INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

A SIMPLE, EFFICIENT AND SOLVENT FREE ONE POT SYNTHESIS OF 3, 3 DIHETEROAROMATIC OXINDOLE

Syed Shahed Ali*, Maqdoom Farooqui, Sayyad Sultan

Maulana Azad college and Research Center, Dr. Rafiq Zakaria Campus, Dr. Babasaheb Ambedker Marathwada University, Aurangabad- 431001, India.

Email: shahedali444@gmail.com

Article Received on: 04/02/13 Revised on: 09/03/13 Approved for publication: 11/04/13

DOI: 10.7897/2230-8407.04431

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

ABSTRACT

Formic acid catalyzed, single step and environmentally friendly process for synthesis of 3, 3- diheteroaromatic oxindole derivatives is described. This adopted protocol for Friedel- Crafts substitution reaction has the advantage of reusability of the catalyst, high yields and ease of separation of pure products.

Keywords: Isatin, indole, pyrrole, 3, 3- diheteroaromatic oxindole, catalysis.

INTRODUCTION

The woman contraceptive products available for many years are mostly based on Nonoxynol -9 (N-9)[1, 2], the use of N-9 may or may not meet further safety regulation. Several European nation have banned or restricted the use of N-9 and related compounds on the basis of health risks and potential environmental toxicity[3]. Isatin is known to possess a broad spectrum of bioactivity as many of which were assessed anti-HIV[4], antiviral[5], anti-tumor[6], antifungal[7], anti-angiogenic[8], anticonvulsants [9], anti-Parkinson's disease therapeutic [10] and effective SARS coronavirus 3 CL protease inhibitor [11]. Oxindole is an integral constituent of many natural products [12]. The varied biological activities of oxindole derivatives have attracted the synthetic chemists to a number of synthetic strategies [13]. Especially, 3, 3- diheteroaromatic oxindoles have not been widely explored and the use of formic acid as a catalyst in the synthesis of 3, 3- di (indolyl) oxindoles and 3, 3- di (pyrrolyl) oxindole under solvent free conditions at room temperature has not been reported in literature.

Recently, Interest in the field of organocatalysis has increased spectracularly in the last few years as a result of both the novelty of the concept and more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions [14]. Formic acid is achieving enormous significance in organic synthesis of dihydropyrimidinones [15]. Considering the significance of all above discussed aspects and in continuation of our endeavor [16] towards the development of eco-friendly synthetic protocols for the construction of bioactive molecules, it was thought worthwhile to develop a new, simple, greener and expeditious route for the synthesis of 3, 3- diheteroaromatic oxindole derivatives under solvent free conditions at room temperature using formic acid as an organocatalyst.

MATERIALS AND METHODS

All chemical were purchased from Merck, Aldrich and Rankem Chemical Companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography). IR Spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR Spectra were recorded on FT-NMR Spectrometer in $CDCl_3$ and DMSO as a solvent and chemical shift values are recorded in units δ (PPM) relative to tetramethylsilane (Me_4Si) as an internal standard.

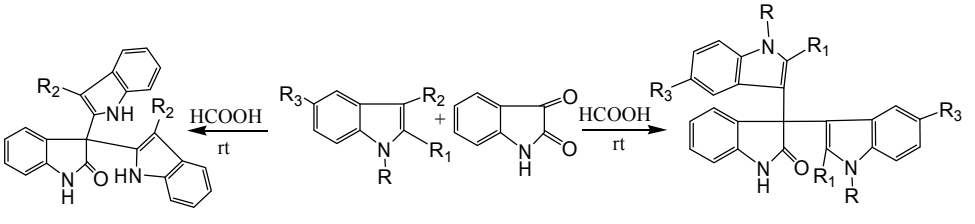
General Procedure for the Synthesis of 3, 3- Diindolyl and 3, 3- dipyrrolyl oxindoles 3a-n

To the reaction mixture containing isatin **1** (1 mmol) indole or pyrrole **2** (1 mmol) and formic acid (15 mol %) were ground together in a mortar with pestle at room temperature for appropriate time in (1 min). After completion of reaction confirmed by TLC, the mixture was ice-water to furnish the crude products. The crude was further purified by column chromatography by using petroleum ether: ethyl acetate (9:1) eluent and get the corresponding of 3, 3- Diindolyl oxindoles **(3 a-m)** and 3, 3- dipyrrolyl oxindole **(3n)** were confirmed by comparison with authentic sample, elemental analysis and melting points.

