http://dx.doi.org/10.5012/bkcs.2012.33.4.1231

Convenient One-Pot Synthesis of 2,4,5-Triaryl-1*H*-imidazoles from Arylaldehydes, Benzyl Alcohols, or Benzyl Halides with HMDS in the Presence of Molecular Iodine

Hojat Veisi,[*] Ardashir Khazaei,[†,*] Leila Heshmati, and Saba Hemmati[‡]

Department of Chemistrt, Payame Noor University, 19395-4697 Tehran, I.R. of Iran. [*]E-mail: hojatveisi@yahoo.com
[†]Faculty of Chemistry, Bu-Ali Sina University, P.O. Box 6517838683, Hamedan, Iran. [*]E-mail: Khazaei_1326@yahoo.com
[‡]Young Researchers Club, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran
Received October 24, 2011, Accepted January 7, 2012

A one-pot efficient procedure for the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives in good to excellent yields by reaction between hexamethyldisilazane and arylaldehydes, benzyl alcohols, benzyl halides in the presence of molecular iodine has been developed. The remarkable advantages of this method are the simple workup procedure, high yields of products, and the availability of reagents.

Key Words : 2,4,5-Triaryl-1*H*-imidazole, Hexamethyldisilazane, Iodine, Aldehydes

Introduction

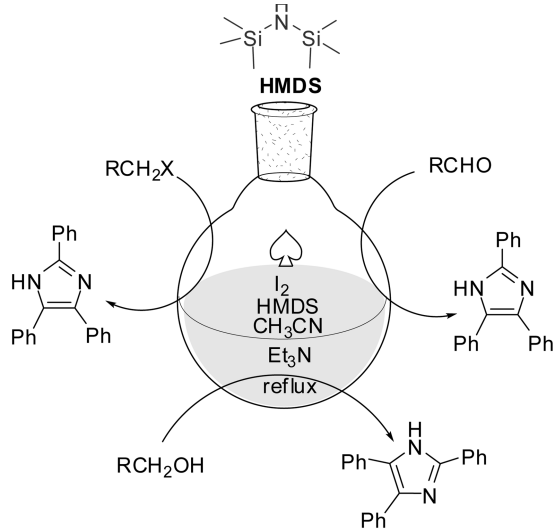
Synthetic study of imidazole units is very important due to their potent biological activity[1] and synthetic utility.[2] Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes.[3a] The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites[3b] (*e.g.*, Zn, Fe, Mg). Various substituted imidazoles act as inhibitors of p38MAPkinase,[4a] B-Raf kinase,[4b] glucagon receptors,[5] plant growth regulators,[6] therapeutic agents,[7] antibacterial,[8] antitumour,[9] and also pesticides.[10] Recent development of green chemistry and organometallic chemistry expands the utility of imidazoles as ionic liquids[11] and *N*-heterocyclic carbenes.[12] Trifenagrel[13] is a 2,4,5-triaryl-1*H*-imidazole that reduces platelet aggregation in several animal species and humans.

Due to their great importance, many synthetic strategies for synthesis of 2,4,5-triarylylimidazoles from reaction of a 1,2-dicarbonyl compound, various aldehydes, and ammonia have been developed.[14,15] Also, Grimmett *et al.* proposed the synthesis of imidazole using nitriles and esters.[16]

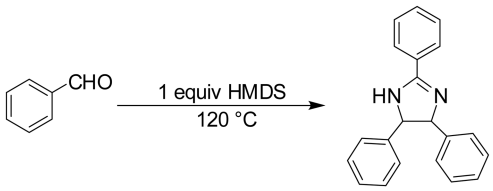
Recently, there have been several methods reported in the literature for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzil/benzoin, aldehydes, and ammonium acetate using different catalyst such as zeolite HY/silica gel,[17] zirconium tetrachloride,[18] nickel(II) chloride hexahydride,[19] iodine,[20] sodium bisulfite,[21] acidic aluminum oxide,[22] acetic acid,[23] ammonium acetate,[24] heteropolyacid,[25a] $BF_3{\cdot}SiO_2$,[25b] silica gel/$NaHSO_4$ [25c] or $HClO_4$-SiO_2[25d], L-Prolin,[26] SBPPSA,[27] molten TBAB[28] and ytterbium triflate.[29,30] The application of these methods suffer from some disadvantages such as the use of costly or less easily available reagents, harsh reaction conditions, long reaction times, poor yields, and the use of toxic solvents. Therefore, despite a number of precedents, an efficient, practical and facile method for these transformations is desired.

Herein, as part of our ongoing study on the application of *N*-halo reagents in organic synthesis[31,32] and molecular iodine,[33] we would like to report the use of molecular iodine as an inexpensive and effective activator and oxidant for the efficient one-pot synthesis of 2,4,5-triaryl-1*H*-imidazoles in high yields (Scheme 1).

We initially performed the reaction of benzaldehyde (1 equiv.) with 1 equiv. of hexamethyldisilazane (HMDS) at



Scheme 1. Synthesis of 2,4,5-triaryl-1*H*-imidazoles.



