Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(1):866-871

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and characterization of some new 1, 4, 5-trisubstituted imidazole-2-thiols derivatives

Amol K. Dhawas*[1], S. S. Thakare[2] and N. R. Thakare[2]

[1]*Postgraduate Department of Chemistry, Shri Shivaji Science College, Amravati*
[2]*Sant Gadge Baba Amravati University, Amravati*

ABSTRACT

An efficient and practical synthesis of 5-[1-substituted-5-(4-substitutedphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl-1H-imidazole-2-thiols was achieved through cyclisation of α, β-unsaturated ketones (chalcones) with hydrazine hydrate, phenyl hydrazine, 2, 4-dinitrophenyl hydrazine, isoniazide in catalytic amount of sulphuric acid under thermal condition in ethanol gives (3a-c), (4a-c), (5a-c), (6a-c) respectively and (7a-c) has been synthesized by the treatment of (3a-c) with benzoyl chloride in pyridine. All the synthesized compounds were characterized on the basis of melting point, IR spectra, NMR spectra and MASS spectra.

Keywords: Imidazole-2-thiols, α, β-unsaturated ketones, phenyl hydrazine, sulphuric acid, isoniazide.

INTRODUCTION

The discovery of this class of compounds provides an outstanding case history of modern drug development and also emphasizes the unpredictability of biological activity from structural modification of a prototype drug molecule. Considerable interest has been focused on the imidazole structure, which is known to possess a broad spectrum of biological activities, such as antibacterial, fungicidal [1], sympathomimetic activity [2], anti-retrovirus activity and pharmaceutical compositions effective for the treatment of retrovirus infection such as human immunodeficiency syndromes [3].

Keeping in view their biological activities, synthesis of some new 1, 4, 5-trisubstituted imidazole-2-thiols derivatives have been carried out.

The chalcones 1-[2-mercapto-4-methyl-1-phenyl-1H-imidazol-5-yl]-3-(4-substitutephenyl)-prop-2-en-1-ones (2a-c) were synthesized by the Claisen-Schmidt condensation reaction of 1-[1-(4-phenyl)-2- mercapto-4-methyl-1H-imidazol-5-yl]-ethanone with different aromatic aldehydes. 5-[1-substituted-5-(4-substitutedphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl-1H-imidazole-2-thiols (3a-c), (4a-c), (5a-c) and (6a-c) have been synthesized by the treatment of appropriate chalcones (2a-c) with hydrazine hydrate, phenyl hydrazine, 2, 4-dinitrophenyl hydrazine and isoniazide in catalytic amount of sulphuric acid in ethanol and (7a-c) have been synthesized by the treatment of (3a-c) with benzoyl chloride in pyridine.

EXPERIMENTAL SECTION

Materials: 3-Chloro-2, 4-pentanedione, Aniline, Potassium thiocynate, Benzaldehyde, 4-Methoxybenzaldehyde, N, N-Dimethylbenzaldehyde, Hydrazine hydrate, Phenyl hydrazine, 2, 4-Dinitrophenyl hydrazine, Isoniazide, Benzoylchloride, Sulphuric acid, Ethanol, Pyridine.

All the melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr using Perkin Elmer model 2000 spectrophotometer and reported wave numbers are given in cm^{-1}. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Brucker Advance II 400 MHz spectrophotometer using TMS as an internal standard. Chemical shift values are shown in δ ppm. Mass spectra were recorded on Agilent 6320 Ion Trap mass spectrometer. The purity of all the synthesized compounds was checked by TLC on silica gel plates by using appropriate solvents.

Synthesis of 1-[1-(4-phenyl)-2- mercapto-4-methyl-1H-imidazol-5-yl]-ethanone (1a): 3-Chloro-2, 4-pentanedione (0.01mol) was added slowly in a dropwise fashion to the solution of aniline (0.01 mol) in ethanol (20 ml) with constant stirring for 1 hour at 0-5 ^{o}C. After the addition of 3-chloro-2, 4-pentanedione the reaction mixture was stirred for 1 hour at room temperature and kept the reaction mixture for 12 hours. Then potassium thiocynate (0.01 mol) was added to the reaction mixture which was reflux for 1 hour. Finally the reaction mixture was poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (1a).

