, 1H), 7.2-7.7(m, 5H, Ar-H), 2.2 (s, 2H, CH_2), 3.5(q, 2H, CH_2) 1.5(t, 3H, CH_3)., MS (EI, 70 eV) : m/z (%) = 567 (M^+, 100).

1-((3-(4-fluorohenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(thiazol-4-yl)acetate) hydrazine (4d):

IR data:1735(C=O, ester), 3450(NH), 1565 (C=C), 1120(C-O), 3100, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.7(bs, 1H, NH), 8.2(s, 1H, pyrazolyl-H), 8.4 (s,1H, thiazolyl-H), 8.3 (s, 1H, CH=N), 7.7(dd, J = 8/5 Hz, 2H), 7.4(dd, J = 8/13 Hz, 2H), 7.0-7.4(m, 5H, Ar-H), 2.4 (s, 2H, CH_2), 3.6(q, 2H, CH_2), 1.6(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 170, 167, 159.5(d, $^1J_{CF}$= 260 Hz), 157, 150.3, 142, 140, 131, 130, 129.5, 128.5, 127.6, 118.5, 116 (d, $^2J_{CF}$= 24 Hz), 115, 111.9, 61, 40.3, 15.5., MS (EI, 70 eV) : m/z (%) = 449 (M^+, 100).

1-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(thiazol-4-yl)acetate) hydrazine (4e)

IR data:1726(C=O, ester), 3474(NH), 1521 (C=C), 1163(C-O), 3117, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.9(bs, 1H, NH), 8.1(s, 1H, pyrazolyl-H), 8.4 (s,1H, thiazolyl-H), 8.2 (s, 1H, CH=N), 7.8(d, J = 8.0 Hz, 2H), 7.6(d, J = 8.0 Hz, 2H), 7.2-7.4(m, 5H, Ar-H), 2.4 (s, 2H, CH_2), 3.4(q, 2H, CH_2), 1.4(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 169, 167, 158, 149.3, 142,140.3, 133.3, 131.2, 131.9, 130, 129.3, 129.1, 125.5, 119, 113, 112.7, 60, 40, 12.5., MS (EI, 70 eV): m/z (%) = 511 (M^+, 100), 509 (M^+, 97)

1-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(4-methylthiazol-4-yl)acetate) hydrazine (5a):

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.8(bs, 1H, NH), 8.3(s, 1H, pyrazolyl-H), 8.4 (s, 1H, CH=N), 7.3-7.6(m, 10H, Ar-H), 2.4 (s, 3H, CH_3), 3.4(q, 2H, CH_2), 1.4(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 171,168, 156.5, 151.5, 143, 140, 131.5, 131, 129.6, 129.3, 128.8, 127.6, 116.5, 118.5, 115, 112, 59, 16.3, 14.5., MS (EI, 70 eV): m/z (%) = 431 (M^+, 100).

1-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(4-methylthiazol-4-yl)acetate) hydrazine (5b)

IR data:1730(C=O, ester), 3400-3500(NH), 1550, 1355 (NO_2), 1100(C-O), 3000, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.7(bs, 1H, NH), 8.0(s, 1H, pyrazolyl-H), 8.2 (s, 1H, CH=N), 8.3(d, J = 8.1 Hz, 2H), 8.6(d, J = 8.1 Hz, 2H), 7.1-7.6(m, 5H, Ar-H), 2.3 (s, 3H, CH_3), 3.4(q, 2H, CH_2), 1.4(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 169, 166, 155, 150.3, 145, 142.5,142, 139, 132.2, 131.5, 129, 122, 119.5, 116.7, 114.3, 112.5, 61.4, 16.7, 14.1., MS (EI, 70 eV): m/z (%) = 476 (M^+, 100).

1-((3-(3,5,bistrifluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(4-methylthiazol-4-yl)acetate) hydrazine (5c):

IR data:1735(C=O, ester), 3450-3510(NH), 1110(C-O), 3000, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 9.2(bs, 1H, NH), 8.3(s, 1H, pyrazolyl-H), 8.2 (s, 1H, CH=N), 7.9(s, 2H), 7.6(s, 1H), 7.1-7.6(m, 5H, Ar-H), 2.2 (s, 3H, CH_3), 3.2(q, 2H, CH_2), 1.2(t, 3H, CH_3)., MS (EI, 70 eV): m/z (%) = 567 (M^+, 100).

