Research article
International Journal of Heterocyclic Chemistry,
Vol. 7, No. 3, pp. 39-47 (Summer 2017)
© Islamic Azad University, Ahvaz Branch
http://ijhc.iauahvaz.ac.ir

Synthesis of some isatin Schiff bases in microwave irradiation condition

Mohammad K. Mohammadi
Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz ,
Iran

E-mail : mkmohamadi@gmail.com

Abstract

An efficient and mild methodology for rapid and efficient synthesis of isatin Schiff bases was described under microwave irradiation and solvent free condition.aromatic or heterocyclic Primary amines and isatin could be selectively reacted under microwave irradiation into the corresponding isatin Schiff bases in high yields and short reaction time.

Keywords: Synthesis, isatin- Schiff bases, Microwave

Introduction:

Isatin [1] is a natural product found in a number of plants including those of the genus Isatis.[1] It has also been found as a metabolic derivative of adrenaline in humans.[2] Various derivatives of isatin are known to possess a range of pharmacological properties including antiprotozoal activities.[3,4] Within the context of enzyme inhibitors, isatins (also known as 2,3-dioxindoles) have seen recent applications in the inhibition of cysteine and serine proteases.[5,6] Thus isatin is a biologically validated starting point for the design and synthesis of chemical libraries directed at these targets.[7] Due to the privileged nature of isatin, libraries designed and synthesized around the basic structure of this scaffold should yield medicinally active compounds with high hit rates at significantly reduced library size compared to large classical libraries obtained from combinatorial chemistry efforts based on non-privileged templates.

Systematic investigation of spiroindoles is of great interest due to the fact that if the indole ring is joined to the other heterocyclic systems through a spiro carbon atom at C-3, the resulting compounds show an increased spectrum of biological activities.[8,9] Also, varied pharmacological properties are associated with1,2,4-triazolidines. [10.11.12]Thus it is expected that production of a 1,2,4-triazolidine moiety at C-3 of the 2-indolinone system would enhance the biological activity significantly. Development of new solid phase (solvent-free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug candidates.[13] The potential for application of microwave technology in organic synthesis, particularly in solid phase (solvent-free) reactions, is increasing rapidly because of its simplicity, causing less pollution and having minimum reaction times, thus providing rapid access to libraries of diverse small molecules.[14]

The application of microwave (MW) irradiation as a nonconventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry.[15,16] The combination of microwave irradiation and solvent-free reaction conditions leads to enhanced reaction rates, higher yields of pure products, easier work-up and, sometimes, to selective conversions with several advantages of the eco-friendly approach in the framework of green chemistry.[15,16] Consequently, this protocol should be welcome in these environmentally conscious days.

Considering the above reports and In continuation of our work on synthesis of biologically active compounds and evaluate of some their biological activity ,[17,18,19] we report the synthesis of some hydrazones and Schiff bases of isatin in fairly good yields and short reaction times along with their docking evaluation.

Experimental

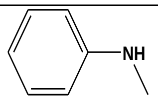
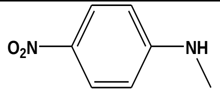
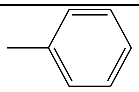
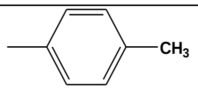
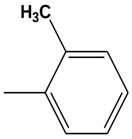
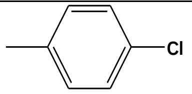
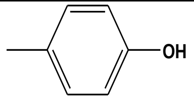
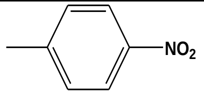
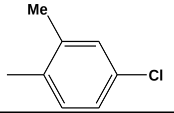
Material and methods

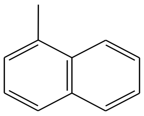
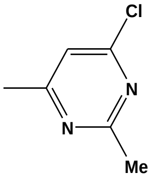
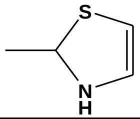
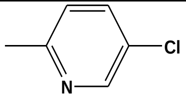
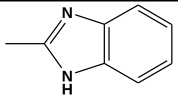
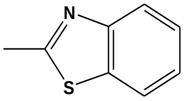
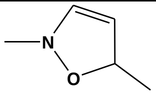
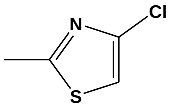
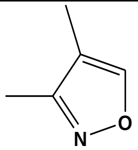
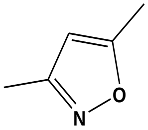
The reactions were carried out with a microwave oven (2.45 GHz, 1500 w; Microsynthesis, Milstone). Melting points were measured on the Electrothemal 9100 apparantus and are uncorrected. IR spectra were measured on a Bomem FT-IR-MB 100 spectrometer(ABB Bomem Inc, QC, Canada). 1H and 13C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer (Bruker, Ettlingen, Germany) in DMSO-d6 at 300 and 75 MHz using tetra methyl sylan as internal standard. Mass spectra were recorded on a MS model 5973 Network apparatus at ionization potential of 70 eV. All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures.

