International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Synthesis of Schiff's Bases of Dihydropyrimidones by Organic Red Clay as a Mild Catalyst Under Microwave Irradiation

S. P. Babar[1]
[1]Department of Chemistry, University of Mumbai, Ramsheth Thakur College of Commerce & Science, Kharghar, Navi Mumbai, Maharashtra, India-410210

Abstract— *In the present study, we have developed Schiff' bases of dihydropyrimidones (DHPMs) with aniline by using organic red clay as mild catalyst under solvent-free condition. Compounds S1a-S1f obtained in almost good yield. A simple multicomponent one pot method was developed for synthesis of DHPMs by combining substituted aromatic aldehydes, ethyl acetoacetate/ acetyl acetone with urea/thiourea in the presence of red clay as a catalyst by microwave irradiation technique under solvent-free condition. The compounds were obtained in good yield. Then these were combined with aniline to form their Schiff's bases*.

Keywords— *Schiff's base, Dihydropyrimidones,Organic Red Clay,Solvent-free,Microwave irradiation*

I. INTRODUCTION

Pyrimidines are one of the aromatic heterocyclic compounds containing the nitrogen atoms at positions 1 and 3 in a six member unsaturated ring. [1] 3,4- Dihydropyrimidone is an example of class of compounds exhibiting pharmacological activity which contains pyrimidine moiety. Schiff bases containing imines or azomethine are present in various natural, natural-derived and non-natural compounds. Imine group present in schiff bases which are most widely used organic compounds has been shown to be critical to their biological activities. Schiff bases still remains as one of the most versatile class of compounds against microbes [2] and therefore, are useful substructures for further molecular exploration.[3] Heterogenous catalyst such as natural clays with the microwave irradiation provides the more efficient and greener process involving low cost, easily available, easy to handle, efficient and recyclable catalysts.

With the application of microwave irradiation, chemical transformations that took hours or even days to complete can now be accomplished in minutes. The use of microwave energy for performing synthesis has many advantage such as increased reaction rates, selectivity of reaction, enhanced yields and cleaner chemistries. Microwave irradiation of organic reactions accelerates the reaction towards a variety of synthetic transformations, solvent-less procedures without the use of supporting reagents and hence eco-friendly.[4] According to literature search it reveals that less attention has been given on the synthesis of Schiff bases derived from dihydropyrimidone heterocycle. [5]

Here first we prepared DHPMs derivatives by multi-component one pot biginelli synthesis under microwave irradiation by red natural clay as a catalyst in solvent-free condition. [6] Microwave irradiation technique under solvent free conditions are extremely useful in offering reduced pollution compared to the traditional organic synthesis involving heating by conventional methods.

When primary amines react with carbonyl compounds such as aldehydes and ketones by the loss of a water molecule Schiff bases are formed. [7] Here the carbonyl group of DHPMs derivatives reacts with primary amine moiety of aniline and forms Schiff bases. [8] A wide variety of intresting biological activities such as anticancer [9] anti-viral [10] antitumor [11, 12] anti-inflammatory [13, 14] antimicrobial [14, 15, 16] activities are observed in pyrimidine derivatives and heterocyclic annulated pyrimidines. From literature survery it was found that Schiff bases derived from various heterocyclic possess cytotoxic [17, 18] anticonvulsant [19, 20] antiproliferative [21, 22] antimicrobial [23, 24] anticancer [25] antifungal [26, 27] activities.

Schiff base formation is two step reaction first is addition and then elimination step. The amines are basic compounds which gets protonated and become non-nucleophile, equilibrium is pulled to the left and carbinolamine formation cannot occur. [28] Therefore, many Schiff bases synthesis are best carried out at mild acidic pH [29] By taking account of this we carried out the reaction by using red clay which is mild acidic in nature. [6] Variety of reactions can be carried out by using clay as a catalyst. Iron rich clays exhibit impressive and varied activity. The mechanism of reactions by using clay as catalyst is not fully known but as from the literature survey most of clay chemistry is driven by lattice energy and its energy storage, redistribution and conversion, and release by clays. Other applications of clay chemistry reveal by such studies. [30]

