Vidyabharati International Interdisciplinary Research Journal ISSN 2319-4979

Facile Synthesis and Antimicrobial Assessment of Novel Heterocyclic Derivatives via Substituted Diketone Precursors

Chandrakant U Dhanwad
PG & Research Department of Chemistry,M.S.P.and K.PT.CollgeManora, Washim,Maharashtra,India

Sopan D Ingole
PG & Research Department of Chemistry,M.S.P.and K.PT.CollgeManora, Washim,Maharashtra,India

Gangadhar S Bhopalkar
Indira Gandhi Sr.College Cidco Nande Department of Chemistry, Nanded, Maharashtra, India
cdhanwad@gmail.com

Abstract
In the present work a some new heterocyclic compound has been prepared by using Substituted 1,2 & 1,3-diketones with a amine group present compounds. Since the unsymmetrical 1,2, and 1,3-diketone moiety may have up to three nucleophilic and two electrophilic centers with negligible reactivity differences, selectively performing chemical transformations with substrate at a single centers appears to be very difficult. Because of their closely spaced, highly reactive carbonyl groups, Substituted1,2- diketone and 1,3- diketone molecules have a variety of biological functions.
Keywords: *1, 2& 1, 3-diketones, 2-Mercaptobenzimidazole,1-Amino-2-naphthol-4-sulfonic acid,2-aminothiophenol, acetamide, orthophenylenediamine,antimicrobial activity*

Introduction:

Heterocyclic compounds are an important class of organic molecules because of their wide applications in medicinal, pharmaceutical, and material sciences [1]. Nitrogen-containing heterocycles are particularly important because many biologically active compounds contain nitrogen heterocyclic frameworks [2].Diketones are versatile organic compounds that are widely used as building blocks in organic synthesis [3]. Among them, 1,2-diketones are particularly useful because the two adjacent carbonyl groups can readily undergo condensation and cyclization reactions with different nucleophiles [4]. They have been successfully employed for the synthesis of imidazoles, pyrazines, oxazoles, triazines, and other heterocyclic compounds [5].Several synthetic methods have been reported for the preparation of symmetrical and unsymmetrical 1,2-diketones [6]. Transition-metal-catalyzed approaches have provided efficient methods for the synthesis of structurally diverse diketones [7]. Green and visible-light-assisted methods have also been developed for the preparation of substituted 1,2-diketones under relatively mild conditions [8]. Heteroaryl 1,2-diketones have attracted additional interest because of their structural diversity and synthetic applications [9].

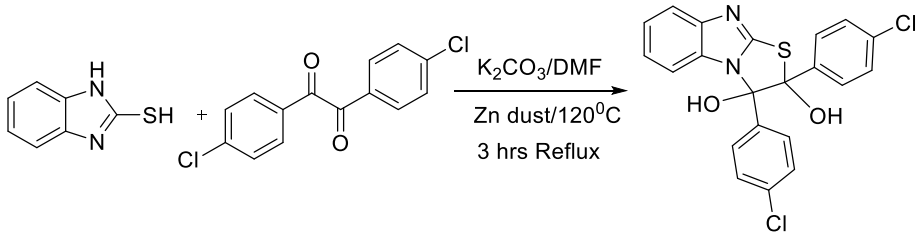
Diketones are also valuable precursors for biologically important nitrogen-containing heterocycles. Various substituted imidazoles and triazines have been synthesized using diketone-based reactions [10]. Copper-catalyzed reactions of diketones have also been used for the preparation of imidazoles, oxazoles, and diazepine derivatives [11]. Green one-pot methods provide an attractive approach for the synthesis of substituted heterocyclic compounds [12].

Therefore, substituted diketones represent useful starting materials for the development of new heterocyclic molecules. In the present work, substituted diketone precursors were used for the synthesis of novel heterocyclic derivatives. The synthesized compounds were characterized by spectroscopic techniques and evaluated for their antimicrobial activity. The study may provide new heterocyclic compounds with potential biological applications [13].