1-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(4-methylthiazol-4-yl)acetate) hydrazine (5d):

IR data:1735(C=O, ester), 3450(NH), 1565 (C=C), 1120(C-O), 3100, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 8.9(bs, 1H, NH), 8.1(s, 1H, pyrazolyl-H), 8.3 (s, 1H, CH=N), 7.5(dd, J = 7.8/5.2 Hz, 2H), 7.3(dd, J = 7.8/11.5 Hz, 2H), 7.6-7.8(m, 5H, Ar-H), 2.4 (s, 3H, CH_3), 3.4(q, 2H, CH_2), 1.2(t, 3H, CH_3)., ^{13}C NMR (75 MHz, $CDCl_3$-d_6): 171, 169, 158 (d, $^1J_{CF}$= 265 Hz), 156, 150, 142, 140, 131, 129.5, 128.5, 127.4, 117.4, 116.5(d, $^2J_{CF}$= 25 Hz), 116, 115, 112, 61, 16.1, 15.5., MS (EI, 70 eV): m/z (%) = 449 (M^+, 100).

1-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- Ethyl -2-(4-methylthiazol-4-yl) acetate) hydrazine (5e):

IR data:1725 (C=O, ester), 3460 (NH), 1540 (C=C), 1130(C-O), 3100, (Ar-H).

^{1}H NMR data (300 MHz, $CDCl_3$-d6):δ 9.1(bs, 1H, NH), 7.9(s, 1H, pyrazolyl-H), 8.1 (s, 1H, CH=N), 7.5(d, J = 8.0 Hz, 2H), 7.3(d, J = 8.0 Hz, 2H), 7.1-7.4(m, 5H, Ar-H), 2.3 (s, 3H, CH3),3.6(q, 2H,CH_2) 1.2(t, 3H, CH_3),^{13}C NMR (75 MHz, $CDCl_3$-d_6): 168, 165, 155.7, 148.8, 141,140.7, 132.8, 132, 131.2, 129.4, 129, 124.4, 120, 115.9, 113.5, 112.2, 57, 16.6, 12.5., MS (EI, 70 eV): m/z (%) = 511 (M^+, 100), 509 (M^+, 97).

All the synthesized pyrazole derivatives (4a-e and 5a-e) were tested for their in vitro antibacterial activity against clinically isolated standard strains B. subtilis (2250), S. aureus (2079), E. coli (2109) and P. aeruginosa (2036) and for their antifungal activity against C. albicans (3471) and A. niger (545). All the strains were obtained from microbial type culture collection (MTCC) at the NCIM, Pune, India. The results are presented in Table 2.

Table 2. Antimicrobial activity of synthesized compounds **(4a-e** and **5a-e)**

Compound	S. aureus	E. coli	B. subtilis	P. aeruginosa	A. niger	C. albicans
4a	20.5	19	-	16	14.3	-
4b	12.3	-	11.1	7.5	-	4.8
4c	24.4	21	-	18.4	15.3	16.2
4d	26.5	-	25.3	19.6	16.1	17.3
4e	11.6	-	10.5	-	5.9	-
5a	-	18.7	17.5	15.2	14.5	-
5b	18.2	15.3	-	15.7	10.8	-
5c	23.5	-	19.5	-	15.6	14.6
5d	24.0	20.3	-	17.3	15.4	16.4
5e	17.6	14.0	16.4	12.1	-	10
Nystatin	NA	NA	NA	NA	21.12	21.96
Chloramphenicol	32.8	29.14	30.11	24.68	NA	NA

Zone diameter of growth inhibition in mm., NA: not applicable. Chloramphenicol (100 µg /disc) and Nystatin (100 µg /disc) were used as reference; synthesized compounds (100 µg /disc).

It was found that, most of the compounds showed good activity against both the Gram positive as well as Gram negative bacteria. Compound 4d and 5d in which R groups is fluoro exhibited excellent activity against S. aureus, P. aeruginosa, A. niger and C. albicans, while

compounds 4a, 5a, 4c and 5c in which R groups are bis trifluormethyl and H exhibited better activity against S. aureus, P. aeruginosa, A. niger and C. albicans. Compounds like 4a, 4b, 4e and 5e showed weak activity against S. aureus E. coli, B. Subtilis P. aeruginosa A. niger and C. albicans. It was noted that substituent on thiazole ring does not affect the biological activity but substituent on pyrazole ring was found to play important role in deciding the biological activity. It was observed that when R group is fluorine and Bis trifluoro methyl (compound 4e, 4c, and 5e, 5c) showed enhancement in antifungal as well as antibacterial activities as compared to other compounds where the substituent's are nitro and bromo (4b, 4e, 5b and 5e) showed less antimicrobial activities.

CONCLUSION

In the present work on the basis of literature search we designed a synthesis of compounds containing different heterocyclic clubbed together. On the basis of the results obtained from the biological activity it can be concluded that pyrazole and thiazole containing heterocycles could be a good combination of heterocyclic compounds in order to design new potent drugs.

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