II. MATERIAL AND METHODS

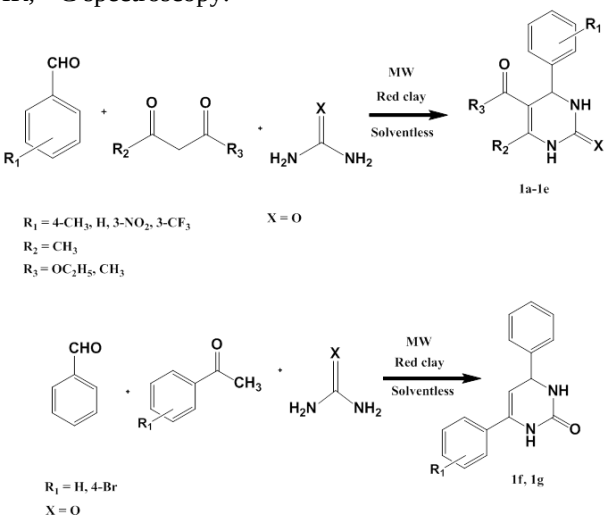
All the chemicals were obtained from SD fine chemicals Ltd and the solvents were of laboratory grade. Each reaction was monitored by TLC by using pet ether: ethyl acetate (7:3) solvent system. Precoated TLC plates (Silica gel GF254) were obtained from E. Merck. All the synthesized compounds were purified by recrystallisation. Melting points were noted on open capillary and they are uncorrected.

S. P. Babar, "Synthesis of Schiff's Bases of Dihydropyrimidones by Organic Red Clay as a Mild Catalyst Under Microwave Irradiation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 9-12, 2022.

International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

General procedure for 3, 4-dihydropyrimidone derivative synthesis:

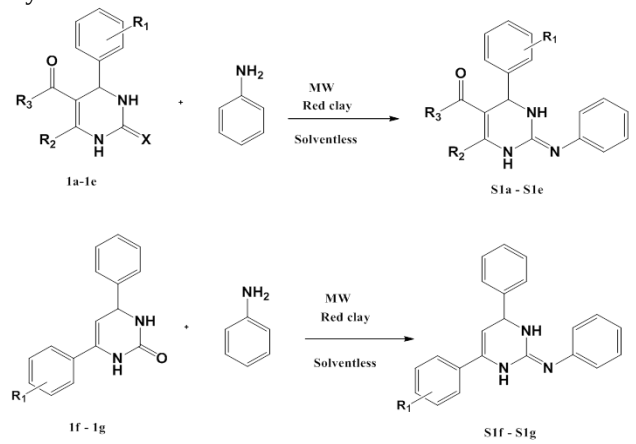
Scheme 1: A mixture of appropriate aromatic aldehyde (0.01 mol), acetyl acetone or ethyl aceto acetate (0.01 mol, 1.3 g)/ substituted acetophenones (0.01mol), urea (0.015 mol, 0.9 g) / thiourea (0.01 mol, 0.76 g) and red clay (a) /white clay (b) / black clay (c) as a catalyst (0.2 g) was subjected to microwave irradiation for appropriate time without solvent. Cool the reaction mixture and quenched with crushed ice. The solid separated out was filtered, washed with cold water, dried and recrystallized from 95% ethanol to give pure products (1a-1g). The spent catalysts were collected by filtration and then washed with hot ethanol. Products are characterized by IR, ^{1}H NMR, ^{13}C spectroscopy.



Scheme 1

General procedure for Schiff bases of 3, 4-dihydropyrimidone derivatives with aniline:

Scheme 2: A mixture of (0.001mol) DHPMs derivatives (1a-1g) and 0.2g red clay as a catalyst grinded together. Then added (0.01mol) aniline into it. This reaction mixture mixed thoroughly in a beaker and was irradiated in microwave oven. The reaction was monitored by TLC. After completion of reaction, cool the reaction mixture and recrystallized it with 95% ethanol. Filtered it and collected separated catalyst. A precipitate was formed which was collected by filtration, and recrystallized from ethanol.