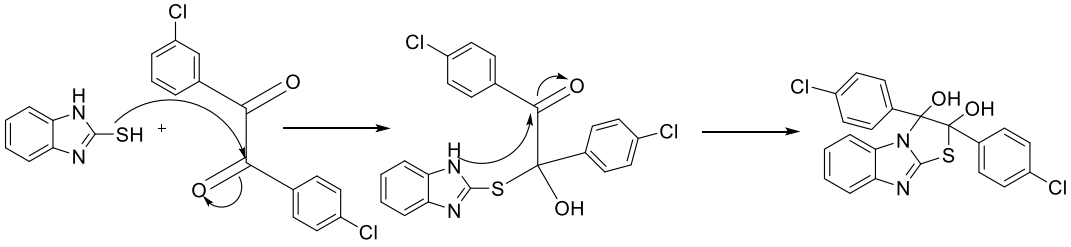
Methods Of Sythesis Of Heterocylic Compounds

2-bis(4-chlorophenyl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole-1,2-diol (Ia)

In reaction of 1.05gm of Substituted benzil (0.005 mol), 0.75gm of 2-Mercaptobenzimidazole (0.005 mol), were taken in 100 ml round bottom flask with 15ml DMF in presence K_2CO_3 as a base & Zn dust was added as a catalyst keep on reflux for about 3hr, the reaction mixture pouredin crushed ice then solid product is formed ,recrystallization the product by ethyl alcohol and checking aTLC in 5:5EtOAc /n-hexane.



Mechanism:-

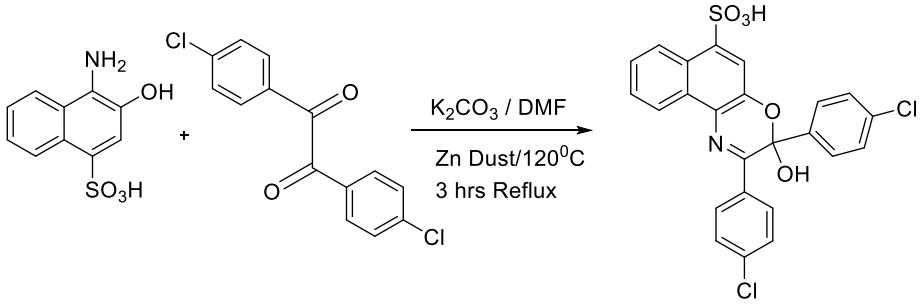


Spectral Analysis:-

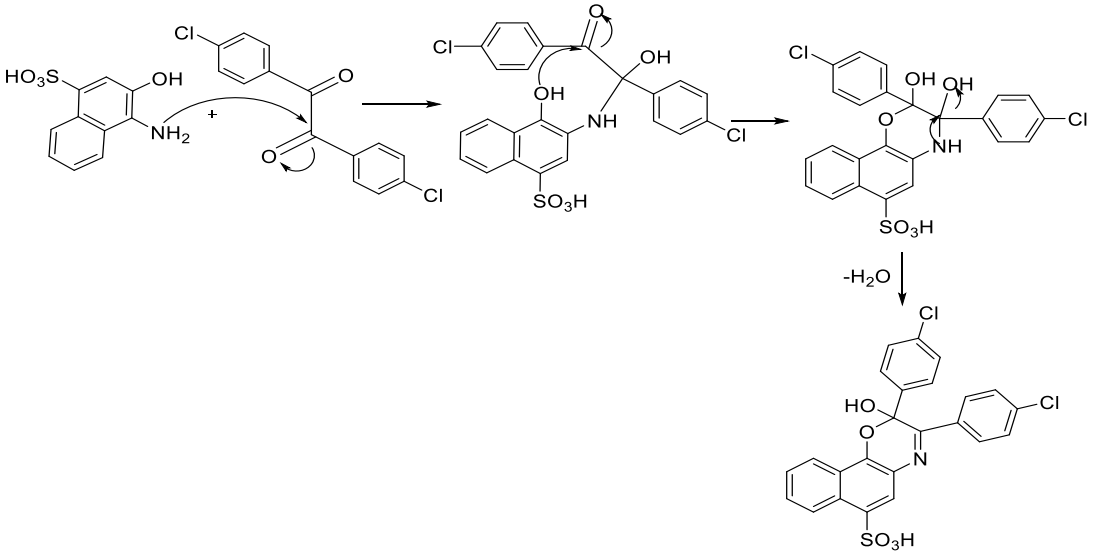
Yellowish solid,$C_{21}H_{14}N_2O_2SCl_2$ mp- 144-147^{0}C , yield 70%,^{1}H NMR (400 MHz,$CDCl_3$ δppm),δ 7.38-7.52 (d-9H-CH) 7.29 (dd-H-CH), 7.20 (dd-H-CH), , 5.32 (-OH),IR (cm^{-1})- 3726 (-OH) , 3000 (Ar-C=C-H) , 2100 (C=N) 680 (C-S), 1500 (C=C), 1400 (C-C)

