Plant Archives Vol. 20, Supplement 1, 2020 pp. 476-478 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

SYNTHESIS OF NOVEL MANNICH BASES OF 2,4,5-TRIPHENYL IMIDAZOLE USING PHARMACOLOGICALLY ACTIVE SECONDARY AMINES

Ramit Kapoor[1], Pooja Mittal[2] and Archana Sharma[1*]
[1]Amity Institute of Pharmacy, Amity University, Noida.
[2]Maharishi Markandeshwar University, Sadopur, Ambala- Haryana
Email**:** ramit3108@gmail.com
*Corresponding Author

Abstract

The compounds wee synthesized and characterized by elemental analysis, IR and ^{1}H NMR spectroscopic techniques. Triphenyl imidazole mannich bases were obtained in good yields. The reactions were closely monitored by using silica gel thin layer chromatography. From the results obtained by elemental analysis, the percentage of various compounds present was calculated. Pyrrolidine Mannich Base of 2,4,5 triphenyl imidazole was obtained in highest yield. R_f values of all the synthesized Mannich Bases of Pyrrolidine, Piperazine and Piperidine were between 0.50 and 0.70.

***Keywords*:** Mannich Bases, 2,4,5, Triphenyl imidazole, Thin layer chromatography

Introduction

Diabetes is a worldwide problem. According to WHO, by 2025, there will be more than 300 million people affected by Diabetes Mellitus and in India, the count will increase to 57 million from 15 million in 1995 (Association, 2004). There are 2 basic types of Diabetes: Diabetes Mellitus (type 1) and Diabetes insipidus (type II). Diabetes mellitus is a most common disorder of endocrine system which occurs due to the resistant or less work insulin secretion system by pancreatic beta cells (Eisenbarth, 1986) (Association, 2004). A vast no. of treatment strategies including natural as well as synthetic ways were investigated for the treatment of this disorder. Heterocyclic compounds are rich source of diverse physical, chemical and biological properties. Imidazoline derivatives have been reported to show anti hyperglycemic activity in vivo. Imidazole's are the well-known heterocyclic being the important components of the wide variety of natural and synthetic compounds. They are well known for their anti-inflammatory, analgesic, tuberculostatic, antimicrobial and anti-convulsant properties (Abdul-Ghani *et al.*, 1996; Bahekar *et al.*, 2007; Larsen *et al.*, 2001; Vicente-Pedrós *et al.*, 1983).

Imidazole is amphoteric compound with 5 membered planner rings. It can act as both acid and base. The protonation of its basic site i.e. n-3 results in production of imidazolium cation. The aromatic nature of the compound is owed to existence of pie electrons which are consisted of a couple of electrons obtained from the nitrogen atom and the remaining atoms of the ring. Much of the drugs with this basic moiety were reported earlier. Their derivatives posse's vast no of therapeutic applications and some of them are used in synthesis of medicinal compounds (Bahekar *et al.*, 2007; Kumar *et al.*, 2012; Rani *et al.*, 2015; Yar *et al.*, 2015).

Materials and Methods

Chemicals

All the chemicals used were of analytical grade and were obtained from Loba chem., Merck Limited and SD Fine chemicals. Readymade silica gel plates were used to monitor the reactions which were obtained from Merck Limited. The solvent system used was Methanol: Chloroform (1:1). Potassium bromide was purchased from SD Fine chemicals.

Apparatus & Equipments

Iodine chamber was utilized to view the plates. Melting point was checked by utilizing Buchi 530 melting point apparatus. Infra Red Spectra of the synthesized compounds was analyzed by utilizing KBr disc method on Agilent FT-IR spectrometer. The proton magnetic resonance spectra (^{1}H-NMR) was analyzed by using Bruker NMR (300 MHz). The solvent used was DMSO and the internal standard used was Tetra Methyl Silane (TMS). Analysis of various elements was performed by using CHNS (O) analyzer.

Synthesis of 2,4, 5 Triphenyl Imidazole (4)

2,4,5 Triphenyl Imidazole's were synthesized by condensation of benzoin (0.023 mol) (1), ammonia (0.05 mol) (2) and benzaldehyde (0.07 mol) (3). Monitoring of the reaction was performed with the help of thin layer chromatography (TLC). The scheme of the reaction is depicted in figure 1.