Yield: 73%, M.P.: 149-152 ^{o}C, M.W.: 232.30, Anal. Calculation for $C_{12}H_{12}N_2OS$: Found: C: 62.08, H: 5.24, N: 12.02, Calcd. C: 62.04, H: 5.21, N: 12.06. IR (KBr, cm^{-1}): 1611 (C=O), 1557 (C=N), 1481 (C=C), 1172 (C-O). H^1NMR: ($CDCl_3$, 400 MHz): 2.44 (s, 3H, $COCH_3$), 2.55 (s, 3H, Ar-CH_3), 7.43-7.17 (m, 5H, Ar-H). Mass: m/z 232 (M^+), 233 (M+1).

Synthesis of 1-[2-mercapto-4-methyl-1-phenyl-1H-imidazol-5-yl]-3-(4-methoxy- phenyl) -prop-2-en-1-one (2a): 1-[1-(4-phenyl)-2-mercapto-4-methyl-1H-imidazol-5-yl]-ethanone (1a) (0.01 mol) dissolved in ethanol (40 ml) and 4-methoxybenzaldehyde (0.01 mol) was added with constant stirring at room temperature. Then KOH solution (40%) was added to the reaction mixture with constant stirring, keeping the temperature of the reaction mixture below 10 ^{o}C through out the addition. The flask was corked and kept the reaction mixture for 48 hours at room temperature. Finally the reaction mixture was poured over crushed ice and neutralized with glacial acetic acid. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (2a).

Yield: 71%, M.P.: 174-177 ^{o}C, M.W.: 350.43, Anal. Calculation for $C_{20}H_{18}N_2O_2S$: Found: C: 68.49, H: 5.23, N: 8.02, Calcd. C: 68.55, H: 5.18, N: 7.99. IR (KBr, cm^{-1}): 1642 (C=O), 1567 (C=N), 1494 (C=C), 1169 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.69 (s, 3H, $COCH_3$), 3.85 (s, 3H, Ar-CH_3), 6.93-6.91 (m, 2H, Ar-H), 7.05-7.01 (d, 1H, CO-CH=), 7.56 - 7.18 (m, 7H, Ar-H), 7.74-7.70 (d, 1H, Ar-CH=). Mass: m/z 350 (M^+), 351 (M+1). Other compounds of this type (2b-c) were prepared similarly and are recorded in Table-1.