2,3-bis(4-chlorophenyl)-3-hydroxy-3H-naphtho[2,1-b][1,4]oxazine-6-sulfonic acid. (Ib)

1.05 gm of Substituted benzil (0.005 mol), 1.15 gm of 1-Amino-2-naphthol-4-sulfonic Acid (0.005 mol),were taken in 100 ml RBF with15 ml DMF in presence K_2CO_3 base &Zndust was added as a catalyst keep onreflux,3hr poured the mixture in crushed ice,then acidified with conc.H_2SO_4 ,recrystallization,take TLC in 5:5(EtOAc/n-hexane)



Mechanism:-

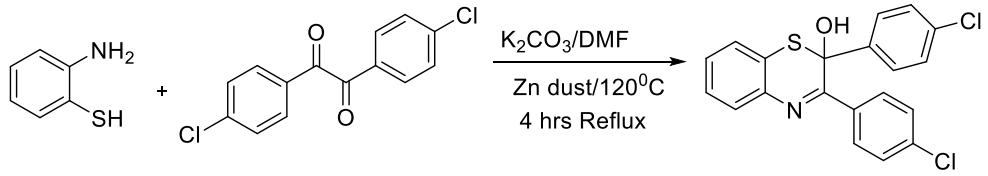


Spectral Analysis:-

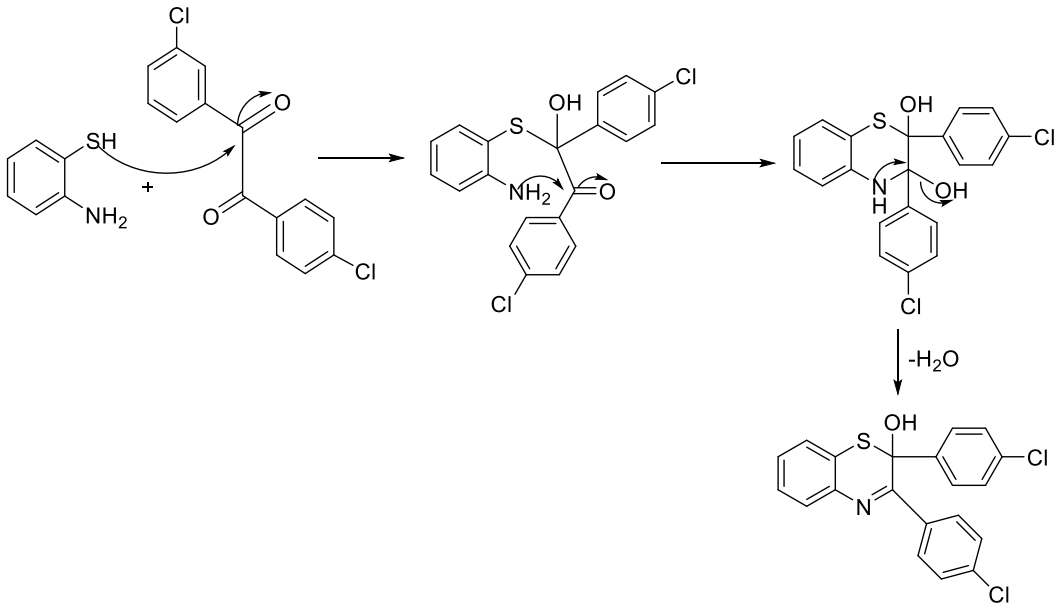
blacksolid,mp- 155-157^{0}C,$C_{24}H_{15}O_5NSCl_2$,yield 56%,^{1}H NMR (400 MHz,$CDCl_3$ δppm)6.95–7.10(m-4H-Ar),7.15(d-2H-Ar),7.45(d-2H-Ar),7.82(dd-1H-Ar),8.10(d-1H-Ar)10.45(s-OH),IR(cm^{-1})-3600(-OH),3060(Ar-C=C-H),1400(-C-C-)1500(-C=C-),1209(-C-O),2150(-C=N)

