Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2023, Vol. 39, No.(1):
Pg. 167-171

One-pot Multicomponent Synthesis of 3-(substitutedphenyl)-5 -oxo-3,4,5,6-tetrahydroimidazo[4,5-c] Pyrazole-2(1H)-carbaldehyde Derivatives act as Antibacterial agents

PRAVIN NANDKUMAR MULI[1], MEGHA MUKUND MULEY[2], and BHASKAR SADASHIV DAWANE[1]*

[1]School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, (MS), India.
[2]Nanded Pharmacy College, Nanded-431602, (MS), India.
*Corresponding author E-mail: dawanebhaskar@gmail.com

http://dx.doi.org/10.13005/ojc/390120

(Received: November 10, 2022; Accepted: January 07, 2023)

ABSTRACT

A new class of 3-(substituted phenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde derivatives 5(a-l) was synthesized in four-component cyclocondensation one-pot reaction. This was done using the catalytic amount of Bleaching Earth Clay (pH 12.5 wt%) and PEG-400 as a sustainable solvent. The structures of the produced substances were verified using spectral and analytical data. *In vitro* antibacterial activity of the targeted compounds was examined against *S. Typhi, E. coli, B. subtilis* and *S. aureus*. The outcome of antimicrobial screening explains that compounds 5a-l showed good to moderate activities.

KEYWORDS: Imidazolidine-2,4-dione, Hydrazine hydrate, Pyrazole-2-carbaldehyde, Antimicrobial activity.

INTRODUCTION

Microbial infection is still one of the most dangerous side effects in several industries, including those that deal with medical devices, pharmaceuticals, water purification systems, healthcare tools, fabrics, packaged food, and food storage. Due to their potential to improve the quality and safety of numerous materials, antimicrobials are attracting more and more attention through both academic and industrial research.[1] The process of antibacterial activity is extremely complicated since it involves living things whose basic needs, such as nourishment, respiration, metabolism, and capacity for reproduction, could be impacted if harmful substances are present.[2]

In synthetic anion receptor systems, the ring of imidazole functions as an efficient donor moiety for hydrogen bonds. Due to the great therapeutic effectiveness of medications related to imidazole, medicinal chemists have been inspired to create five-membered heterocyclic structures with an imidazole nucleus that display a range of qualities, such as

antifungal and antibacterial, anti-inflammatory and analgesic, antitubercular, anti-depressant, anti-cancer, antiviral, and antileishmanial activities.[3-4] Multi-component processes are also used to synthesize tetra-substituted imidazoles.[5-7] Tetra-substituted imidazoles are important in biochemical and pharmacological processes.[8-11]

Different configurations with the pyrazole nucleus allow for a variety of uses in fields like engineering, pharmacy, and agriculture. They are specifically described as potent activities[12-13] anti-tuberculosis.[14-15] Imidazopyrazole plays a vital role in medicinal chemistry and is a crucial element in the chemistry of heterocyclics because of its extensive spectrum of bioactivities,[16-23] The therapeutic potential of pyrazole-carbaldehydes and related pharmaceuticals has drawn medicinal chemists' attention, leading them to develop a variety of pyrazole-carbaldehyde derivatives.[24-27] Pyrazole-carbaldehyde derivatives may be important in anticancer[28] and antibacterial activity[29–30] because of their significant biological and pharmacological benefits.

To further our research, we synthesized 3-(substitutedphenyl)-5-oxo-3,4,5,6 -tetrahydroimidazo [4,5-c]pyrazole-2(1H)-carbaldehyde motifs, a multicomponent synthesis that can be completed in one pot. Because of step and atom economy, avoiding protective group tactics, and a quick purification process, MCR transforms into a potent chemical tool for the creation of complex molecules. However, a number of heterocyclic compounds can be synthesized with considerably greater efficiency using the multicomponent reaction technique.[31]

MATERIAL AND METHODS

Instrumentation

Melting points have been established in nursing associates who are uncorrected and seem to have open capillaries. The solvents and chemicals utilized were pure and of laboratory standard. By using TLC, the reaction was observed. Shimadzu spectrometers were used to record FT-IR spectra in KBr. The ^{1}H NMR measurements were made in DMSO-d_6 by means of TMS as an internal standard with an advanced spectrometer at a frequency of 300 MHz, DMSO-d_6 was used to record ^{13}C NMR, and a GC-MS (EI-Shimadzu QP2010PLUS) system was used to record mass spectra.