Scheme 2

III. RESULT

3, 4-dihydropyrimidin-2(1H) – one derivatives (1a-1e) and 4, 6-diphenyl - 3, 4-dihydropyrimidin-2(1H) – one derivatives (1f-1g) were synthesized as shown in Scheme 1 by method reported [6]. Schiff bases were prepared from dihydropyrimidone derivatives by reacting with the aniline and at power 400w. All the Schiff base compounds were characterized by physicochemical techniques like melting point and spectral technique like FT-IR, ^{1}H and ^{13}C NMR spectroscopy.

3. 1 Physical properties of prepared Schiff's bases.

Physical properties of Schiff's bases of 3, 4 dihydropyrimidin-2(1H) – one derivatives and 4, 6-diphenyl - 3, 4-dihydropyrimidin-2(1H) – one derivatives including melting point, yield and reaction time is given in Table I and Table II.

TABLE I. Microwave assisted solvent free synthesis of Schiff bases of 3, 4-dihydropyrimidone derivatives by red clay as a catalyst (0.2g)

Compound Names	R_1	R_2	R_3	Reaction time	% Yield	M.P. (˚C)
S1a	4-CH_3	CH_3	OC_2H_5	4 min	79.53	198
S1b	H	CH_3	OC_2H_5	7 min	80.76	228
S1c	H	CH_3	CH_3	7 min	65.84	238
S1d	3-NO_2	CH_3	OC_2H_5	4 min	70.06	210
S1e	3-CF_3	CH_3	OC_2H_5	6 min	78.00	160

TABLE II. Microwave assisted solvent-free synthesis of Schiff bases of 4, 6-diphenyl - 3, 4-dihydropyrimidin-2(1H) - one derivatives by red clay as a catalyst (0.2g)

Compound Names	R_1	Reaction time (min)	% Yield	M.P. (℃)
S1f	H	7	81.12	106
S1g	4-Br	4	37.12	182

Spectral analysis of 1a-1e and 1f-1g (Scheme 1) compounds were given below.

1. 5-(Ethoxycarbonyl)-4-(4-methylphenyl)-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)- one (1a):
   IR (KBr): 3260, 3129, 1709, 1677, 1631 cm^{-1}
   ^{1}H NMR (DMSO- d6): δ 9.13 (s, 1H), 7.66 (s, 1H), 7.11 (m, 4H), 5.12 (d, 1H), 4.01(q, 2H), 2.50 (s, 3H), 2.25 (s,3H), 1.11 (t, 3H)
   ^{13}C NMR: δ 165.3, 152.1, 148.0, 141.9, 136.2, 128.7, 126.1, 99.4, 59.06, 53.6, 20.6, 17.7, 14.0
2. 5-(Ethoxycarbonyl)-6-methyl- 4-(phenyl)-3,4-dihydropyrimidin-2(1H)- one (1b):
   IR (KBr): 3242, 3117, 1727, 1706, 1645 cm^{-1}
   ^{1}H NMR (DMSO - d6): δ 9.21 (s,1H), 7.75 (s, 1H), 7.22-7.32 (m, 5H), 5.17 (d, 1H), 4.01 (q, 2H), 2.25 (s ,3H), 1.11 (t, 3H)
   ^{13}C NMR: 165.2, 152.1, 148.3, 144.8, 127.2, 128.3, 126.2, 99.2, 59.1, 53.9, 17.7, 14.01
3. 5-(acetyl)-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H) - one (1c):
   IR (KBr): 3260, 1703, 1677, 1602 cm^{-1}
   ^{1}H NMR (DMSO- d6): δ 9.20 (s, 1H), 7.85 (s, 1H), 7.27-7.33 (m, 5H), 5.28(d, 1H), 2.30 (s, 3H), 2.11 (s, 3H)
   ^{13}C NMR: 194.2, 152.1, 148.0, 144.2, 128.4, 127.3, 126.4, 109.5, 53.8, 30.2, 18.8

S. P. Babar, "Synthesis of Schiff's Bases of Dihydropyrimidones by Organic Red Clay as a Mild Catalyst Under Microwave Irradiation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 9-12, 2022.