Synt2,3-bis(4-chlorophenyl)-2H-benzo[b][1,4]thiazin-2-ol).(Ic)

Take 1.05 g of Substituted benzil (0.005 mol), 0.6 g of 2-aminothiophenol (0.005 mol), and place them in 100 ml of RBF with 15 ml of DMF in the presence of anhydrous K_2CO_3 as a base. Add Zn dast a catalyst and let the mixture reflux for 4 hours. Pour the mixture into crushed ice, acidify it with diluted HCL, recrystallize it with ethanol, and take TLC in a solvent EtOAc and n-hexane in a ratio 5:5



Mechanism:-

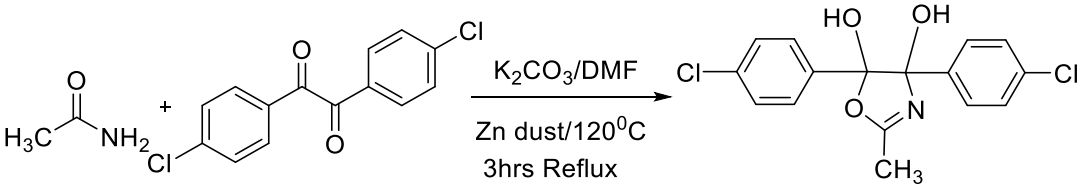


Spectral Analysis:-

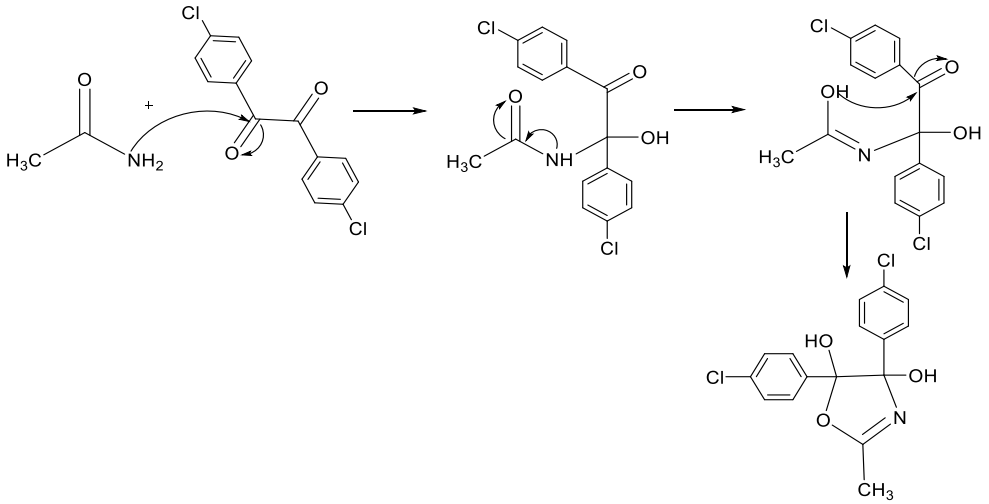
blacksolid,mp- 98-100^{0}C,$C_{20}H_{13}ONSCl_2$, yield 60%,^{1}H NMR (400 MHz,$CDCl_3$ δppm)5.10(s-1H-OH) ,6.85-7.02(m-4H-Ar),7.20(d-2H-Ar),7.48(dd-2H-Ar),7.70-7.85(m-2H-Ar),IR(cm^{-1})3500(-OH),2200(-C=N),3000(-C=CH-),1577(-C=C-),1448(Ar-C-C),679(-C-S).