Typical procedure for the preparation of (4a–4g) Microwave irradiation conditions (MWI) method

A mixture of isatin (1 mmol) and aromatic (heterocyclic primary) amines (1 mmol), were mixed and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 100 _C for 4–6 min. After completion of the reaction (monitored by TLC, the ethyl acetate ⁄ n-hexane), reaction mixture was poured into cold water (25 mL) and stirred for 5–10 min. The precipitates were filtered and washed with cold water (2 * 15 mL) and then with 90% ethanol (2 *10 mL) to give pure products. Products were characterized by analyzing their ^{1}H and ^{13}C NMR, mass spectra and Characteristic data for some synthesized compounds are compared and then proved with those reported in earlier literature (1–10).[20,21,22]

Table 1 : synthesis of isatin Schiff bases in solvent free condition under microwave irradiation

Comp. code	Ar	m.p (°C)	Yield (%)	Time (min)	Compound name
1		170-172	86	4	3-(2-phenylhydrazono)indolin-2-one
2		183-184	85	4	3-(2-(4-nitrophenyl)hydrazono)indolin-2-one
3		145-143	82	5	3-(phenylimino)indolin-2-one
4		156-157	88	6	3-(p-tolylimino)indolin-2-one
5		152-153	80	5	3-(o-tolylimino)indolin-2-one
6		167-169	88	5	3-(4chlorophenylimino)indolin-2-one
7		177-178	82	7	3-(4-chlorophenylimino)indolin-2-one
8		179-180	90	5	3-(4-nitrophenylimino)indolin-2-one
9		174-175	80	6	3-(4-chloro-2-methylphenylimino)indolin-2-one

10		181-182	82	8	3-(naphthalen-1-ylimino)indolin-2-one
11		193-194	80	5	(Z)-3-(6-chloro-2-methylpyrimidin-4-ylimino) indolin-2-one
12		194-195	86	6	(dihydrothiazol-2-ylimino) indolin-2-one
13		197-199	80	5	(Z)-3-(5-chloropyridin-2-ylimino) indolin-2-one
14		154-155	90	7	(Z)-3-(1H-benzo[d]imidazol-2-ylimino) indolin-2-one
15		168-171	92	7	(Z)-3-(benzo[d]thiazol-2-ylimino) indolin-2-one
16		153-154	85	6	(3Z)-3-(5-methylisoxazol-2(5H)-ylimino) indolin-2-one
17		172-174	80	6	(Z)-3-(4-chlorothiazol-2-ylimino) indolin-2-one
18		179-181	88	8	(Z)-3-(4-methylisoxazol-3-ylimino) indolin-2-one
19		193-195	90	5	(Z)-3-(5-methylisoxazol-3-ylimino) indolin-2-one

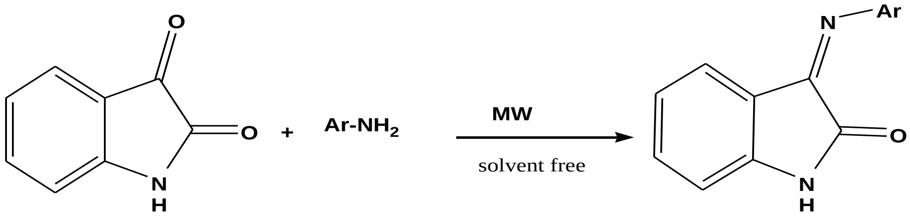


Figure4. synthesis of isatin schiff base

Results:

The original protocol for the preparation of the isatin schiff bases consisted of heating a mixture of the components (isatin and aromatic or heterocyclic primary amines) in ethanol containing a catalytic amount of H_2SO_4. The major drawback associated with this protocol are the low yields particularly for substituted aromatic and aliphatic amines and high solvent pollution . This has led to the development of multistep synthetic strategies, However, many of these methods involve expensive reagents, long reaction times, and high stoichiometric amount of catalysts, and difficult to handle especially on a large scale. Therefore, the discovery of a new and an inexpensive procedure for the preparation of isatin Schiff bases under mild and efficient conditions is of prime importance. For the increasing environmental and economic concerns in recent years, it is now essential for chemists to search environmentally benign reactions as many as possible. Here, we wish to report the rapid and efficient method for this reaction under microwave-assisted solvent-free conditions. Some new isatin-Schiff base compounds were obtained by condensation of different aromatic and heterocyclic amines and isatin, under microwave irradiation and under solvent free condition (see Fig. 1). The isolated compounds were then characterized by elemental analyses, IR and NMR spectroscopy. Spectroscopic properties were compared to those of related compounds that previously isolated and described to correlate their structural features. Electronic spectra of all the complexes were carried out in aqueous, DMSO or CH_3CN solution, depending on their solubility. This method offers some advantages in terms of simplicity of performance, mild operation condition, no side product formation, very short reaction time and a wide range of substrates. There wasn't need to add some lowis acid (ex ;H_2SO_4) as a catalyst that reported in past literature for accelerating of the reaction rate .

