RESEARCH PAPER | Chemistry | Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

One Pot Synthesis of 1 (2-(2, 4, 5-Triphenyl-1H-Imidazol-1-Yl) Ethyl) Piperazine Derivatives Under Solvent Free Conditions

KEYWORDS: 1, 2, 4, 5-tetrasubstituted imidazoles, Aromatic aldehydes, fermenting baker's yeast, ammonium acetate.

Rehana Anjum
Department of Chemistry, Institute of Basic and Applied Science, NIMS University, Jaipur, 303121, India.

Renu Sharma
Department of Chemistry, Institute of Basic and Applied Science, NIMS University, Jaipur, 303121, India.

ABSTRACT *Various 1, 2, 4, 5-tetrasubstituted imidazoles were synthesized from fermenting baker's yeast (Saccharomyces Cerevisiae) catalyzed multi-component reaction of benzil, an aromatic aldehyde, aminoethylpiprazine and ammonium acetate at room temperature in excellent isolated yield. This is a simple and straight forward, high yielding, not involving and hazardous or expensive catalyst method.*

Introduction

To design and conduct chemical reaction with "green experiment" protocol is an enormous challenge that chemists have to conform to improve the quality of the environment for present and future generations. Target areas for achieving this goal are the exploration of alternative reaction condition and reaction media to accomplish the desired chemical transformation with minimized by product or waste and elimination of the use of conventional organic solvents, wherever possible (eg. Zn, Fe, Mg) Also, improved pharmakinetics and bioavailability of peptide based protease inhibitors have been observed by replacing an amide bond with imidazole[1]. In addition, the substituted imidazole ring systems are substantially used in ionic liquids[2] that have been given a new approach to "Green Chemistry". Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewki and Japp reported the first synthesis of the imidazoles from 1,2-dicarbonyl compound various aldehydes and ammonia to obtain the imidazols [3,4]. Also Siddiqui et al proposed the synthesis of the imidazole using ionic liquids [5]. Recently, there are several methods reported in the literature for the synthesis of imidazoles using Zeolite HY/silica gel [6], iodine [7], $ZrCl_4$ [8], sodium bisulfate [9], acetic acid [10]. However these methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method for the synthesis of imidazoles derivatives would be highly desirable. Multi-component condensation (MCCs) constitute an especially attractive synthesis strategy for rapid and efficient generation of molecules due to the fact that the product are formed in a single step and also the diversity could be achieved simply by varying the reacting components. The use of catalysts [11] bakers yeast use for Biginelli compounds, hereafter bakers yeast (*Saccharomyces Cerevisiae*) is a well known catalyst for the reduction of ketones to optically active alcohols[12]. Bakers yeast has also been successfully used in acyloin type condensation, reduction of carbon-carbon double bonds and oxidative coupling of thiols to disulfide [13]. We were interested to investigate the generality of this method and successfully carried out the three- component Biginelli reaction of aldehyde, β- keto esters, and urea/ thiourea to form 3, 4- dihydropyrimidin-2-(1*H*)-ones derivatives in high yield [11]. Encouraged by these results, we turned our attention towards the four-component 1-(2-(2, 4, 5- triphenyl-1H- imidazol-1-yl) ethyl) piperazine coupling reaction of benzil, an aromatic aldehyde, aminoethylpiperazine and ammonium acetate under solvent free condition conditions. Herein, we were used fermenting yeast as a catalyst, it has gained a vast importance in organic synthesis due to their several advantages such as, operationally simplicity, no toxicity reusability, low cost, and ease of isolation after completion of the reaction under solvent free conditions.

Experimental

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 progress of the reactions were monitored by TLC (thin layer chromatography). IR spectra were recorded on Perkin- Elmer FT spectrophotometer in KBr disc. H NMR spectra were recorded on an 400-500 MHz, FT- NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in unit δ relative to tetramethyl silane (Me_4Si) as an internal standard.

General procedure for the synthesis of 1-(2-(2, 4, 5- triphenyl-1H- imidazol-1-yl) ethyl) piperazine.

Bakers yeast (200 mg) and D-glucose (300 mg) were taken in 5ml of phosphate buffer (Ph 7.0) and stirred overnight. A mixture of benzil (1 mmol), aromatic aldehyde (1 mmol), aminoethylpiperazine (1 mmol) and ammonium acetate (2 mmol) were added to the fermenting yeast and the reaction mixture stirred for a further 24 h under solvent conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, diluted with cold water and extraction with ethyl acetate. The organic layer was dried over anhydrous Na2SO4, and then the solvent was removed under reduced pressure. The crude products were subjected to purification by column chromatography with silica gel (100-120 mesh) size using methanol: ethyl acetate as the eluent to yield 1, 2, 4, 5 – tetrasubstituted imidazoles (**5a-5o**).