4,5-bis(4-chlorophenyl)-2-methyl-4,5-dihydrooxazole-4,5-diol(Id)

Take 1.05 g of benzil (0.005 mol), 0.3 g of acetamide (0.005 mol), and place them in 100 ml of RBF with 15 ml of DMF in the presence of anhydrous K_2CO_3 as a base. Add Zn dust as a catalyst and let the mixture reflux for 3 hours. Pour the mixture into crushed ice, acidify it with diluted HCL, recrystallize it with ethanol, and take TLC in a solvent EtOAc and n-hexane in a ratio 5:5



Mechanism:-

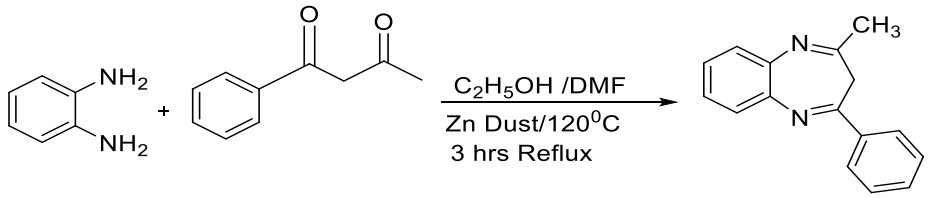


Spectral Analysis:-

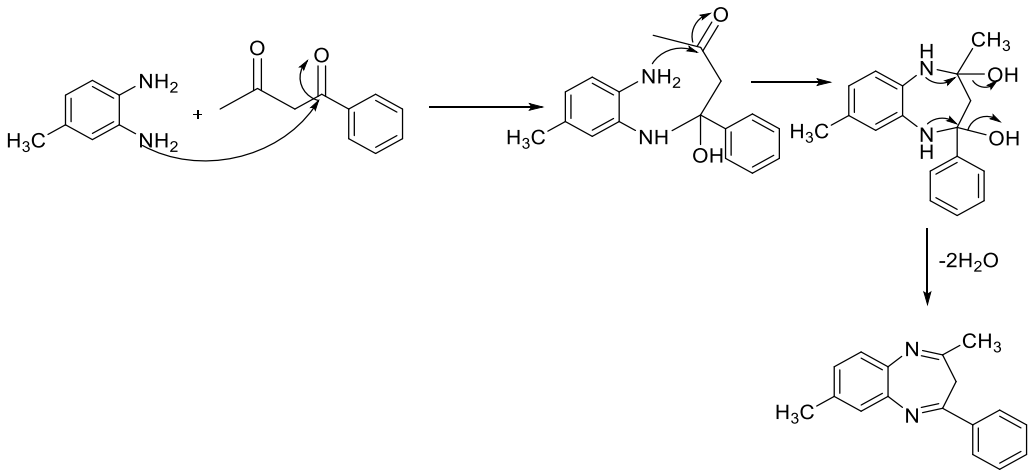
Yellowsolid,mp- 92-95^{0}C,$C_{16}H_{13}O_3NCl_2$, yield 70%, ^{1}H NMR(DMSO d_6δppm) 2.85(s-3H-CH_3),5.45(s-IH-OH),6.75-6.90(m-Ar),7.12(dd-2H-Ar),7.30-7.45(m-4H-Ar)9.90(s-OH),IR(cm^{-1}) δ 3600(-OH),3036(-C=CH-),2900(-C-CH-), 2200(-C=N),1172(-C-O).

2,7-dimethyl-4-phenyl-3H-benzo[b][1,4]diazepine.