RESULTS AND DISCUSSION

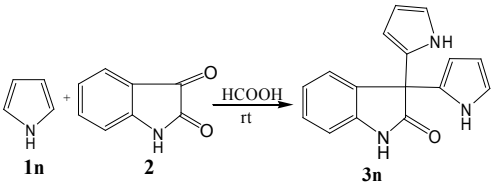
As part of current studies on the design of new routes for the preparation of biologically active heterocyclic compounds [17], we herein disclose a simple and convenient method for the efficient synthesis of 3, 3- diindolyl oxindoles and 3, 3- dipyrrolyl oxindole from isatin with substituted indoles or pyrrole in the presence of formic acid under solvent free condition (**Scheme 1, 2**).

The experiment was carried out simply by mixing isatin **1** and indole **2** in the presence of a catalytic amount (15 mol %) of formic acid under solvent free condition. The mixture was ground together in a mortar with a pestle at room temperature for short reaction time, and then purified by column chromatography, substituted oxindole derivatives were obtained in excellent yields. The result provided the incentive for further study of reaction with various other isatin derivatives and substituted indoles to further the corresponding 3, 3- diindolyl oxindoles and 3, 3-dipyrrolyl oxindole.



3 k-m 1 a-m 2 3 a-j

Scheme 1



1n 2 3n

Scheme 2

Table 1: Formic acid- catalyzed one pot synthesis of 3, 3- diheteroaromatic oxindole derivatives under solvent-free conditions

Entry	R	R1	R2	R3	Product (3a-n)	Yield (%)[a, b]
1a	H	H	H	H	**3a**	97
1b	H	H	H	Br	**3b**	96
1c	H	Me	H	H	**3c**	96
1d	H	H	H	OMe	**3d**	90
1e	Me	H	H	H	**3e**	94
1f	H	COOH	H	H	**3f**	93
1g	H	H	H	Cl	**3g**	90
1h	H	H	H	F	**3h**	91
1i	H	H	H	I	**3i**	93
1j	H	H	H	Me	**3j**	97
1k	H	H	Me	H	**3k**	93
1l	H	H	Br	H	**3l**	90
1m	H	H	CH_2COOH	H	**3m**	95
1n	H	H	H	H	**3n**	93

[a]Yield of isolation pure products,

[b]Products were characterized by IR, NMR, mass elemental analysis and comparison with authentic sample[18]

Accordingly, (10 mol %) of catalyst was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher molar ratios of formic acid were used. However no product formation was observed in absence of formic acid. By getting this result, we have extended this protocol to a variety of substituted indoles summarized in (**Table 1).** 3- methyl indole **(1k)** 3-bromoindole **(1l)** and indole-3-acetic acid **(1m)** took longer time (5-6 min) for completion **(Table 1).** Furthermore, pyrrole **(1n)** also reacted efficiently with isatin under similar condition, to afford 3, 3- dipyrrolyl-2-oxindole **(3n) (Scheme 2, Table 1)**.

CONCLUSION

In conclusion, formic acid has shown to be an excellent for one pot synthesis of large size 3, 3- diheteroaromatic oxindoles under solvent free conditions. The protocol offers several advantages such as excellent % yields of product, short reaction time, simple work up procedure and easy isolation making it an important supplement to the existing methods.

ACKNOWLEDGEMENTS

We thank the University Grand Commission UGC, New Delhi, for financial support. S. S. A. thanks the UGC India for the award of a research fellowship.