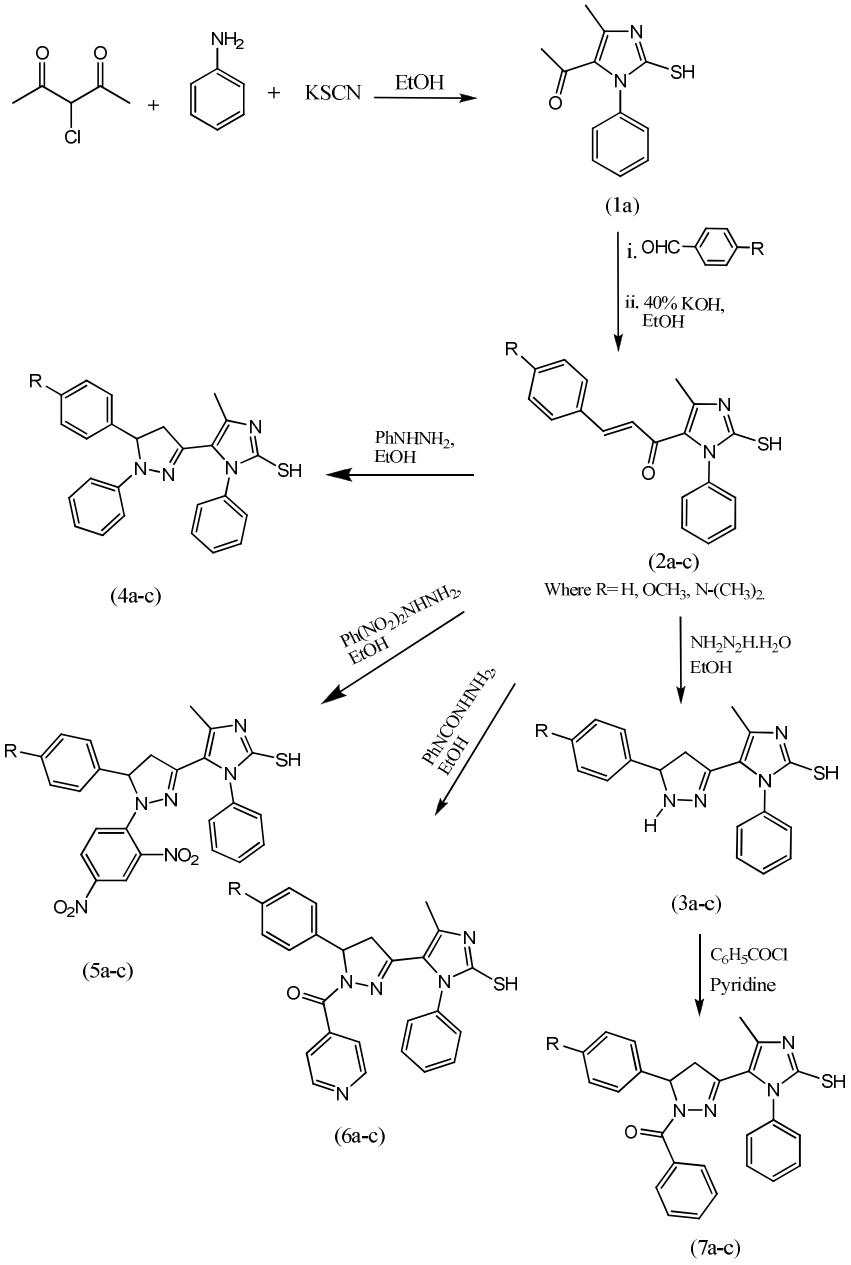
Synthesis of 5-[5-(4-methoxyphenyl)-4, 5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl -1H-imidazole-2-thiol (3a): A mixture of (2a) (0.01 mol) and hydrazine hydrate (0.01 mol) in ethyl alcohol (30 ml) was refluxed for 8 hours. After cooling the reaction mixture was poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (3a).

Yield: 71%, M.P.: 153-155 ^{o}C, M.W.: 364.46, Anal. Calculation for $C_{20}H_{20}N_4OS$: Found: C: 65.88, H: 5.55, N: 15.42, Calcd. C: 65.91, H: 5.53, N: 15.37. IR (KBr, cm^{-1}): 3311 (N-H), 1554 (C=N), 1453 (C=C), 1174 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.40 (s, 3H, Ar-CH_3), 3.13-3.07 (dd, 1H, -CH_2 of pyrazoline), 3.50-3.43 (dd, 1H, -CH_2 of pyrazoline), 3.79 (s, 3H, OCH_3), 4.27-4.21 (dd, 1H, -CH of pyrazoline), 7.22 – 6.93 (m, 9H, Ar-H). Mass: m/z 364 (M^+), 365 (M+1). Other compounds of this type (3b-c) were prepared similarly and are recorded in Table-1.

Synthesis of 5-[5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl-1H-imidazole-2-thiols (4a): A mixture of (2a) (0.01 mol) in ethyl alcohol (30 ml), phenyl hydrazine (0.01 mol) and 2-3 drops of sulphuric acid was refluxed for 12 hours. After cooling the reaction mixture was poured over crushed ice. The

product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (4a).