A general method for preparation of compounds 5(a-l)

In this section, we describe the synthesis of 3-(substitutedphenyl)-5-oxo-3,4,5,6 -tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde derivatives a one-pot multicomponent reaction, which an equimolar quantity of imidazolidine-2,4-dione (1) is reacted with substituted aromatic aldehydes 2(a-g). Bleaching Earth Clay (pH 12.5 wt%) was used as a catalyst, and PEG-400 was used as a sustainable solvent while stirring at 70-80°C for one hour. Hydrazine hydrate (3) was then added to this mixture, and it was shaken for nearly an hour. An excess of formic acid (4) was added to the reaction mixture. After the reaction is over (monitored by TLC). The mixture was placed on ice-cold water once the reaction was finished, and it was shaken for five minutes. Diluted HCl was used to neutralize if necessary. The solid crude material was separated using a water aspirator, washed with ice-cold water, and recrystallized from ethanol. The prepared products 5(a-l) were identified by spectroscopic investigation and comparison of their melting points.

Spectral data of some synthesized compounds.

3-(3-Chlorophenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde 5a: $C_{11}H_9ClN_4O_2$, m.p. 220°C, this compound was obtained in 90% yield; IR ν_{max}: 3334 (N-H), 1769 (C=O, CHO), 1700 (C=O). ^{1}H NMR (δ,ppm); 10.60 (s, 1H, CHO), 8.20-8.23 (d, 2H, Ar-H), 7.56-7.73 (d, 2H, Ar-H), 7.50 (s, 1H, NH), 6.00 (s, 1H, NH), 5.03 (s, 1H, NH), 4.20 (s, 1H). ^{13}C NMR (δ,ppm); 173.8, 158.1, 149.2, 146.4, 143.1, 127.8, 126.8, 125.2, 124.0, 70.3, 63.2. MS (EI): m/z (M^+) 264.5.

3-(3-Bromophenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde 5b: $C_{11}H_9BrN_4O_2$, m.p. 218°C, this compound was obtained in 92% yield; IR ν_{max}: 3334 (N-H), 1765 (C=O, CHO), 1703 (C=O), 1599. 1H NMR (δ,ppm); 10.57 (s, 1H, CHO), 8.22-8.23 (d, 2H, Ar-H), 7.60-7.69 (d, 2H, Ar-H), 7.55 (s, 1H, NH), 6.09 (s, 1H, NH), 5.07 (s, 1H, NH), 4.32 (s, 1 H). ^{13}C NMR (δ,ppm); 173.8, 158.0, 149.6, 146.1, 145.7, 143.3, 127.8, 126.8, 123.0, 70.3, 63.4. MS (EI): m/z (M^+) 307.99.

3-(3-Nitrophenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde 5c: $C_{11}H_9N_5O_4$, m.p. 223°C, this compound was obtained in 85% yield; IR ν_{max}: 3343 (N-H), 1768 (C=O, -CHO), 1702 (C=O). ^{1}H NMR (δ,ppm); 10.59 (s, 1H, CHO), 8.22-8.27 (d, 2H, Ar-H), 7.60-7.66 (d, 2H, Ar-H), 7.51 (s, 1H, NH), 6.00 (s, 1H, NH), 5.01 (s, 1H, NH), 4.29 (s, 1H). ^{13}C NMR (δ, ppm); 173.0, 158.0, 149.4, 146.7, 143.1, 127.8, 125.2, 123.0, 124.3, 70.2, 63.5. MS (EI): m/z (M^+) 275.

3-(4-Fluorophenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde 5d: $C_{11}H_9FN_4O_2$, m.p. 230°C, this compound was obtained in 90% yield; IR cm^{-1} ν_{max}: 3333 (N-H), 1770 (C=O, -CHO), 1700 (C=O). ^1H NMR (δ,ppm); 10.63 (s, 1H, -CHO), 8.20-8.23 (d, 2H, Ar-H), 7.66-7.69 (d, 2H, Ar-H), 7.57 (s, 1H, -NH), 6.09 (s, 1H, -NH), 5.06 (s, 1H, -NH), 4.34 (s, 1 H). ^{13}C NMR (δ,ppm); 173.8, 158.0, 149.1, 146.4, 145.4, 142.9, 127.8, 125.5, 124.3, 70.3, 63.2. MS (EI): m/z (M^+) 247.