REFERENCES

1. Zaneveld LJD, Vaginal Contraception since 1984: Chemical Agents and Barrier Devices. In Contraceptive Research and Development 1984-1994; Van Look, PFA Perez-Palacios G. Eds.; Oxford University Press; Delhi, 1994; p 69.
2. Trussell J, Contraceptive Efficacy of Barrier Contraceptives, Current Status and Further Prospects; Mauck CK, Cordero M, Gabelnick HL, Spieler JM, Rivera R, Eds; Wiley –Liss; New York, 1994; p. 17.
3. Renner R, Sophorolipids, Microbial Glycolipids with Anti-Human, Environ Sci. Technol. 1997; 31: A316 http://dx.doi.org/10.1021/es972366q PMid:21650741 (b) Thiele B, Gunther K, Schwuger M, Alkyphenolethoxylates: Trace Analysis and Environmental Behaviour, Chem. Rev. 1997; 97: 3247. http://dx.doi.org/10.1021/cr970323m PMid:11851490
4. Ratan Bal T, Anand B, Yogeeswari P, Sriram Dh, inhibition of HIV-1 integrase, Bioorg. Med. Chem. Lett. 2005; 15: 4451-4455.
5. Jiang T, Kuhen KL, Wolff K, Yin H, Bieza K, Caldwell J, Bursulaya B, Tuntland T Zhang K, Karanewsky D, He Y, Design, synthesis, and biological evaluations of novel oxindoles as, Bioorg. Med. Chem. Lett. 2006; 16: 2109-2112. http://dx.doi.org/10.1016/j.bmcl.2006.01.066
6. Tripathy R, Reiboblt A, Messina PA, Iqbal M, Singh J, Bacon ER, Angeles Th. S, Yang Sh. X, Albom MS, Robinson C, Chang H, Ruggeri BA, Mallamo JP, Structure-guided identification of novel VEGFR-2 kinase inhibitors, Bioorg. Med. Chem. Lett. 2006; 16: 2158-2162. http://dx.doi.org/10.1016/j.bmcl.2006.01.063 PMid:16460933
7. Amal Raj A, Raghunathan R, Sridevikumaria MR, Raman N, synthesis and evaluated the analgesic activity of 3-substituted indole derivatives, Bioorg. Med. Chem. 2003; 11: 407-419. PMid:12517436
8. Maskell L, Blanche EA, Colucci MA, Whatmore JL, Moody Ch. A tandem radical cyclization approach to 3-(2-oxopyrrolidin-3-yl) indolin-2-ones, potential intermediates toward complex indole-heterocycles, J Bioorg. Med. Chem. Lett. 2007; 17: 1575-1578. http://dx.doi.org/10.1016/j.bmcl.2006.12.108 PMid:17254788
9. Verma M, Nath Pandeya S, Nandsingh K, Stables JP, Anticonvulsant activity of Schiff bases of isatin derivatives, Acta Pharma 2004; 54: 49-56. PMid:15050044
10. Igosheva N, Lorz C, O'Conner E, Glover V, Mehmet H, Isatin interaction with glyceraldehyde-3-phosphate dehydrogenase, Neurochem. Int. 2005; 47: 216-224. http://dx.doi.org/10.1016/j.neuint.2005.02.011 PMid:15876476
11. Chen L-R, Wang Y-Ch Lin YW, Chou Sh-Y Chen Sh- F Liu LT, Wu YT, Kuo Ch. J Sh- Sh Chen T, Juang Sh-H, Bioorg. Med. Chem. Lett.

2005; 15: 3058-3062. http://dx.doi.org/10.1016/j.bmcl.2005.04.027 PMid:15896959
12. Yamada Y, Kitajima M, Kogure N, Takayama H, Four novel gelsedine-type oxindole, Tetrahedron 2008; 64: 7690-7694. http://dx.doi.org/10.1016/j.tet.2008.06.030
13. Klumpp DA, Yeung KY, Prakash GKS, Olah GA, J. Org. Chem. 1998; 63: 4481. http://dx.doi.org/10.1021/jo980588g
14. Dalko PI, Moisan L, Trifunctional Organocatalysis - ACS Organic Division, Angew. Chem. Int. Ed. 2004; 43: 5138. http://dx.doi.org/ 10.1002/anie.200400650 PMid:15455437
15. Jiang C, You QD, An efficient and solvent-free one-pot synthesis, Chin. Chem. Lett. 2007; 18: 647-650. http://dx.doi.org/10.1016 /j.cclet.2007.04.002
16. Ali SS, Chin. Chem. Lett. 2011; 22: 793- 796. http:/ /dx.doi.org/10.1016/j.cclet.2011.01.017
17. Savita G, Niveditha SK, Muralidharan D, Perumal PT, Tetrahedron Lett. 2007; 48: 1943.
18. Wang S-Y, Ji S-J, (3RS)-2'-Amino-2,5'-dioxo-1,2-dihydro-5'H-spiro[indole-3,4'-pyrano, Tetrahedron 2006; 62: 1527-1535. http://dx.doi.org/ 10.1016/j.tet.2005.11.011

Cite this article as:
Syed Shahed Ali, Maqdoom Farooqui, Sayyad Sultan. A simple, efficient and solvent free one pot synthesis of 3, 3 diheteroaromatic oxindole. Int. Res. J. Pharm. 2013; 4(4):158-160

Source of support: Nil, Conflict of interest: None Declared