MICROWAVE ASSISTED ONE POT SYNTHESIS OF *N*-ALKYL TRIARYL IMIDAZOLE IN PRESENCE OF PHASE TRANSFER CATALYST

Arvind Tapase
Department of Chemistry, Abasaheb Marathe Arts and New Commerce, Science College, Rajapur (Vikhare-Gothane) Dist. Ratnagiri 416 702

Abstract:

Number of substituted 2,4,5 triaryl imidazole reacts fast with alkyl halide, base, alcohol and phase transfer catalyst, under microwave irradiation to obtain the corresponding N-alkyl 2,4,5 triaryl imidazoles. The short reaction time (120 to 170 sec.), cleaner reaction and easy work up make this protocol practically and economically attractive.

Key words: Triaryl imidazoles, alkyl halides, microwave irradiation, N-alkyl triaryl imidazoles, Phase transfer catalyst.

Introduction

Triarylimidazole compounds have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent intimidate,[1] the antiulcer-active agent cimetidine,[2] the proton pump inhibitor omeprazole,[3] the fungicide ketoconazole,[4] and the benzodiazepine antagonist flumazenil,[5] are imidazole derivatives.

The synthesis, reactions and biological properties of substituted imidazole constitutes a significant part of modern heterocyclic chemistry.[6] Compounds with the imidazole ring system have many pharmacological properties play important roles in biochemical processes.[7] Many of substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase.[8]

In recent years, substituted imidazoles are substantially used in ionic liquid,[9] that has been given a new approach to 'Green Chemistry'. In addition, they are used in photography as photosensitive compound.[10] Literature survey reveals several methods for synthesizing them, mainly using nitriles and esters [11-13] as the starting substrates. Japp and Radziszewski proposed the first synthesis of the imidazole core in 1882, starting from 1, 2, dicarbonyl compounds aldehydes and ammonia to obtain 2, 4, 5 triphenylimidazoles.[14-15] Subsequently, many other syntheses of this important heterocycle have been published.[16] For example, 2, 4 – diaryl -1*H* - imidazoles are often obtained from amidines and R-bromo arylketones.[17]

There are several methods for the synthesis of highly substituted imidazoles. The mostly used methods in the last decade are as follow: (a) synthesis via hetero- Cope rerrangment.[18] (b) four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin,[19] (c) reaction of *N*-(2- oxo)-amides with ammonium trifluroacetate,[20] (d) reaction of *N*-alkyl-*N*-(β- keto)amides with ammonium acetate.[21]

The number of methods have been developed for the synthesis of 2, 4, 5 trisubstituted imidazoles. 2, 4, 5 trisubstituted imidazoles are generally synthesized by three-component cyclocondensation of a 1,2-diketone, α- hydroxyketone or α-ketomonoxime with an aldehyde and ammonium acetate, which comprise the use of microwaves,[22-25] ionic liquids,[26-30] refluxing in acetic acid,[31-33] silica sulfuric acid,[34-35] $NiCl_2.6H_2O/Al_2O_3$,[36] $Yb(OTf)_3$,[37] $Yb(OPf)_3$,[38] iodine,[39] $Zr(acac)_4$,[40] $InCl_3.3H_2O$,[41] heteropolyacid,[42] sodium bisulfite,[43] potassium aluminum sulfate (alum),[44] ceric ammonium nitrate (CAN),[45-46] polymer- supported $ZnCl_2$ [47] and L-proline.[48]

On the other hand, the synthesis of 1,2,4,5 tetrasubstituted imidazoles are carried out by four component condensation of a 1,2 diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde, primary amine and ammonium acetate using microwaves,[49] heteropolyacid,[50] silica gel/$NaHSO_4$.[51] In addition, they can also be accessed by the cycloaddition reaction of mesoionic 1,3-oxazolium-5-olates with N-(arylmethylene)-benzenesulfonamides,[52] condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation[53] and by N-alkylation of trisubstitued imidazoles.[54]

Experimental

All compounds were characterized by modern spectral and elemental techniques. IR spectra was recorded in KBr disc on a Perkin Elmer spectrometer for all products ^{1}H-NMR spectra was recorded on NMR spectrometer in $CDCl_3$ using chloroform as an internal standard. The mass spectra was recorded on GCMS-QP 2010 mass spectrometer. All the reagents used were of AR grade and were used without further purification. The reactions were carried out in microwave oven (CE2977 Samsung).

General procedure for Synthesis of N – alkyl 2, 4, 5 triaryl imidazole.