Spectral Data:

1-(2-(2, 4, 5- triphenyl- 1H- imidazol- 1- yl) ethyl) piperazine (**5a**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.02 (s, 4H), 2.23 (t, J= 7.5 Hz, 2H), 2.4 (s, 1H), 2.64 (t, 4H), 4.03 (t, J= 7.5 Hz, 2H), 7.12-7.73 (m, 15H); ^{13}H NMR ($CDCl_3$, 125 MHz) δ 41.88, 45.62, 54.07, 58.36, 126.31, 126.31, 126.83, 128.08, 128.35, 128.67, 128.79, 128.96, 129.14, 129.29, 129.58, 131.09, 131.35, 131.37, 134.50, 134.50, 137.75, 147.96; HR MS (ESI): calculated for $C_{27}H_{28}N_4$[M+H]$^+$409.23; Found409.24

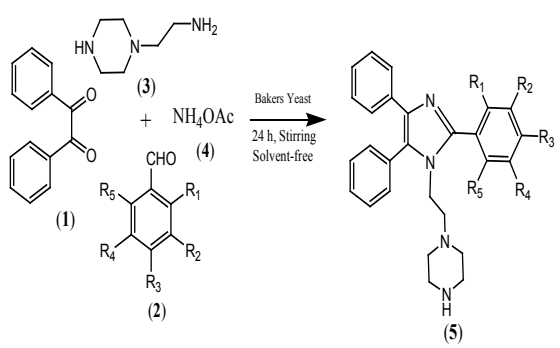
Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

1-(2-(4, 5- diphenyl-2-(p-tolyl)-1H- imidazol-1-yl) ethyl) piperazine (**5b**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 4H), 2.24 (t, J= 7.0 Hz 4H), 4.02 (t, J= 7.5 Hz, 2H), 7.12-7.48 (m, 14H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.40, 41.85, 45.69, 54.22, 58.34, 126.26, 126.84, 127.42, 127.81, 128.05, 128.34, 128.51, 128.73, 129.10, 129.14, 129.33, 129.44, 129.91, 131.01, 131.11, 131.43, 134.51, 137.62, 138.90, 148.06. HR MS (ESI): calculated for $C_{28}H_{30}N_4$ $[M+H]^+$ 423.25 Found 423.26

4-(4, 5- diphenyl-1-(2-(piperazine-1-yl) ethyl)-1H- imidazol-2-yl)- N,N- dimethylaniline (**5c**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.01 (d, J= 2.8 Hz, 4H) 2.23 (t, J= 7.6 Hz, 2H), 2.40 (s, 1H), 2.63 (t, J= 4.4 Hz, 4H), 2.97 (s, 6H), 3.99 (t, J=7.6 Hz, 2H), 6.75-7.54 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.27, 41.80, 45.70, 54.20, 58.30, 112.05, 118.73, 126.08, 126.82, 128.00, 128.58, 129.04, 130.06, 131.13, 131.69, 134.75, 137.28, 148.63, 150.71. HR MS (ESI): calculated for $C_{29}H_{33}N_5$ $[M+H]^+$452.28, Found 452.29

Results and Discussion

As a part of our ongoing investigation in developing a versatile and efficient method [14-17]. Herein, we report efficient synthesis method for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles from benzil, aromatic aldehyde, aminoethylpiperazine, ammonium acetate in the presence of bakers yeast (**Scheme 1**).



Scheme 1. Synthesis of 1, 2, 4, 5- tetrasubstituted imidazole imidazoles.

Reaction was carried out simply by mixing benzil, aminoethylpiperazine with an aromatic aldehyde, ammonium acetate in the presence of a catalytic amount 15 mol % of beakers yeast. After work-up, a crude mixture was obtained, which on purification by column chromatography yielded 30% of 1, 2, 4, 5- tetrasubstituted imidazoles **5a**. In other experiment, bakers yeast, D-glucose, benzil, benzaldehyde, aminoethylpiperazine and ammonium acetate were taken together in 5 ml of phosphate buffer and stirred for 24 h. The reaction mixture, after work-up and purification, yielded **5a** (95 %). Thus it was concluded that fermenting beakers yeast provides a good catalytic medium for efficient coupling of benzil, aldehyde, aminoethylpiperazine and ammonium acetate. It is also clear that adding the four components (benzil, aldehyde, aminoethylpiperazine and ammonium acetate) in pre-stirred yeast glucose mixture gives a good yield in comparison to that in which all the components were added simultaneously. In order to study the generality of this procedure a series of tetrasubstituted imidazole compounds were synthesized. The results are listed in Table 1.