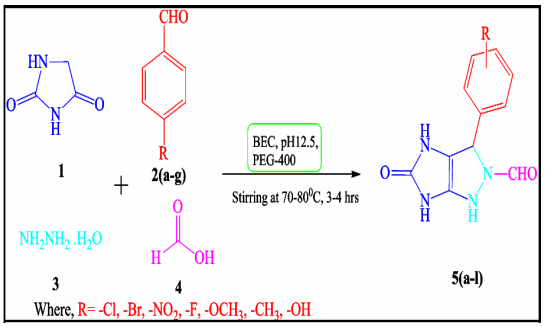
Antibacterial activity against different bacteria by Well plate diffusion Method

The bacterial cultures were used to prepare the microorganism's inoculum. Clean, sanitized Petri plates received nutrient agar (15 mL) (Hi media), which was then allowed to cool and harden. A spreading stick was used to uniformly distribute bacterial strain broth (100 µL) across the medium until it had fully dried; using a sterile cork borer, 6 mm-diameter wells were drilled. All of the substances were produced as DMSO solutions (10 mg/mL). Plant extract solutions containing 100 µL were poured into the wells. Petri plates were incubated for 24 h at 37°C. Positive control was constructed using streptomycin. It was used with DMSO as a negative control.[32] All measurements were made in triplicates, and the zone of inhibition (ZI) widths served as a measure of antibacterial activity.

RESULT AND DISCUSSION

3-(Substitutedphenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde derivatives 5(a-l) were synthesised as shown in Scheme. The synthesis of the target molecule was achieved by a one-pot multicomponent reaction by adding equimolar quantities of imidazolidine-2,4-dione (1) with substituted aromatic aldehydes 2(a-g), hydrazine hydrate (3), and an excess of formic acid (4). This method is efficient and green because all reactions are preferred in the presence of Bleaching Earth Clay (pH 12.5 wt%) as a catalyst, and greener PEG-400 was used to afford the title 5(a-l) compounds in good yields as shown in Table 1 within a very short reaction time.

The structures of the prepared products 5a-l were determined using FT-IR, ^1H NMR, ^{13}C NMR spectroscopy, and mass spectrometry. The FT-IR spectra of compounds 5a-l appear in bands at 3334-3333 cm^{-1} due to the N-H vibration. The characteristic absorption of the aldehyde hydrogen appeared between 1770 cm^{-1} and 1768 cm^{-1}. Also, the C=O stretching of the imidazolone carbonyl group at 1701-1700 cm^{-1}. In ^1H NMR, the NH protons appeared in three sharp singlets: 5.06, 6.11, and 7.57ppm. The characteristic aldehyde proton appears in a more deshielded region at 10.62ppm, and the aromatic protons are found to be in the expected region between 7.66 and 8.23ppm for four protons. The most distinguishing signal in the ^{13}C NMR spectrum data of the title compounds is associated with the carbon of the carbonyl group and is located at 173ppm due to the aldehydic group, and 158ppm belongs to the ketonic group. The signal at 63ppm is due to -CH, which confirms that there is one hydrogen atom at that carbon. While all aromatic carbons of the compounds exhibit signals between 123 and 149 ppm. The anticipated M^+ peak, which corresponds to the actual molecular mass, can be found in the mass spectra of all substances. Table 1 displays the physiochemical properties of all synthesized derivatives (5a-l).



Scheme: Synthesis of 3-(substitutedphenyl)-5-oxo-3,4,5,6-tetrahydroimidazo [4,5-c] pyrazole-2(1H)-carbaldehyde derivatives

Table 1: Physiochemical properties of synthesized derivatives (5a-l)

Compound number	Structure	Time (hours)	Yield (%)	m.p. (°C)
5a	3-Cl	2.5	90	220-222
5b	3-Br	2.5	92	230-232
5c	3-NO_2	3	85	225-227
5d	4-F	3	90	223-225
5e	3,4-Cl	3.5	80	228-230
5f	4-Cl	2.5	92	221-223
5g	4-Br	2.5	90	228-230
5h	4- NO_2	3	89	226-228
5i	4-OH	3.5	85	235-238
5j	4-CH_3	3	82	200-202
5k	4-OCH_3	3	87	232-234
5l	3-Cl, 4-OCH_3	3.5	82	237-239