Different 2, 4, 5 triaryl imidazole (5 mmol), sodium hydroxide (10 mmol), 5 ml ethanol and tetrabutyl ammonium bromide (0.5 mmol) as a catalyst were taken in 50 ml beaker, stirred for few second and placed in microwave oven for irradiation at 600 Watt for 30 sec. to obtain 2, 4, 5 triaryl imidazole salt. The mixture was cooled at room temperature. The alkyl halide (7.5 mmol) was mixed with the resulting mixture and irradiated in microwave oven at 600 Watt for 120 to 170 sec. to obtain *N* – alkyl 2, 4, 5 triaryl imidazole. The progress of reaction was monitored by TLC (ethyl acetate: hexane as eluent). After completion of alkylation reaction the content was cooled at room temperature. The reaction mixture was

poured in ice-water (20 ml) and washed with (2 x 25 ml) 2N hydrochloric acid to remove unreacted salt. The crude product was purified by crystallization using ethanol as a solvent to obtain solid product of *N* – alkyl 2, 4, 5 triaryl imidazole **(Scheme - IV).**

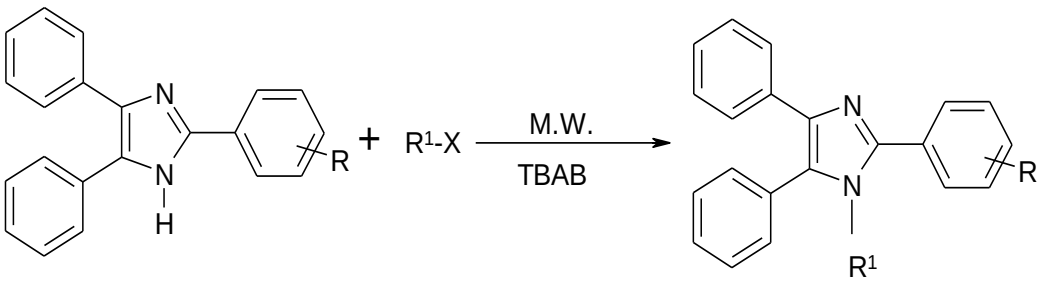
All the synthesized compounds **(4a – 4k)** were characterized by spectral analysis. Representative spectral characterization of the compounds is as below

4b. methyl - 2, 4, 5-triphenyl - 1H - imidazole

FT-IR (KBr, ν cm^{-1}): 3082 (C - H), 2885, 2805 (C-H alphatic), 1594 (C=C), 1357, 1167 (C-N aromatic), 1660 (C=C), 1494 (C=N).

^{1}H NMR (400Mz, $CDCl_3$): δ = 8.03 - 7.15 (m, 15 H Ar - H), 8.23 (brs, NH), 3.16 (s, 3H, CH_3), ES/MS m/z = 310 [M - H].

Reaction



Results and Discussion

Table - 1 - Physical data of the synthesized compounds (*N* – alkylation of 2, 4, 5 triaryl imidazole) (1a – 1k).

Entry	R	R^1	Watt W	Time Sec.	Yield (%)	M. P. (^OC) Found	M. P. (^OC) Reported[63,64]
1a	H	$C_6H_5CH_2$	600	140	92	159-160	160-162
1b	H	CH_3	600	125	88	143-144	144-145
1c	H	C_2H_5	600	120	90	168-169	166-167
1d	4-CH_3	$C_6H_5CH_2$	600	165	94	164-165	165-166
1e	4-CH_3	CH_3	600	170	91	207-208	209-210
1f	4-CH_3	C_2H_5	600	130	80	122-123	123-125
1g	4-CH_3	iso-C_4H_9	600	145	91	148-150	150-152
1h	3-Br	$C_6H_5CH_2$	600	135	93	156-157	157-160
1i	4-Br	CH_3	600	140	92	172-173	173-174
1j	4-Br	C_2H_5	600	150	90	192-194	190-191
1k	4-Cl	$C_6H_5CH_2$	600	130	95	164-166	164-165

In order to find optimum reaction conditions, condensation of benzil, benzaldehyde and ammonium acetate in the presence of sodium bisulfite as catalyst was done. The optimum molar ratio of benzil: benzaldehyde: ammonium acetate 1:2:1 and sodium bisulfite (2 mol %) using ethanol solvent under microwave irradiation, 2(phenyl) 4, 5- diphenyl 1H – imidazole was obtained with 97 % yield at 600 Watt for 118 Sec. Results with benzaldehydes were encouraging in a similar fashion, a variety of aromatic and heterocyclic aldehyde and benzil subjected to this microwave assisted procedure gives high yields of corresponding 2, 4, 5 triaryl imidazole.