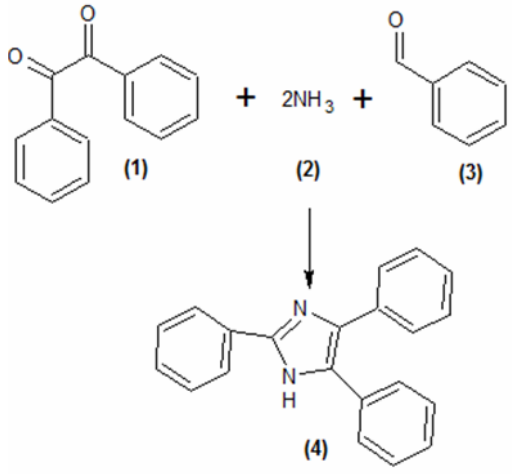


Fig. 1: Scheme of the reaction for the synthesis of 2,4, 5 Triphenyl Imidazole (4).

Mannich Bases of 2,4, 5 Triphenyl Imidazoles

10 ml Formaldehyde (0.131mol) was added drop wise to the mixture of 2,4,5 Triphenyl imidazole (2.5gms, 0.006mol) which was already dissolved in 10 ml Dimethyl

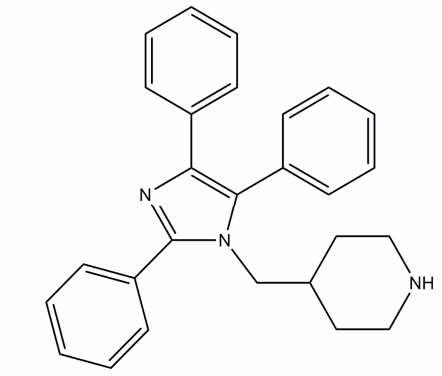
Formamide (0.131mol). The mixture was then stirred for half an hour to produce its methoxyl derivative. In another beaker, various secondary amines (4a-4e) were added in different quantities (2.5 g, 0.0121 mol) using Dimethyl Formamide (DMF) (10 ml, 0.131mol) as a solvent. The formulated methoxyl derivative was further stirred for 5-10 minutes with secondary amines (4a-4e). Reflux was performed for 4 hrs after that and the reaction was monitored over TLC. Then after, we collected the precipitates which were filtered, washed and kept for drying and were recrystallized using chloroform: methanol system (Arora *et al.*, 2012; Kapoor *et al.*, 2014; Shiba, 1970; Yaseen, 2010).

Table 1: Synthesis of mannich bases of triphenyl imidazole

S.No	Compound	Secondary amines
1	5 a	Piperidine
2	5 b	Piperazine
3	5 c	Pyrrolidine

Results and Discussion

The synthesized mannich bases of 2,4,5 Triphenyl Imidazole were identified by utilizing various spectroscopic techniques like H^1NMR, FTIR and were further screened on TLC plates. The yield of the Pyrrolidine derivative (5c) was higher in comparison to other other compounds which were produced along with that and retention factor values of the compounds ranged from 0.45 to 0.75 range. The highest melting point of 93 °C was acquired by 5c derivative of Pyrrolidine. The results of FTIR, NMR and Elemental analysis of the synthesized compounds are given below. The reaction involved the addition of the basic amino alkyl chain, thatmodifies the biological profile of the parent drug and its physiochemical characteristics. The synthesized derivatives of Mannich reaction hadestablished the pharmacological profile which is having the therapeutic index more towards effectiveness and less towards toxicity as compared to the parent compound (Arora *et al.*, 2012; Chitturi, 2008; Krentz, 2006; Luo *et al.*, 2013; Panigrahy *et al.*, 2002; Ricote *et al.*, 1998; Sahoo *et al.*, 2006)



4-((2,4,5-triphenyl-1*H*-imidazol-1-yl)methyl)piperidine

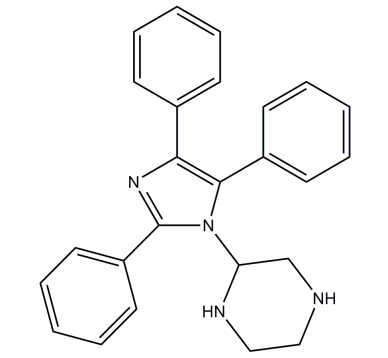
Fig. 2 : 2,4,5 Triphenyl Imidazole with Piperidine as secondary amine:

M.F: $C_{29}H_{22}N_4$, M.wt. (g/mol): 427.18, Percentage Yield-61.4 %, M.pt (^{0}C): 257-262 °C and R_f: 0.55.