Yield: 67%, M.P.: 167-170 ^{o}C, M.W.: 440.46, Anal. Calculation for $C_{26}H_{24}N_4OS$: Found: C: 70.91, H: 5.52, N: 12.82, Calcd. C: 70.88, H: 5.49, N: 12.72. IR (KBr, cm^{-1}): 1592 (C=N), 1499 (C=C), 1111 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.40 (S, 3H, Ar-CH_3), 3.13-3.07 (dd, 1H, -CH_2 of pyrazoline), 3.81 (S, 3H, OCH3), 4.27-4.21 (dd, 1H, -CH_2 of pyrazoline), 5.25-5.20 (dd, 1H, -CH of pyrazoline), 6.96 – 6.77 (m, 10H, Ar-H), 7.22 – 7.13 (m, 4H, Ar-H). Mass: m/z 440 (M^+), 441 (M+1). Other compounds of this type (4b-c) were prepared similarly and are recorded in Table-1.



Scheme-I

Synthesis of 5-(1-(2,4-dinitrophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4-methyl-1-phenyl-1H-imidazole-2-thiol (5a): A mixture of (2a) (0.01 mol) in ethanol (30 ml), 2, 4-dinitrophenyl hydrazine (0.01 mol) and 2-3 drops of sulphuric acid was refluxed for 12 hours. After cooling the reaction mixture was poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (5a).

Yield: 63%, M.P.: 256-259 ^{o}C, M.W.: 530.56, Anal. Calculation for $C_{26}H_{22}N_6O_5S$: Found: C: 58.90, H: 4.24, N: 15.81, Calcd. C: 58.86, H: 4.18, N: 15.84. IR (KBr, cm^{-1}): 1581 (C=N), 1507 (C=C), 1256 (Ar-O), 1138 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.47 (s, 3H, Ar-CH_3), 3.88-3.85 (dd, 1H, -CH_2 of pyrazoline), 3.87 (S, 3H, OCH_3), 4.29-4.23 (dd, 2H, -CH_2 & -CH of pyrazoline), 7.91 – 6.94 (m, 12H, Ar-H). Mass: m/z 530 (M^+), 531 (M+1). Other compounds of this type (5b-c) were prepared similarly and are recorded in Table-1.

Synthesis of 5-[1-(pyridin-4-yl)-methanone-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl-1H-imidazole-2-thiol (6a): A mixture of (2a) (0.01 mol) in ethyl alcohol (30 ml), isoniazide (0.01 mol) and 2-3 drops of sulphuric acid was refluxed for 12 hours. After cooling the reaction mixture was poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (6a).

Yield: 64%, M.P.: 213-216 ^{o}C, M.W.: 469.56, Anal. Calculation for $C_{26}H_{23}N_5O_2S$: Found: C: 66.55, H: 4.92, N: 14.94, Calcd. C: 66.50, H: 4.94, N: 14.91. IR (KBr, cm^{-1}): 1640 (C=O), 1564 (C=N), 1465 (C=C), 1167 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.40 (S, 3H, Ar-CH_3), 3.13-3.07 (dd, 1H, -CH_2 of pyrazoline), 3.78 (S, 3H, OCH3), 4.27-4.21 (dd, 1H, -CH_2 of pyrazoline), 5.26-5.21 (dd, 2H, -CH_2 & -CH of pyrazoline), 7.22 – 6.85 (m, 13H, Ar-H). Mass: m/z 469 (M^+), 470 (M+1). Other compounds of this type (6b-c) were prepared similarly and are recorded in Table-1.