The results are summarized in **Table-1**. From the results mentioned in Table the aldehyde with electron-donating substituents favour the reaction and it was completed with shorter reaction time and high yields than the aldehyde with electron-withdrawing substituents. Also, the present method was found to be effective for hetero-aromatic aldehyde for the synthesis of 2-heteroaryl 4, 5 diphenyl 1Himidazole with better yield. To determine the role of sodium bisulfite the same reaction was carried out in the absence of catalyst at same conditions, which resulted in no product formation after 15 min. these result indicate that sodium bisulfite exhibits a high catalytic activity in this transformation. The procedure gives high yield products.

Comparison of results as mentioned in Table-1 with results obtained by some other reported procedures for synthesis of 2, 4, 5 triaryl imidazoles shows the promising feature of this method in terms of reaction rate and the yield of products as compared with reports in the literature.

Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of N-alkyl 2,4,5 triaryl imidazole using tetra butyl ammonium bromide as a eco-friendly, inexpensive and efficient catalyst. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.

Acknowledgement

The author is thankful to the Principal, Abasaheb Marathe Arts and New Commerce, Science College, Rajapur Dist. Ratnagiri for providing necessary facilities.

References

1. Wauquir A., Van Den Broeck W. A. E., Verheyen J. L. and Janssen P. A. J., *Eur. J. Pharmacol*, 47, 367, **(1978)**.
2. Brimblecombe R. W., Duncan W. A. M., Durant G. J., Emmett J. C., Ganellin C. R. and Parons M. E., *J. Int. Med. Res*, 3, 86, **(1975)**.
3. Tanigawara Y., Aoyama N., Kita T., Shirakawa K., Komada F., Kasuga M. and Okumura K., *Clin. Pharmacol Ther.*, 66, 528, **(1999)**.
4. Heers J., Backx L. J. J., Mostmans J. H. and Van Cutsem J., *J. Med. Chem.*, 22, 1003, **(1979).**
5. Hunkeler W., Mo'hler H., Pieri L., Polc P., Bonetti E. P., Cumin R., Schaffner R. and Haefely W., *Nature*, 290, 514, **(1981)**.
6. Grimmett M. R., *In Comprehensive Heterocyclic Chemistry II*, Katritzky A. R., Rees C. W., Eds., Pergamon Prss, London, 5, 374, **(1984)**.
7. Lambardino J. G. and Wiesman E. H., *J. Med. Chem.*, 17, 1182, **(1974)**.
8. Liverton N. J., Butcher J. W., Claiborne C. F., Claremon D. A. and O'Keefe S. J., *J. Med. Chem.*, 42, 2180, **(1999)**.
9. Bourissou D., Gherret O., Ggabbai F. T. and Bertrand G., *Chem. Rev.*, 100, **(2000).**
10. Satoru I., *Imidazoles derivative for chemiluminescence microanalysis.* Japn Kokkai Tokyo Koho JP 01, 117, 867, **(1989)**. *Chem Abstr*., 111, 214482, **(1989).**
11. Grimmett M. R., *In Comprehensive Heterocyclic Chemistry*, Katritzky A. R. and Rees C. W., Eds., Pergamon, New York 5, 457, **(1984)**.
12. Grimmett M. R., *In Comprehensive Heterocyclic Chemistry II*, Katritzky A. R., Rees C. W. and Scriven E. F. V., Eds., Pergamon, New York 3, 77, **(1996)**.
13. Balalaie S., Arabanian A., and Hashtroudi M. S. *Monatsh Chem.*,131,945, **(2000)**.
14. Radzisszewski B., *Chem Ber.*, 15, 1493, **(1882)**.
15. Japp F. R. and Robinson H. H., *Chem Ber.*, 15, 1268, **(1882)**.
16. Grimmett M. R., *In Comprehensive Heterocyclic Chemistry II*, Katritzky A. R., Rees C. W. and Scriven E. F. V., Eds., Pergamon Prss, Elmsford, New York 3, 77-220, **(1996)**.