Take 0.95gm of ortho phenylenediamine (0.005mol), 0.81benzoylacetone(0.005mol) were taken in100 ml RBF with 15 ml EtOH in presence K_2CO_3base & Zn dust was added as a catalyst keep on reflux ,3hr poured the mixture in crushed ice,then acidified with conc.H_2SO_4,recrystallization,takeTLCin 5:5(EtOAc/n-hexane)



Mechanism:-



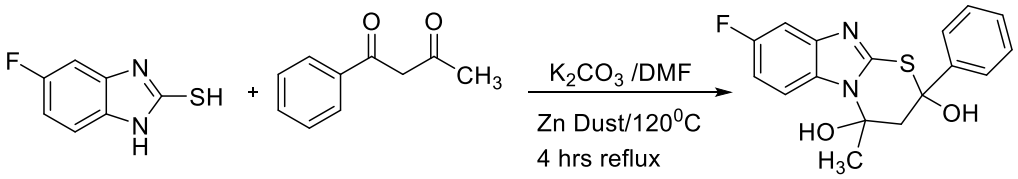
Spectral Analysis:-

Yellowsolid,mp- 125-128^{0}C, $C_{15}H_{13}N_2$, yield 65%,^{1}H NMR(DMSO d_6δppm) δ2.48(s-3H-CH_3),2.62(s-3H-CH_3),7.22-7.38(m-5H-Ar),7.50-7.68(m-3H-Ar) IR(cm^{-1}) 2929(Ar-C=C-H),2127(C=N),1500(C=C),3730(-CH_3)

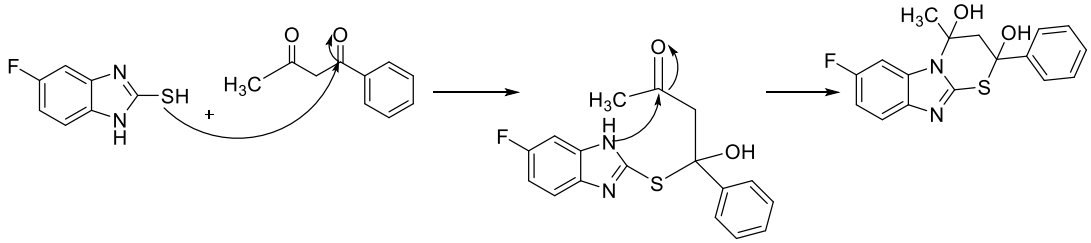
8-fluoro-4-methyl-2-phenyl-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine-2,4-diol

Take 0.8 g of benzoylacetone (0.005mol), 0.7 g of 5-Floro-2-mercaptobenzimidazole (0.005mol), and place them in 100 ml of RBF with 15 ml of DMF in the presence of anhydrous K_2CO_3 as a base. Add Zn dust as a catalyst and let the mixture reflux for 4 hours. Pour the

mixture into crushed ice, acidify it with diluted HCL, recrystallize it with ethanol, and take TLC in a solvent EtOAc and n-hexane in a ratio 5:5



Mechanism:-



Spectral Analysis:-Brownsolid,mp- 110-113^{0}C,$C_{17}H_{16}O_2N_2S$, yield 45%,^{1}H NMR(DMSO d_6δppm)δ1.78(s-3H-CH_3) 5.25(s-1H-OH),6.78(ddd-IH-Ar),7.04(dd-1H-Ar),7.22-7.48(m-6H-Ar)IR(cm^{-1})3637(OH),3789(CH),3000(C=CH),2358(C=N),1502(C=C),1442(C-C),630(C-S).