4. 5-(Ethoxycarbonyl)-6-methyl- 4-(m-nitro phenyl)-3,4-dihydropyrimidin-2(1H)- one (1d):
   IR (KBr): 3300, 3115, 1703, 1685, 1631 cm^{-1}
   ^1H NMR (DMSO-d6): δ 9.43 (s, 1H), 8.45 (s, 1H), 7.59-7.62 (m, 2H), 8.07-8.15 (m, 2H), 5.29 (d, 1H), 4.2 (q, 2H), 2.26 (s, 3H), 1.29(t, 3H)
   ^{13}C NMR: 167.2, 147.7, 147.3, 144.2, 150.2, 133.0, 129.4, 121.9, 120.7, 106.4, 61.7, 52.2, 17.6, 14.0
5. Ethyl -6-methyl-2-oxo-4-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1e):
   IR (KBr): 3235, 3100, 1698, 1637 cm^{-1}
   ^1H NMR (DMSO- d6): δ 9.11 (s, 1H), 7.70 (s, 1H), 7.20-7.50 (m, 4H), 5.13 (d, 1H), 4.20 (q, 2H), 2.25 (s, 3H), 1.30 (t, 3H)
   ^{13}C NMR: δ 167.2, 150.2, 147.3, 143.6, 130.8, 130.2, 128.8, 124.9, 124.4, 123.1, 106.4, 61.7, 53.5, 17.6, 14.2
6. 4,6-diphenyl-3,4-dihydropyrimidin-2(1H)- one (1f):
   IR (KBr): 3359, 3150, 1631, 1396 cm^{-1}
   ^1H NMR (DMSO- d6): δ 9.16 (s, 1H), 7.61 (s, 1H), 7.23-7.33 (m, 5H), 5.94 (s, 1H), 7.35- 7.75 (m, 5H)
   ^{13} C NMR: 150.2, 143.3, 138.0, 136.6, 128.6, 128.5, 128.3, 127.9, 126.9, 126.7, 97.5, 55.6
7. 6-(4-bromophenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1g):
   IR (KBr): 1627, 1546, 1399, 1490, 824, 534 cm^{-1}
   ^1H NMR (DMSO- d6): δ 9.15 (s, 1H), 7.60 (s, 1H), 7.21-7.33 (m, 5H), 5.93 (s, 1H), 7.27-7.55 (m, 4H), 5.56 (d, 1H)
   ^{13} C NMR: 150.1, 143.4, 137.0, 136.6, 131.5, 131.4, 128.7, 128.6, 128.5, 128.4, 126.9, 126.7, 122.3, 97.5, 55.6

Schiff bases of all the compounds except the 1g were obtained in good yield (65-81%). Schiff base shown in the aromatic C-H bands has the region 3037-3047 cm^{-1}. The absence of the cyclic C=O stretching band and the presence of bands of C=N in the frequency stretching range between 1620-1587 cm^{-1} shows the Schiff base formation. The formation of Schiff base was also confirmed by the absence of a NH_2 peak and presence of C=N peak.

IV. Conclusion

We have developed a simple new method for the schiff's bases of synthesized DHPMs derivatives by reaction with red organic clay by employing microwave heating. Synthesized different specific DHPMs in solvent-free condition under microwave irradiation resulted in new Schiff's bases S1a-S1f in good yield (65-81%) by using natural red clay as a mild catalyst. All the compounds were characterized by FT-IR spectroscopy, ^1H NMR, ^{13}C NMR spectroscopy.

Acknowedgement

The author is grateful to the SAIF Chandigarh for ^1H and ^{13} C NMR facilities.