Elemental Analysis for $C_{30}H_{23}N_3$: C, 84.64 %; H, 5.45 %; N, 9.87 %.

FTIR (cm^{-1}): 3437 (N-H, str), 2956 (C-H, str), 1580 and 1453 (C=C, Ar), 1358 (C-N), 1434 (C=N) ,1599 (C=C, str), 1411 (C-H, bend), 1559 (N-H, bend).

^{1}HNMR (DMSO-d6) (δ ppm): 7.50 (1H, s, fused Ar-H), 7.48-7.42 (6H, d, fused AR-H), 7.27-7.13 (3H, t, fused AR-H), 7.39-7.30 (6H, t, fused AR-H), 8.024 (IH, d, AR-H), 5.96 (1H, s, N-H), 4.98(1H, s, C-H).



2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)piperazine

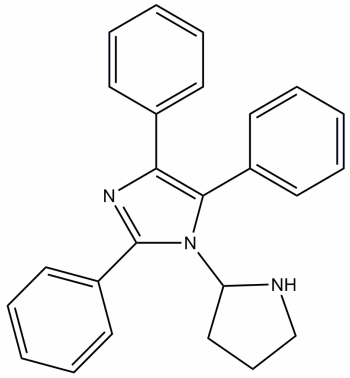
Fig. 3 : 2,4,5 Triphenyl Imidazole with Piperazine as secondary amine

M.F: $C_{28}H_{21}N_5$, M.wt. (g/mol): 427.18, Percentage Yield- 66.7%, M.pt (^{0}C): 273-275 °C and R_f: 0.57.

Elemental Analysis for $C_{28}H_{21}N_5$: C, 78.67 %; H, 4.95 %; N, 16.38 %.

FTIR (cm^{-1}): 3368 (N-H, str), 3181 (C-H, str), 1551 and 1592 (C=C, Ar), 1305 (C-N), 1430 (C=N), 1600 (C=C, str), 1388 (C-H, bend), 1451 (N-H, bend), 1236 (N=N).

^{1}HNMR (DMSO-d6) (δ ppm): 8.21 (1H, s, fused Ar-H), 7.88 (2H, s, fused Ar-H), 7.5606-7.418 (6H, d, fused Ar-H), 7.39-7.38 (6H, t, fused Ar-H), 7.22 (3H, t, fused Ar-H), 4.98 (2H, s, C-H).



2,4,5-triphenyl-1-(pyrrolidin-2-yl)-1*H*-imidazole

Fig. 4: 2,4,5 Triphenyl Imidazole with Pyrrolidine as secondary amine:

Conclusion

In the present research, the synthesis of mannich bases of Triphenyl substituted imidazole was carried out by taking a reference from the work of Carl Mannich who had utilized different aryl and alkyl amines and created the pharmacologically more potent synthetic derivatives. The basic idea behind the current study was to use the abstractable hydrogen of the secondary amine and to synthesize various pharmacologically active moieties from it. Mannich Bases were exploited in various fields of pharmaceutical industry like polymers, dispersants in lubricating oils etc. This thoughtfulness paved a pathway for amino alkyaltion of different secondary amines by the process of mannich reaction. The reaction involved the addition of the basic amino alkyl chain that modifies the biological profile of the parent drug and its physiochemical characteristics. The synthesized derivatives of Mannich reaction had established the pharmacological profile whose therapeutic window is more towards effectiveness and less towards toxicity then the moiety of its origin. (Arend, Westermann, *et al.*,1998, Lieberman, Wagner,1949).

References

Abdul-Ghani, A.-S.; Abu-Hijleh, A.-L.; Nahas, N. and Amin, R. (1996). Hypoglycemic effect of copper (II) acetate imidazole complexes. Biological trace element research, 54(2): 143-51.