Table-1: Physicochemical data of the synthesized compounds

Sr. No.	Compds	R	M.P. (^{o}C)	Yield (%)	Molecular Weight	Molecular Formula
1	3a	OCH_3	153-155	71	364.46	$C_{20}H_{20}N_4OS$
2	3b	H	90-93	63	334.44	$C_{19}H_{18}N_4S$
3	3c	$N(CH_3)_2$	168-170	68	377.51	$C_{21}H_{23}N_5S$
4	4a	OCH_3	167-170	65	440.46	$C_{26}H_{24}N_4OS$
5	4b	H	137-140	61	410.53	$C_{25}H_{22}N_4S$
6	4c	$N(CH_3)_2$	160-163	68	453.60	$C_{27}H_{27}N_5S$
7	5a	OCH_3	256-259	63	530.56	$C_{26}H_{22}N_6O_5S$
8	5b	H	190-193	71	500.53	$C_{25}H_{20}N_6O_4S$
9	5c	$N(CH_3)_2$	245-248	66	543.60	$C_{27}H_{25}N_7O_4S$
10	6a	OCH_3	213-216	64	469.56	$C_{26}H_{23}N_5O_2S$
11	6b	H	188-192	69	439.33	$C_{25}H_{21}N_5OS$
12	6c	$N(CH_3)_2$	270-273	71	482.60	$C_{27}H_{26}N_6OS$
13	7a	OCH_3	125-128	73	468.57	$C_{27}H_{24}N_4O_2S$
14	7b	H	120-123	69	438.54	$C_{26}H_{22}N_4OS$
15	7c	$N(CH_3)_2$	180-182	65	481.61	$C_{28}H_{27}N_5OS$

Synthesis of 5-[1-(phenyl)-methanone-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-4-methyl-1-phenyl-1H-imidazole-2-thiol (7a): To the ice cold mixture of (3a) (0.01 mol) was dissolved in pyridine (30 ml). Then benzoyl chloride (0.01 mol) was added dropwise to the reaction mixture with constant stirring at 0-5 ^{o}C. After completion of addition stirred the reaction mixture for 1 hour at room temperature. Finally the reaction mixture was poured over crushed ice and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (7a).

Yield: 73%, M.P.: 128-131 ^{o}C, M.W.: 468.57, Anal. Calculation for $C_{27}H_{24}N_4O_2S$: Found: C: 69.24, H: 5.19, N: 11.95, Calcd. C: 69.21, H: 5.16, N: 11.90. IR (KBr, cm^{-1}): 1604 (C=O), 1561 (C=N), 1447 (C=C), 1245 (Ar-O), 1176 (C-O). ^{1}NMR: ($CDCl_3$, 400 MHz): 2.47 (S, 3H, Ar-CH_3), 3.18-3.13 (dd, 1H, J= 8 & 6.4 Hz, - CH_2 of pyrazoline), 3.77-3.73 (dd, 1H, -CH_2 of pyrazoline), 3.78 (s, 3H, OCH_3), 5.78-5.74 (dd, 1H, -CH of pyrazoline),

7.48–6.86 (m, 14H, Ar-H). Mass: m/z 468 (M^+), 469 (M+1). Other compounds of this type (7b-c) were prepared similarly and are recorded in Table-1.

RESULTS AND DISCUSSION

The structures of the synthesized compounds were characterized with the help of TLC, IR and NMR, MASS. The IR spectrum of compound 2a shows the characteristic band at 1642 cm^{-1} due to the –C=O group. The IR spectrum of compounds 3a, 4a, 5a, 6a and 7a shows the characteristic band at 1500-1600 cm^{-1} due to the –C=N group. There are no absorptions in the region of 1600-1700 cm^{-1} indicating the absence of –C=O group in 3a, 4a and 5a compounds. The IR spectrum of compound 6a and 7a shows the characteristic band at 1600-1700 cm^{-1} indicating the presence of –C=O group.

The ^{1}H NMR spectrum of compound 2a showed doublet of –CO-CH= at δ 7.03-6.99 ppm and Ar-CH= at δ 7.76-7.72 ppm, which confirmed the presence of chalcone moiety. The ^{1}H NMR spectrum of compound 3a, 4a, 5a, 6a and 7a showed doublet of -CH_2 near about δ 3.00-5.00 ppm confirmed the cyclisation in pyrazoline.