17. Li B., Chiu C. K. F., Hank R. F., Murry J., Roth J. and Tobiassen H., *Org. Proc. Res.*, 6, 682, **(2002)**.
18. Lantos I., Zhang W. Y., Shui X. and Eggleston D. S., *J. Org. Chem.*, 58, 7092, **(1993).**
19. Zhang C., Moran E. J., Woiwode T. F., Short K. M. and Mjalli A. M. *Tetrahedron Lett.*, 37, 751, **(1996)**.
20. Claiborne C. F., Liverton N. J. and Nguyen K. T., *Tetrahedron Lett.*, 39, 8939, **(1998).**
21. Lee H. B. and Balasubramanian S., *Org. Lett.*, 2, 323, **(2000)**.
22. Usyatinsky A. Y. and Khemelnitsky Y. L., *Tetrahedron Lett.*, 41, 5031, **(2000)**.
23. Wolkenberg S. E., Wisnoski D. D., Leister W. H., Wang Y., Zhao Z. and Lindsley C. W., *Org. Lett.*, 6, 1453, **(2004)**.
24. Sparks R. B. and Combs A. P., *Org. Lett.*, 6, 2473, **(2004)**.
25. Oskooie H. A., Alimohammadi Z. and Heravi M. M., *Heteratom Chem.*, 17, 699, **(2006).**
26. Siddiqui S. A., Narkhede U. C., Palimkar S. S., Daniel T., Lahoti R. J. and Srinivasan K. V., *Tetrahedron*, 61, 3539, **(2005)**.
27. Xia M. and Lu Y., *J. Mol. Catal A. Chem.*, 265, 205. **(2007)**.
28. Chary M. V., Keethysri N. C. Vupallapati S., Lingaiah N. and Kantevari S., *Catal. Commun.*, 9, 2013, **(2008)**.
29. Shaabani A., Rahmati A., Aghaaliakbari B. and Safaei-Ghomi J., *Synth. Commun.* 36, 65, **(2006)**.
30. Khosropour A. R., *Can. J. Chem.*, 86, 264, **(2008)**.
31. Wang J., Mason R., Derveer D. V., FengK. and Bu X. R., *J. Org. Chem.*, 68, 5415, **(2003).**
32. Sarshar S., Siev D. and Mjalli M. M., *Tetrahedron Lett.*, 37. 835, **(1996)**.
33. Gallagher T. F., Seibel G. L., Kassis S. and Laydon J. T., *Bioorg. Med.Chem.*, 5, 49, **(1997)**.
34. Shaabani A. and Rahmati A., *J. Mol. Catal. A. Chem.* 249, 246, **(2006)**.
35. Shaabani A., Rahmati A., Farhangi E. andBadri Z., *Catal. Commun.* 8, 1149, **(2007).**
36. Heravi M. M., Bakhtiari K., Oskooie H. A. and Taheri S., *J. Mol. Catal. A.Chem.*, 263, 279, **(2007)**.
37. Wang L., Wang Y., Tian H., Yao Y., Shao J. and Liu B., *J. Fluorine Chem.*, 127, 1570, **(2006)**.
38. Shen M., Cai C. and Yi W., *J. Fluorine Chem.*, 129, 541, **(2008)**.
39. Kidwai M., Mothsra P., Bansal V., Somvanshi R. K., Ethayathulla A. S., Dey S. and Singh T. P., *J. Mol. Catal. A. Chem.*, 265, 177, **(2007).**
40. Khosropour A. R., *Ultrason. Sonochem.* 15, 659, **(2008)**.
41. Sharma S. D., Hazarika P. and Konwar D., *Tetrahedron Lett.*, 49, 2216, **(2008)**.

42. Heravi M. M., Sadjadi S., Oskooie H. A., H ekmatshoar R. and Bomoharram F. F., *J.*

43. *Chin. Chem. Soc.*, 55, 1199, **(2008)**.

44. Sangshetti J. N., Kokare N. D., Kotharkar S. A. and Shinde D. B., *Monatsh Chem.*, 139, 125, **(2008)**.

45. Mohamadi A. A., Mivech M. and Kefayati H., *Monatsh. Chem.*, 139, 935, **(2008)**.

46. Sangshetti J. N., Kokare N. D., Kotharkar S. A. and Shinde D. B., J. C*hem., Sci.* 120, 463, **(2008)**.

47. Shaabani A., Maleki A. and Behnam M., *Synth. Commun.*, 39, 102, **(2009)**.

48. Wang L. and Cai C., *Monatsh. Chem.*, 140, 541, **(2009)**.

49. Samai S., Nandi G. C., Singh P. and Singh M. S., *Tetrahedron,* 65, 10155, **(2009)**.

49. Balalaie S., Arabanian A. *Green Chem.* 2, 274, **(2002).**

50. Heravi M. M., Derikvand F., Bamoharram F. F. *Mol. Catal. A: Chem.* 263, **(2007).**

51. Karimi A. R., Alimohammadi Z., Azizian J., Mohammadi A. A., Mohammadizadeh M. R. *Catal Commun.* 7, 728, **(2006).**

52. Consonni R., Croce P. D., Ferraccioli R., Rosa C. L. *J. Chem. Res*. (S) 188, **(1991).**

53. Balalaie S., Hashemi M. M., Akhbari M. *Tetrahedron Lett*. 44, 1709, **(2003).**

54. Ucucu U., Karaburun N. G., Iskdag I. *II Farmaco* 56, 285, **(2001).**