Scheme 2. Synthesis of 2,4,5-triphenylimidazoline.

Table 1. Synthesis of 2,4,5-Triaryl-1*H*-imidazoles From Arylaldehydes, Aryl Alcohols and Aryl Halides

Entry	Substrate	Time (h)	Yield (%)	mp	mp/[Lit.]
1	PhCHO	3	96	273-275 ºC	273-276 ºC/28
2	2-MeO-C_6H_4CHO	3.5	90	234-237 ºC	
3	4-MeO-C_6H_4CHO	3.5	85	226-227 ºC	225-228 ºC/28
4	4-Me-C_6H_4CHO	4	80	254-257 ºC	256-258 ºC/28
5	4-Cl-C_6H_4CHO	2	96	272-274 ºC	275-276 ºC/28
6	2-Cl-C_6H_4CHO	2	92	270-272 ºC	268-270 ºC/28
7	4-NO_2-C_6H_4CHO	2.5	96	271-273 ºC	273-274 ºC/28
8	3-NO_2-C_6H_4CHO	2.5	90	d.	d./28
9	2-Furylaldehyde	2	96	d.	d./28
10	$PhCH_2OH$	4	90	273-275 ºC	273-276 ºC/28
11	2-MeO-$C_6H_4CH_2OH$	4.5	85	234-237 ºC	
12	4-MeO-$C_6H_4CH_2OH$	4.5	88	224-225 ºC	225-228 ºC/28
13	4-Cl-C_6H_4 CH_2OH	4	95	272-274 ºC	275-276 ºC/28
14	2-Furfural	4	96	d.	d./28
15	4-NO_2-C_6H_4 CH_2OH	6	70	271-273 ºC	273-274 ºC/28
16	$PhCH_2Br$	4	90	273-275 ºC	273-276 ºC/28
17	$PhCH_2Cl$	4	90	273-275 ºC	273-276 ºC/28

120 °C for 6 h under solvent free conditions (Scheme 2). 2,4,5-triphenylimidazoline in 85% yield was obtained.

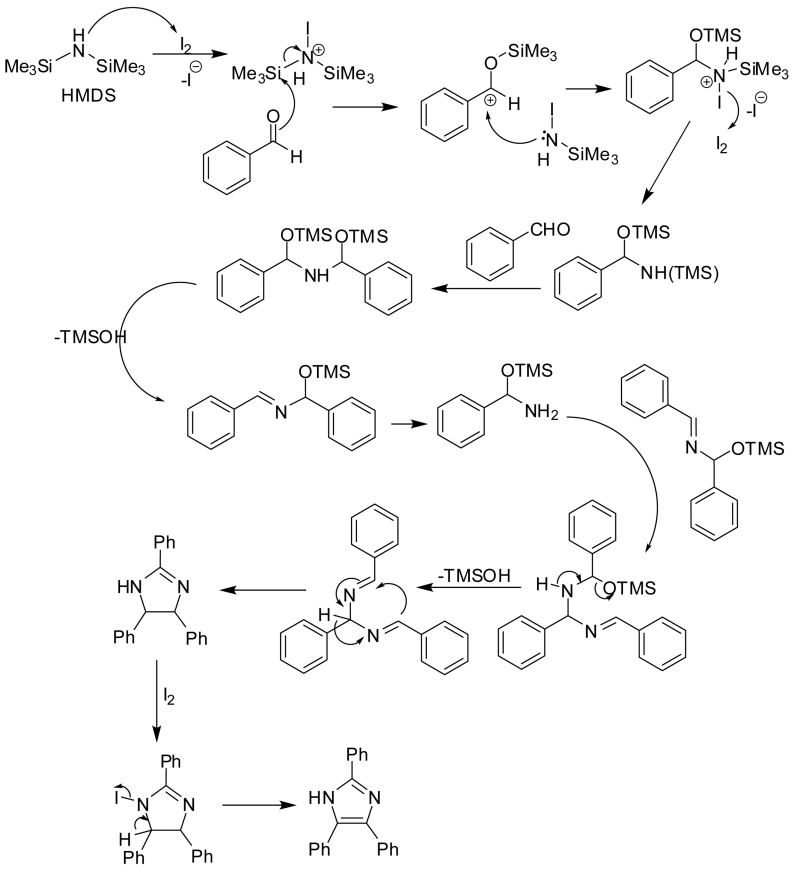
In continuation of our work, we were interested to synthesis of triarylimidazole compounds in one-pot. For this purpose the above reaction condition was repeated by adding molecular iodine (1 equiv), Et_3N (1 equiv) and CH_3CN for 3 hours under reflux conditions. 2,4,5-Triphenyl-1*H*-imidazoles was formed in 96% yield. Encouraged by our initial studies, we then investigated the generality and versatility of this procedure using a series of structurally different aldehydes (commercially available) under this optimized condition. A wide range of aromatic aldehydes were employed and all imidazoles were obtained in high to excellent yields (Table 1), which demonstrated that this is a general method that tolerates both electron-withdrawing and electron-donating constituents.