CONCLUSION

In conclusion, a efficient, practical, high yield, simple, economic, readily available system, and convenient procedure for the synthesis of some new 1, 4, 5-trisubstituted imidazole-2-thiols derivatives, which compares well with the similar acetic acid system under the same conditions, has been developed.

ACKNOWLEDGMENT

The authors are grateful to the authorities of Shri Shivaji Science College, Amravati for providing necessary facilities. RSIC, Chandigarh for spectral analyses.

REFERENCES

[1] Vineeta Sareen, Urmila Gupta, Vineeta Khatri and Sanjana Chugh, *Indian Journal of Heterocyclic Chemistry*, **2008**, 17, 355-358.
[2] CR Scholz, *Ind. Eng. Chem*., **1945**, 37(2), 120-125.
[3] Hirohiko Sugimoto, Hiroshi Matsumoto, Ken-ichi Sugita, Akihiko Sato, Tamio Fujiwara, *US*, 5,472,965 (Dec.5, **1995**).
[4] Paivi Juujarvi, Seppo Parhi, Jaana Karjalainen, *US* 7,223,871 B2 (May. 29, **2007**).
[5] Robert Zelle, Vincent P. Galullo, Hormoz Mazdiyasni, *US* 7,368,467 B2 (May 6, **2008**).
[6] Karabasanagouda T, Airody Vasudeva Adhikari and Girisha M, *India Journal of Chemistry*, **2009**, 48B, 430-437.
[7] Anjani Solankee, Kishor Kapadia, Ana Ciric, Marina Sokovic, Irini Doytchinova and Athina Geronikaki, *European Journal of Medicinal Chemistry*, **2009**, 48B, 1442-1446.
[8] Anjani Solankee, Smruti Lad, Sejal Solankee & Ghanshyam Patel, *India Journal of Chemistry*, **2009**, 48B, 1442-1446.
[9] Albert Levai and Jozsef Jeko, *ARKIVOC*, **2007**, 134-145.
[10] Rashmi R. Dubey, Amol K. Dhawas, SS Thakare, and NR Thakare, *India Journal of Heterocyclic Chemistry*, **2010,** 19, 281-284.
[11] Vineeta Sareen, Urmila Gupta, Vineeta Khatri and Sanjana Chugh, *India Journal of Heterocyclic Chemistry*, **2008**, 17, 355-358.
[12] DS Ghotekar, PG Mandhane, RS Joshi, SS Bhagat and CH Gill, *India Journal of Heterocyclic Chemistry*, **2010,** 19, 341-344.
[13] SN Thore and Ashwani Kumar Gupta, *India Journal of Heterocyclic Chemistry*, **2010**, 19, 373-376.
[14] Udo, Bauer, Bryan, J. Egner, Ingemar Nilson and Maric Berghult, *Tetrahedron Letter*, **2000**, 41, 2713.
[15] Mohammad Abid and Amir Azam, *Bioorganic & Medicinal Chemistry Letters*, **2006**, 16(10), 2812-16.
[16] Kakul Husain, Mohammad Abid and Amir Azan, *European Journal of Medicinal Chemistry*, **2008**, 43(2), 393-403
[17] Asha Budakoti, Mohammad Abid and Amir Azam, *European Journal of Medicinal Chemistry*, **2007**, 42(4), 544-551.
[18] Shankaralah Konda, Vishnu Khedkar and Bhaskar Dawane, *Journal of Chemical and Pharmaceutical Research*, **2010**, 2(1), 187-191.

[19] Chirag Patel, CS Rami, B Panigrahi and CN Patel, *Journal of Chemical and Pharmaceutical Research*, **2010**, 2(1), 73-78.
[20] SB Zangade, JD Jadhav, Lalpod, YB Vibhute and BS Dawane, *Journal of Chemical and Pharmaceutical Research*, **2010**, 2(1), 310-314.