Table 1. Bakers yeast catalyzed synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles[a].

Entry	R_1	R_2	R_3	R_4	Product	Time(h)	Yield[b]
a	H	H	H	H	5a	24	95
b	H	H	CH3	H	5b	24	95
c	H	H	N(CH3)2	H	5c	24	91
d	H	H	Br	H	5d	24	92
e	H	H	Cl	H	5e	24	93
f	H	H	F	H	5f	24	90
g	H	H	NO2	H	5g	24	89
h	H	H	OCH3	H	5h	24	93
i	H	F	H	H	5i	24	83
j	H	Br	F	H	5j	24	83
k	H	Br	OH	H	5k	24	90
l	H	Cl	Cl	H	5l	24	90
m	Cl	Cl	H	H	5m	24	93
n	H	OCH_3	H	OCH_3	5n	24	87
o	H	OCH_3	OCH_3	OCH_3	5o	24	91

[a]**Benzil: benzaldehyde: aminoethylpiperazine: NH_4OAc**

(1 mmol: 1 mmol: 1mmol: 2mmol) under solvent free condition.

[b]Isolated yield.

Several activated and deactivated aromatic aldehydes afforded high yields of products with high purity.

Conclusion

In conclusion, the bakers yeast has been employed as a novel, very efficient, catalyst for the convenient synthesis of tetrasubstituted imidazoles in excellent yields from aminoethylpiperazine and using wide variety of aromatic aldehydes. In addition, low-cost of catalyst, solvent free conditions, environmental friendliness, easy availability, make this methodology a valid condition to the existing processes in the field of tetrasubstituted derivatives synthesis.

Acknowledgements

Author thanks to Dr. S. S. Ali for his valuable guidance for research work.

References

1. Abdel-Meguid, S.S., Meteall, B.W., Corr. T. J et al Biochemistry 33, (1994) 11671.
2. (a) Wasserscheid, P., Keim, W., Angew. Chem. Int. Ed. Engl. 39, (2000) 37872. (b) Bourissou, D., Guerret, O., Ggabbai, F. T., Bertrand, G., Chem. Rev. 100, (2000)
3. Radziswki, B., Chem. Ber. 15, (1882) 1268.
4. Japp, F.R., Robinson, H. H., Chem. Ber. 15, (1882) 1268.
5. (a) Siddiqui, S.A., Srinivasan, K.V., Synthesis 17, (2006) 2849. (b) Wang, J., Jr. Dyers, L., Jr. Mason, R., Amoya, W. P., Bu, X.R., J. Org. Chem. 70, (2005) 2353.
6. Balalaie, S., Arabanian, A., Hashtroudi, M.S., Mont. Fur. Chem. 131, (2000) 945.
7. Kidwai, M., Mothsra, P., Bansal, V., Goyal, R., Mont. Fur. Chem. 137, (2006) 1189.
8. Sharma, G.V.M., Jyothi, Y., Lakshmi, P.S, Synth. Commun. 36, (2006) 2991.
9. Sangshetti, J.N., Kokare, N.D., Kothakar, S.A, Shinde, D.B., Mont. Fur. Chem. 139, (2008) 125.

Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

10. Wolkenberg, S.E., Winoski, D.D., Leister, W.H., et. al Org. Lett. 6, (2004) 1453.
11. Kumar, A., Maurya, R. A., Tetrahedron Lett. 48, (2007) 4569.
12. Sih, C. J., Chen, C. S, Angrew. Chem. Int. Ed. Engl. 23, (1984) 570.
13. (a) Fuganti, C., Grasselli, P., Servi, S., Spreafico, F., Zirotty, C., Casaty, P. J., Org. Chem. 49, (1984) 4087. (b) Fuganti, C., Pure Appl. Chem. 62, (1990) 1442. (c) Utaka, M., Konisi, S., Tkeda, A., Tetrahedron Lett. 27, (1986) 4737. (d) Ohta, H., Kobayashi, N., Ozaki, K. J. Org. Chem. 54, (1989) 1802. (e) Rao, K. R., Kumar, H.M.S., Bioorg. Med. Chem. Lett. 10, (1991) 507.
14. Ali, S. S., Chinese Chem. Lett. 22, (2011) 793.
15. Ali, S. S., Ahmed, S. K., Res. J. Pharmaceutical Biological and Chemical Sci. 2 (1) (2011) 55-60.
16. Ali, S. S., Syed, S. Q., Der Pharma Chemica 3 (1), (2011) 518-522.
17. Ali, S. S., Org. Chem.: An Indian Journal (2010) 05-09.