Antibacterial activity

From the information provided above, it can be seen that the synthetic molecule was developed to suppress the growth of a number of examined species of microbes that are both *Gram-positive* and *Gram-negative*, such as *S. aureus, E. coli, B. subtilis* and *S. Typhi*. According to the findings, compounds 5d and 5g have demonstrated substantial activity against *S. Typhe*. Against *E. coli* and *B. subtilis*, compound 5 g showed impressive antibacterial activity. Against *S. aureus*, compounds 5a, 5f, and 5h demonstrated remarkable antibacterial activity, as indicated in Table 2 and in graphical form in Fig. 1. Generally, we can conclude that the synthetic compound (5a-l) exhibits good to moderate antibacterial activity.

Table 2: Antibacterial Screening of the synthesized derivatives (5a-l).

Compound number	Mean zone inhibition (MZI)a			
	S. typhi	*E. coli*	*B. subtilis*	*S. aureus*
5a	14	12	16	17
5b	16	14	18	15
5c	13	13	13	16
5d	18	11	17	16
5e	11	10	12	13
5f	15	13	19	17
5g	18	16	21	15
5h	13	12	14	17
5i	12	13	13	15
5j	11	10	12	14
5k	12	12	12	13
5l	12	12	11	13
Standard (Streptomycin)	20	19	29	22

[a]Values are mean (n=3), *Salmonella typhi* = *S. typhi*, *Escherichia coli* = *E. coli*, *Bacillus subtilis* = *B. subtilis* and *Staphylococcus aureus* = *S. aureus*

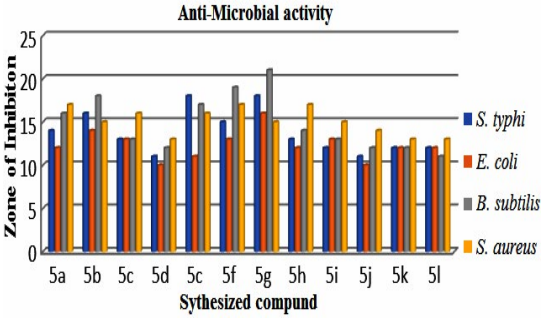


Fig. 1. Graphical form of antibacterial activity

CONCLUSION

The synthesized 3-(substitutedphenyl)-5-oxo-3,4,5,6-tetrahydroimidazo[4,5-c]pyrazole-2(1H)-carbaldehyde compounds have been screened for notable antibacterial activity. The inclusion of halo-substituted phenyl groups may be significant in imparting the growth inhibitory action against *Gram-positive* and *Gram-negative* microbes, as indicated by the substantial antibacterial activity of compounds 5a, 5b, 5d, 5f, and 5g.

ACKNOWLEDGMENT

We appreciate the research facilities provided by the School of Chemical Sciences at S.R.T.M. University, Nanded.

Conflict of interest

No authors have revealed any conflicts of interest.

REFERENCES

1. Kenawy, E. R.; Worley, S. D.; Broughton, R. *Biomacromolecules*., **2007**, *8*(5), 1359-84.
2. Richard, J. F.; Yitzhak, T. *Perspect. Medicin Chem*., **2014**, *6*, 25-64.
3. Molina, P.; Tárraga, A.; Otón, F. *Org. Biomol. Chem*., **2012**, *10*(9), 1711-24.
4. Shalini, K.; Sharma, P. K.; Kumar, N. *Der Chemica Sinica*., **2010**, *1*(3), 36-47.
5. Amir, M.; Ahsan, I.; Akhter, W.; Khan, S.; Ali, I. *Indian J. Chem*., **2011**, *50*, 207–213.
6. Thwin, M.; Mahmoudi, B.; Ivaschuk, O. A.; Yousif, Q. A.; *RSC Adv*., **2019**, *9*(28), 15966-75.
7. Rossi, R.; Angelici, G.; Casotti, G.; Manzini, C.; Lessi, *Adv. Synth. Catal*., **2019**, *361*(12), 2737-803.
8. Çevik, Ua.; Levent, S.; Özkay, Y.; Karaca, H.; Cantürk, Z.; Tunali, Y.; Uçucu, Ü. *Eur. Int. J. Sci. Technol*., **2016**, *5*, 59-76.
9. Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.,* **2004**, *47*(25), 6311-25.
10. Wittine, K.; Babic, M. S.; Maku, D.; Plavec, J.; Pavelic, S.K.; Sedic, M.; Pavelic, K.; Leyssen, P.; Neyts, J.; Balzarini, *J. Biorg. Med. Chem*., **2012**, *20*, 3675–3685.
11. Ganguly, S.; Vithlani, V. V.; Kesharwani, A. K.; Kuhu, R.; Baskar, L.; Mitramazumder, P.; Sharon, A.; Dev, A. *Acta Pharm*., **2011**, *61*, 187–201.
12. Li, M. M.; Huang, H. Pu. Y.; Tian, W.; Deng, Y.; Lu, *J. Eur. J. Med. Chem*., **2022**, *7*, 114739.
13. Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-Aizari, F. A.; Ansar M. H. *Molecules*., **2018**, *23*(1), 134.