Microbial Activity:-

Sr. No.	Compounds	Gram positive Zone of Inhibition in (mm)	Gram negative Zone of Inhibition in (mm)
		S.aureus	***E.Coli***
1	Ia	15	15
2	Ib	NA	NA
3	Ic	15	NA
4	Id	NA	14
5	Ie	17	NA
6	If	NA	NA
7	**Streptomycin**	20	22

- The antimicrobial activity of the synthesized compounds (Scheme-Ia, Scheme-Ib, Scheme-Ic, and Scheme-Id) was evaluated by the **agar diffusion method** against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. The antibacterial efficacy was assessed by measuring the **zone of inhibition (mm)** and compared with the standard antibiotic **streptomycin**.
- Scheme-Ia exhibited **moderate antibacterial activity** against both *S. aureus* and *E. coli*, showing inhibition zones of 15 mm each, indicating a **broad-spectrum nature** of this compound.
- Scheme-Ic showed activity only against *S. aureus* with a zone of inhibition of 15 mm, while no activity was observed against *E. coli*, suggesting **selective Gram-positive antibacterial activity**.
- Scheme-Id demonstrated antibacterial activity exclusively against *E. coli* with a zone of inhibition of 14 mm and showed no effect against *S. aureus*, indicating **selectivity toward Gram-negative bacteria**. Scheme-Ie exhibited the **highest activity among the synthesized compounds against** *S. aureus* with a zone of inhibition of 17 mm, but it was inactive against *E. coli*.
- Scheme-Ib and Scheme-If no activity observed against *S.aureus*and *E.coli* .
- The standard drug showed significantly higher zones of inhibition (20 mm against *S. aureus* and 22 mm against *E. coli*), confirming its **superior broad-spectrum antibacterial efficacy**. Although the synthesized compounds displayed lower activity compared to streptomycin, some compounds demonstrated **promising selective antibacterial properties**, which may be further optimized for enhanced antimicrobial potential.

Conclusion

Heterocyclic compounds play an important role in drug discovery because of their diverse biological activities. Substituted 1,2- and 1,3-diketones are versatile starting materials for the synthesis of various heterocyclic compounds through condensation and cyclization reactions. Their reactions with nitrogen, sulfur, and oxygen nucleophiles provide heterocyclic scaffolds with different ring sizes and substitution patterns, which can influence their physicochemical and biological properties.The synthesis of heterocyclic compounds from 1,2- and 1,3-diketones is an active area of organic chemistry. Recent research focuses on green and sustainable catalytic approaches, including phase-transfer catalysis, supported metal catalysts, and N-heterocyclic carbene catalysis. These methods facilitate the preparation of complex heterocyclic structures with improved efficiency and reduced waste.Biological evaluation of synthesized compounds has shown moderate to selective antibacterial activity. Some derivatives exhibit broad-spectrum activity, whereas others show better activity against Gram-positive bacteria. Although their activity is generally moderate compared with streptomycin, selected compounds show promising antibacterial potential and may serve as lead structures for further optimization.

References

1. Bouchakour, M., Daaou, M., & Duguet, N. (2021). Synthesis of imidazoles from fatty 1, 2-diketones. European Journal of Organic Chemistry, 2021(11), 1647-1652. https://doi.org/10.1002/ejoc.202100053

2. Kaur, N., Bhardwaj, P., & Gupta, M. (2021). Recent developments in the synthesis of five- and six-membered N-heterocycles from dicarbonyl compounds. *Current Organic Chemistry*, *25*(22), 2765-2790. https://doi.org/10.2174/1385272825666210812102416

3. Ghosh, P., & Chakraborty, R. R. (2017). Clean and Green Approach for One-pot Synthesis of Pyrazines from Ethylenediamine and 1, 2-Diketone or Its Analogues Under Neat Reaction Condition. *Letters in Organic Chemistry*, *14*(8), 566-570. https://doi.org/10.2174/1570178614666170609072519

4. Lechel, T., Gerhard, M., Trawny, D., Brusilowskij, B., Schefzig, L., Zimmer, R., ... & Reissig, H. U. (2011). Synthesis of 5-Acetyloxazoles and 1, 2-Diketones from β-Alkoxy-β-ketoenamides and Their Subsequent Transformations. *Chemistry–A European Journal*, *17*(27), 7480-7491. https://doi.org/10.1002/chem.201100382