Arend, M.; Westermann, B. and Risch, N. (1998). Modern variants of the Mannich reaction. Angewandte Chemie International Edition, 37(8): 1044-70.

Arora, R.; Gill, N.; Kapoor, R.; Aggarwal, A. and Rana, A. (2012). Synthesis of 2, 4, 5-triphenylimidazoles novel Mannich bases as potential antiinflammatory and analgesic agents. Curr Res Chem, 4: 99-109.

Association, A.D. (2004). Gestational diabetes mellitus. Diabetes care, 27(suppl 1), s88-s90.

Bahekar, R.H.; Jain, M.R. and Gupta, A.A. (2007). Synthesis and Antidiabetic Activity of 3, 6, 7-Trisubstituted-2-(1H-imidazol-2-ylsulfanyl) quinoxalines and Quinoxalin-2-yl isothioureas. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry, 340(7): 359-66.

Chitturi, S. (2008). Treatment options for nonalcoholic fatty liver disease. Therapeutic advances in gastroenterology, 1(3): 173-89.

Eisenbarth, G.S. (1986). Type I diabetes mellitus. New England journal of medicine, 314(21): 1360-8.

Kapoor, R.; Arora, R.; Mishra, R.; Arora, M. and Mittal, P. (2014). Synthesis of novel Mannich bases of pioglitazone. Current Research in Chemistry, 6(1):10-5.

Krentz, A. and Friedmann, P. (2006). Type 2 diabetes, psoriasis and thiazolidinediones. International journal of clinical practice, 60(3): 362-3.

Kumar, G.G.; Rani, N. and Kumar, V. (2012). Microwave assisted synthesis of imidazoles-A review. Mini-Reviews in Organic Chemistry, 9(3): 270-84.

Larsen, S.D.; Connell, M.A. and Cudahy, M.M. (2001). Synthesis and biological activity of analogues of the antidiabetic/antiobesity agent 3-guanidinopropionic acid: discovery of a novel aminoguanidinoacetic acid antidiabetic agent. Journal of medicinal chemistry, 44(8): 1217-30.

Lieberman, S.V. and Wagner, E. (1949). The course of the mannich reaction1. The Journal of Organic Chemistry, 14(6): 1001-12.

Luo, L.; Luo, B.; Zheng, Y.; Zhang, H.; Li, J. and Sidell, N. (2013). Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia. Cochrane Database of Systematic Reviews (6).

Panigrahy, D.; Singer, S. and Shen, L.Q. (2002). PPARγ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. The Journal of clinical investigation, 110(7): 923-32.

Rani, N.; Sharma, A. and Singh, R. (2015). Trisubstituted imidazole synthesis: A review. Mini Rev Org Chem, 12(1): 34-65.

Ricote, M.; Li, A.C.; Willson, T.M.; Kelly, C.J. and Glass, C.K. (1998). The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature, 391(6662): 79.

Sahoo, S.; Joseph, T. and Halligudi, S. (2006). Mannich reaction in Brönsted acidic ionic liquid: A facile synthesis of β-amino carbonyl compounds. Journal of Molecular Catalysis A: Chemical, 244(1-2): 179-82.

Shiba, T. and Kato, H. (1970). The Reaction of 3-Methyl-5-methylmercapto-2, 4-diphenylthiazolium Iodide with Bases. Preparation of Mesoionic Imidazoles. Bulletin of the Chemical Society of Japan, 43(12): 3941-2.

Vicente-Pedrós, F.; Monge, J.T. and Vert, F.T. (1983). Antidiabetic behavior of biguanides. Journal of pharmaceutical sciences,72(5): 565-7.

Yar, M.; Bajda, M. and Shahzad, S. (2015). Organocatalyzed solvent free an efficient novel synthesis of 2, 4, 5-trisubstituted imidazoles for α-glucosidase inhibition to treat diabetes. Bioorganic chemistry, 58: 65-71.

Yaseen, G. and Sudhakar, J. (2010). Design, synthesis and antimicrobial activity of 2-mercaptobenzimidazole derivatives. International Journal of Pharma and Bio Sciences, 1(4): 281-6.