14. Pawar, D.C.; Gaikwad, S.V.; Kamble, S.S.; Gavhane, P.D.; Gaikwad, M.V.; Dawane, B.S. *Chem. Methodol.*, **2022**, *6*, 677-690.
15. Mogle, P.P.; Meshram, R.J.; Hese, S.V.; Kamble, R.D.; Kamble, S.S.; Gacche, R.N.; Dawane, B. S. *Med Chem Comm.*, **2016**, *7*(7), 1405-1420.
16. El-Shahat, M.; El-Sofany, W. I.; Soliman, A. G.; Hasanin, M. *J. Mol. Struct.*, **2022**, *1250*, 131727.
17. Kalaria, P. N.; Satasia, S. P.; Raval, D. K. *New J. Chem.*, **2014**, *38*(7), 2902-10.
18. Kalaria, P. N.; Satasia, S. P.; Raval, D. K. *New J. Chem.*, **2014**, *38*(4), 1512-21.
19. Zhang, X. Li. X.; Allan, G. F.; Sbriscia, T. Linton, O.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.*, **2007**, *17*(2), 439-43.
20. Moydeen, M.; Al-Deyab, S. S.; Kumar, R. S.; Idhayadhulla, A. *J. Heterocycl. Chem.*, **2017**, *54*(6), 3208-19.
21. Brullo, C.; Massa, M.; Rapetti, F.; Alfei, S.; Bertolotto, M. B; Montecucco, F.; Signorello, M. G.; Bruno, O. *Molecules.*, **2020**, *25*(4), 899.
22. Zhang, X.; Allan, G. F.; Tannenbaum, P.; Sbriscia, T.; Linton, O.; Lai, M. T.; Haynes-Johnson, D.; Bhattacharjee, S.; Lundeen, S. G.; Sui, Z. *J. Steroid Biochem. Mol. Biol.*, **2013**, *134*, 51-8.
23. Zhang, X. Li. X.; Allan, G. F.; Sbriscia, T.; Linton, O.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.*, **2007**, *17*(2), 439-43.
24. Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A. ARKIVOC: *Online J. Org. Chem.*, **2011**, *i*, 196-245.
25. Abdelhamid, I. A.; Hawass, M. A.; Sanad, S. M.; Elwahy, A. H. *ARKIVOC: Online J. Org. Chem.* **2021**, *ix*, 42-74.
26. Patil, S. V.; Gaikwad, N. D.; Bobade, V. D. *J. Chem. Res.*, **2012**, *36*(10), 590-4.
27. Malysheva, S. F.; Kuimov, V. A.; Belogorlova, N. A.; Gusarova, N. K.; Taydakov, I. V.; Albanov, A. I.; Eremenko, I. L.; Trofimov, B. A. *Mendeleev Commun.*, **2019**, *29*(6), 683-5.
28. Mamidala, S.; Aravilli, R. K.; Ramesh, G.; Khajavali, S.; Chedupaka, R.; Manga, V.; Vedula, R. R. *J. Mol. Struct.*, **2021**, *1236*, 130356.
29. Wazalwar, S.S.; Banpurkar, A.R.; Perdih, F. *J. Mol. Struct.*, **2017**, *1150*, 258-67.
30. Patil, S. V.; Gaikwad, N. D.; Bobade, V. D. *J. Chem. Res.*, **2012**, *36*(10), 590-4.
31. Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.,* **2009**, *15*(6), 1300-8.
32. Moonmun, D.; Majumder, R.; Lopamudra, A. *Indian J. Pharm. Sci.*, **2017**, *79*(1), 79-90.