5. Walsh, C. J., & Mandal, B. K. (1999). Improved synthesis of unsymmetrical, heteroaromatic 1, 2-diketones and the synthesis of carbazole ring substituted tetraaryl cyclopentadieneones. *The Journal of Organic Chemistry*, *64*(16), 6102-6105. https://doi.org/10.1021/jo9904213

6. Sharma, Y., & Ansari, A. (2022). Diketones as building block in organic synthesis with versatile applications and medicinal properties. *Materials Today: Proceedings*. https://doi.org/10.1016/j.matpr.2022.12.015

7. Wehrle, R. J., Rosen, A., Nguyen, T. V., Koons, K., Jump, E., Bullard, M., ... & Ma, L. (2022). Investigation on the synthesis, application and structural features of heteroaryl 1, 2-diketones. ACS omega, 7(30), 26650-26660. https://doi.org/10.1021/acsomega.2c02914

8. Kilic, H., Aydin, O., Bayindir, S., & Saracoglu, N. (2016). Condensation of Indoline with Some 1, 2-and 1, 3-Diketones. *Journal of Heterocyclic Chemistry*, *53*(6), 2096-2101. https://doi.org/10.1002/jhet.2580

9. Kumar, Y., Jaiswal, Y., & Kumar, A. (2018). Two-Step One-Pot Synthesis of Unsymmetrical (Hetero) Aryl 1, 2-Diketones by Addition-Oxygenation of Potassium Aryltrifluoroborates to (Hetero) Arylacetonitriles. *European Journal of Organic Chemistry*, *2018*(4), 494-505. https://doi.org/10.1002/ejoc.201701625

10. Kumar, A., & Sridharan, V. (2021). Transition Metal-Catalyzed Synthesis of 1, 2-Diketones: An Overview. *Asian Journal of Organic Chemistry*, *10*(7), 1619-1637. https://doi.org/10.1002/ajoc.202100307

11. Yugandar, S., Konda, S., Parameshwarappa, G., & Ila, H. (2016). One-pot synthesis of 2, 4, 5-trisubstituted imidazoles via [2+ 2+ 1] cycloannulation of 1, 3-bishet (aryl)-monothio-1,

3-diketones, α-substituted methylamines and sodium nitrite through α-nitrosation of enaminones. *The Journal of Organic Chemistry*, *81*(13), 5606-5622. https://doi.org/10.1021/acs.joc.6b00938

12. Zhao, Z., Leister, W. H., Strauss, K. A., Wisnoski, D. D., & Lindsley, C. W. (2003). Broadening the scope of 1, 2, 4-triazine synthesis by the application of microwave technology. *Tetrahedron letters*, *44*(6), 1123-1127. https://doi.org/10.1016/S0040-4039(02)02845-9

13. Sutar, S. M., Prabhala, P., Savanur, H. M., Kalkhambkar, R. G., Aridoss, G., & Laali, K. K. (2021). Copper-Catalyzed Coupling of Arylethynes and Aryltriazenes to Access Libraries of 1, 2-Diketones and Their Efficacy in Synthesis of Triaryloxazoles, Imidazoles and Diaryl-Diazepines. *ChemistrySelect*, *6*(19), 4741-4749. https://doi.org/10.1002/slct.202100505

14. Neerathilingam, N., Prasanth, K., & Anandhan, R. (2022). Substituent-controlled selective synthesis of 1, 2-diketones and internal alkynes from terminal alkynes and arylboronic acids via α-stilbene radicals obtained from heteroleptic Cu (I) complexes under visible light. *Green Chemistry*, *24*(22), 8685-8690. https://doi.org/10.1039/d2gc03011j

15. Bansal, R., Soni, P. K., & Halve, A. K. (2018). Green synthesis of 1, 2, 4, 5-tetrasubstituted and 2, 4, 5-trisubstituted imidazole derivatives involving one-pot multicomponent reaction. *Journal of Heterocyclic Chemistry*, *55*(6), 1308-1312. https://doi.org/10.1002/jhet.3160