References

1. J. H. Tomma, M. S. Khazaal, A. H. Al-Dujaili, "Synthesis and characterization of novel Schiff bases containing pyrimidine unit", *Arabian Journal of Chemistry*, vol. 7 pages 157–163, 2014.
2. C. M. Da silva, D. L. da silva, L.V. Modolo, R. B. Alves, M. A. de Resende, C. V. B & A. de Fa'tima, "Schiff's bases: A shoty review of their antimicrobial activities," *J. Advanced Res*, vol 2, issue 1, 2011.
3. C. A. M. A Huq & S. Fouzia, "Synthesis of novel Schiff bases and evaluation of their antimicrobial activities," *Indian journal of chemistry*, vol 54B, pages 551-555, 2015.
4. V. S. V. Satyanarayana, P. Sreevani, Amaravadi Sivakumar, and V. Vijayakumar, "Synthesis and antimicrobial activity of new Schiff bases containing coumarin moiety and their spectral characterization," *ARKIVOC*, vol (xvii), pages 221-233, 2008.
5. P. Mangaiyarkkarasil and S. Arul Antony, "Synthesis, Characterization And Biological Significance of Some Novel Schiff Base Transition Metal Complexes Derived from 4-Aminoantipyrine And Dihydropyrimidine of Vanillin," *Journal of Applicable Chemistry*, vol 3, issue 3, pages 997-1006, 2014.
6. S. P. Babar, "Synthesis of Dihydropyrimidone Derivatives By Application of Organic Red Clay and their Anti-microbial Screening", *Annals of R.S.C.B.*, Vol. 25, Issue 5, pages 176-183, 2021.
7. H. Schiff, "Mittheilungen aus dem Universitätslaboratorium in Pisa: Eine neue Reihe organischer Basen," *Justus Liebigs Annalen der Chemie*, vol 131, pages 118-119, 1864.
8. Z. Hussain, E. Yousif, A. Ahmed and A. Altaie, "Synthesis and characterization of Schiff's bases of sulfamethoxazole," *Organic and Medicinal Chemistry Letters*, Vol 4(1), pages 1059-1068, 2014.
9. M.M. Kandeel, S.M. Ali, E.K.A. Abed El Ali, M.A. Abdelgawad, P.F. Lamie, "Synthesis and Characterisation of novel Schiff bases containing pyrimidine unit," *Org. Chem. Indian J.*, Vol 9, Issue 3, pages 81-91, 2013.
10. C. R. Petrie, H. B. Cottam, P. A. Mckernan, R. K. Robins and G. R. Revankar, "Synthesis and Biological Activity of 6-Azacadeguomycin and Certain 3,4,6-Trisubstituted Ppyrazolo[3, 4-d]Pyrimidine Ribonucleosides," *Journal of Medicinal Chemistry*, Vol. 28, Issue 8, pages 1010- 1016, 1985.
11. M. N. Nasr, M. M. Gineinah, "Pyrido[2, 3-d]Pyrimidines and Pyrimido[5',4':5,6]Pyrido[2, 3-d]Pyrimidines as New Antiviral Agents: Synthesis and Biological Activity," *Archiv der Pharmazie Chemistry in Life Science*, Vol. 335, Issues 6, pages. 289-295, 2002.
12. P. G Baraldi, M. G Pavani, M. D. Nunez, P. Brigidi, B. Vitali, R. Gambari and R. Romanoli, "Antimicrobial and Antitumor Activity of N-Heteroimmine-1,2,3-Dithiazoles and their Transformation in Triazolo-, Imidazo-, and Pyrazolopirimidines," *Bioorganic & Medicinal Chemistry*, Vol. 10, Issue 2, pages 449-456, 2002.
13. Kandeel, M.M., Ali, S.M., Abed El Ali, E.K.A., Abdelgawad, M.A., Lamie, P.F., "Synthesis and antitumor activity of novel pyrazolo[3,4-d]pyrimidin-4(5h)-one derivatives," *J. Chem. Pharm. Res*. Vol 4 Issue 9, 4097–4106, 2012.
14. Antre, R.V., Cendilkumar, A., Goli, D., Andhale, G.S., Oswal, R.J., "Microwave assisted synthesis of novel pyrazolone derivatives attached to a pyrimidine moiety and evaluation of their anti-inflammatory, analgesic and antipyretic activities", Saudi Pharm. J. Vol 19, Issue 4, pages 233–243, 2011.
15. S.M. Sondhi, M. Johar, S. Rajvanshi, S.G. Dastidar, R. Shukla, R. Raghubir, J.W. Lown, Anticancer, anti-inflammatory and analgesic activity evaluation of heterocyclic compounds synthesized by the reaction of 4-isothiocyanato-4-methylpentan-2-one with substituted o-phenylenediamines, o-diaminopyridine and (Un)substituted o-diaminopyrimidines," *Aust. J. Chem*. Vol 54, pages 69–74, 2001.
16. M.S. Chowdhury, M.M. Matin, M.N. Anwar, "Synthesis and anti-microbial activities of fused pyrimidines: Benzothieno [2, 3-d] imidazo [1, 2-c] pyrimidine," *Chittagong Univ. Stud. Part II Sci*. Vol 21, Issue 2, pages 79–83, 1997.
17. K.S. Parikh, S.P. Vyas, "Synthesis and spectral studies of some novel schiff base derived with pyrimidines," *Pharm. Lett*. Vol 4, Issue 2, pages 638–640, 2012.
18. M.T. Tarafder, A. Kasbollah, N. Saravan, K.A. Crouse, A.M. Ali, O.K. Tin, "Smethyldithiocarbazate and its schiff bases: Evaluation of bondings and biological properties," *J. Biochem. Mol. Biol. Biophs*.,Vol 6, pages 85–91, 2002.
19. H.M. Hassanin, S.M. El-Edfawy, "Novel heterocyclic dertvatives of 2-quinolinone associated with antibacterial and antitumor potencies," *Heterocycles*, Vol 85 Issue 10, pages 2421–2436, 2012.
20. M.R. Shiradkar, A.G. Nikalje, "Synthesis and anticonvulsant activity of clubbed thiazolidinone– barbituric acid and thiazolidinone–triazole