As an reactants, Isatin and primary aromatic and heterocyclic amines was a very well suited compounds for microwave synthesis, because as an ionic and magnetically retrievable material, it carried a benefit of efficient conversion of electromagnetic energy into heat, according to the dielectric heating mechanism .

Conclusion :

In conclusion, we have presented the synthesis of derivatives of istin Schiff bases using the efficient, easily available, and low quantities of reactants under microwave irradiation conditions. This method not only preserved the simplicity of isatin – primary amine condensation but also remarkably improved the yields (>80%) of products in shorter reaction times (4–8 min) as against the longer reaction times required for other conventional methods. The procedure gives the products in good yields and avoids problems associated with solvent use (cost, handling, safety and pollution), and easy experimental work-up procedure, hence, it is a useful addition to the existing methods.

Acknowledgments:

Financial supports of this project by research council of Shiraz University of Medical Sciences are acknowledged. We gratefully acknowledge the financial support from the Medicinal and Natural Products Chemistry Research Centre, Shiraz University of Medical Sciences.

References :

1. Guo, Y.; Chen, F. Zhongcaoyao 1986, 17, 8. 2. Ischia, M.; Palumbo, A.; Prota, G. Tetrahedron 1988, 44, 6441.

3. Imam, S. A.; Varma, R. S. Experientia 1975, 31, 1287.

4. Varma, R. S.; Khan, I. A. Polish J. Pharmacol. Pharm. 1977, 29, 549.

5. Lyer, R. A.; Hanna, P. E. Bioorg. Med. Chem. Lett. 1995, 5, 89.

6. Webber, S. E.; Tikhe, J.; Worland, S. T.; Fuhrman, S. A.; Hendrickson, T. F.; Matthews, D. A.; Love, R. A.; Patick A. K.; Meador, J. W.; Ferre, R. A.; Brown, E. L.; DeLisle, D. M.; Ford, C. E.; Binford, S. L. J. Med. Chem. 1996, 39, ,
5072

7. Shuttleworth, S. J.; Nasturica, D.; Gervais, C.; Siddiqui, M. A.; Rando, R. F.; Lee, N. Bioorg. Med. Chem. Lett. 2000,
10, 2501.

8. Joshi, K. C.; Jain, R.; Chand, P. *Heterocycles* 1985, 23, 957–996.

9. Mogilaiah, K.; Babu Rao, R. *Indian J. Chem*. 1998, 37B, 894–898.

10. Maclauchlin, C.; Hall, I. H.; Izydore, R. A. *Arch. Pharm*. 1999, 332, 225–232.

11. Hall, I. H.; Wong, O. T.; Simlot, R.; Miller, M. C.; Izydore, R. A. *Anticancer Res*. 1992, 12, 1355–1361.

12. Shamsuzzaman, A. S.; Kishwar, S.; Mukhtar, A. K. *Indian J. Chem*. 1997, 36B, 617–619.

13. Tanaka, T.; Toda, F. Chem. Rev. 2000, 100, 1025–1074.

14. (a) Pourashraf, M.; Delair, P.; Rasmaissen, M. O.; Greene, A. E. J. Org. Chem. 2000, 65, 6966–6972; (b)Cossy, J.; Willis, C.; Bellosta, V.; Jalmes, L. S. Synthesis 2002, 951–957.

15. (a) Caddick, S. Tetrahedron 1995, 51, 10403–10432. (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Bouller, F.; Jacquault, P.; Mathe, D. Synthesis 1998, 1213–1234. (c) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Tetrahedron 2001, 57, 9225–9283. (d) Varma, R. S. Green Chem. 1999, 1, 43–55.

16. Perreux, L.; Loupy, A. Tetrahedron 2001, 57, 9199–9223.

17 .Javad Azizian , Mohammad K. Mohammadi , Omidreza Firuzi , Nima Razzaghi-asl , Ramin Miri .
Med Chem Res .2011

18.Javad Azizian , Mohammad K. Mohammadi , Omidreza Firuzi , Behrooz Mirza and Ramin Miri . Chem Biol Drug Des 2010; 75: 375–380

19. Javad Azizian, Ramin Miri, Mohammad Kazem Mohammadi, Fatemeh Sheikholeslami Farahani, Javad Hosseini, and Mohsen Nikpour . *Phosphorus, Sulfur, and Silicon*, 185:1782–1787, 2010

20 . Pandeya, S.N.; Sriram, D. *Acta Pharm. Turc.* 1998, *40*, 33–38.

21. Sarangapani, M., Reddy, V.M. *Indian J. Pharm. Sci.* 1994, *56*, 174–177.

22. da Silva, J.F.M.; Garden, S. J.; Pinto, A.C. *J. Braz. Chem. Soc.* 2001, *12(3)*, 273-324.