derivatives," *ARKIVOC* (Gainesville, FL, United State) Vol XIV, pages 58–74, 2007.
21. S. Sharma, R. Jain, V. Sharma, C. Chawla, "Synthesis and biological evaluation of some new 4-aryl-1-(4,6-diaryl pyrimidine)-2-azetidinone by conventional and microwave methods and their biological activities," *J. Indian Chem. Soc*., Vol 90, Issue 2, pages 221–229, 2013.
22. P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Ooni, C.A. Kabras, Colla, P.L. Colla, "Synthesis and biological evaluation of benzo[d]isothiazole, benzothiazole and thiazole Schiff bases," *Biol. Med. Chem*. Vol 11, pages 4785–4791, 2003.
23. M. Gulcan, M. Sonmez, I. Berber, "Synthesis, characterization, and antimicrobial activity of a new pyrimidine schiff base and its cu(ii), ni(ii), co(ii), pt(ii), and pd(ii) complexes," *Turkish J. Chem.*, Vol 36, Issue 1, pages 189–200, 2012
24. B. Kahveci, O. Bekircan, S.A. Karaoglu, "Synthesis and antimicrobial activity of some 3-alkyl-4-(arylmethyleneamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones," *Indian J. Chem*., Vol 44B, pages 2614–2617, 2005.
25. Betircan, O., Kahveei, B., Kucuk, M., Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4H-1,2,4-triazole derivatives," *Turk. J. Chem*., Vol 30, pages 29–40, 2006
26. P.B.Choudhari, M.S. Bhatia, S.D. Jadhav, "Pharmacophore Modelling, Quantitative Structure Activity Relationship (QSAR) and Docking Studies of Pyrimidine Analogs as Potential Calcium Channel Blockers," *J. Korean Chem. Soc.*, Vol 57 Issue1, pages 99–103, 2013.
27. W.M. Singh, B.C. Dash, "Synthesis of some new schiff bases containing thiazole and oxazole nuclei and their fungicidal activity," *Pesticides*, Vol 22, pages 33–37, 1988.
28. A. Xavier, N. Srividhya, "Synthesis and Study of Schiff base ligands," IOSR- *Journal of Applied Chemistry*, Vol 7 Issue 11, pages 6-15, 2014.
29. S. P. Babar, "Pectin Extraction from Orange Peels by Using Organic Clay," *International Journal of Scientific Research and Engineering Trend*, Vol 7(1), pages 171-173, 2021.
30. Laszlo Pierre, Science, Chemical Reactions on Clay, vol. 235, 1473-1477.