In continuation of this work, we were interested in expanding this method by using benzylic alcohols and benzylic halides. These substrates were separately treated with molecular iodine (2 equiv), trimethylamine (2 equiv) and hexamethyldisilazane (1.1 equiv) in acetonitrile at reflux; 2,4,5-triaryl-1*H*-imidazole derivatives were formed in high yields (Table 1).

The proposed mechanism[28,34] for this reaction is given in Scheme 3. I believe that in this procedure, molecular iodine would act in dual role both as a catalyst to activate the HMDS and as oxidant to oxidation of imidazoline to imidazole.

Conclusion

In conclusion, we have demonstrated a new, straight-



Scheme 3. Proposed mechanism.

forward, and efficient method for the one-pot synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives using molecular iodine as a commercially available catalyst. The significant features of this method include: (a) operational simplicity, (b) the use of available and inexpensive catalyst, (c) high yields of products, (d) easy and clean workup.

Experimental Section

(i) Synthesis of 2,4,5-Triaryl-1*H*-imidazoles from Aryl-aldehyde Derivatives. To a mixture of aldehyde (1 mmol) and HMDS (1.1 mmol) in 3 mL CH_3CN was added I_2 (1 mmol) at room temperature under empty balloon. The reaction mixture was stirred at reflux temperature and the progress of the reaction was monitored by TLC. After complete conversion, the system was cooled to room temperature, and the solvent was evaporated. Then, the mixture was washed with 10% $Na_2S_2O_3$ solution. The separated precipitate was filtered and then washed with H_2O-EtOH (2:1). The solid was recrystallized (EtOH) to give the pure product in good yield.

(ii) Synthesis of 2,4,5-Triaryl-1*H*-imidazoles 1 from Benzyl Alcohols or Benzyl Halides. To a mixture of benzyl alcohol or benzyl halide (1 mmol) and HMDS (1.1 mmol) in 3 mL CH_3CN was added I_2 (2 mmol) and Et_3N (2 mmol) at room temperature under empty balloon. The mixture was stirred at reflux for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the system was cooled to room temperature, and the solvent was evaporated. Then, the mixture was washed with 10% $Na_2S_2O_3$ solution. The separated precipitate was filtered and then washed with H_2O-EtOH (2:1). The solid was recrystallized (EtOH) to give the pure product in good yield.

Analytical Data for Selected Compounds (Table 1).

2,4,5-Triphenyl-1*H*-imidazole: mp 273-275 °C; IR (KBr): ν_{max} 3430, 2995, 2471, 1638, 1216 cm^{-1}; ^1H NMR (DMSO, $CDCl_3$): δ 7.40-8.12 (m, 15H, Ar), 12.62 (br s, 1H, NH).

2,4,5-Tris(4-methoxyphenyl)-1*H*-imidazole: mp 234-237 °C; IR (KBr): ν_{max} 3420, 2857, 2435, 1625, 1214 cm^{-1}; ^1H NMR (DMSO, $CDCl_3$): δ 3.80 (s, 9H, CH_3), 6.93-6.96 (d, J = 8.8 Hz, 6H, Ar), 8.02-8.05 (d, J = 8.8 Hz, 6H, Ar), 12.52 (br s, 1H, NH); Mass: 386.

Acknowledgments. We are thankful to Payame Noor University (PNU) for partial support of this work.

References

1. (a) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; p 345. (b) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; p 77-220. (c) *The Pharmacological Basis of Therapeutics*, 10th ed.; Gilman, A. G., Goodman, L. S., Eds.; Macmillan: New York, 2001. (d) Prisinano, T.; Law, H.; Dukat, M.; Slassi, A.; MaClean, N.; Demchyshyn, L.; Glennon, R. A. *Bioorg. Med. Chem.* **2001**, *9*, 613.
2. For examples see: (a) Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett.* **1990**, *31*, 1771. (b) Langlois, Y.; Dalko, P. I. *J. Org. Chem.* **1998**, *63*, 8107. (c) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (d) Meiere, S. H.; Valahovic, M. T.; Harman, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 15099. (e) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393.
3. (a) Lambardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182. (b) Philips, A. P.; White, H. L.; Rosen, S. *Eur. Pat. Appl.* EP 58890, 1982.
4. (a) Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Keys, J. R.; Vatter, S. W. L.; Strickler, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739. (b) Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 378.
5. de Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantalo, N.; Pivnichny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmenn, W. K. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 641.
6. Schmierer, R.; Mildenberger, H.; Buerstell, H. German Patent 361464, 1987; *Chem. Abstr*. **1988**, *108*, 37838.
7. Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Van Custem, J. *J. Med. Chem*. **1979**, *22*, 1003.
8. Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1023.
9. Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinsky-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem*. **2002**, *45*, 1697.
10. Maier, T.; Schmierer, R.; Bauer, K.; Bieringer, H.; Buerstell, H.; Sachse, B. U.S. Patent 4820335, 1989; *Chem. Abstr*. **1989**, *111*, 19494w.
11. (a) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (b) Nara, S. J.; Naik, P. U.; Harjani, J. R.; Salunkhe, M. M. *Indian J. Chem*. **2001**, *45*B, 2257. (c) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.
12. (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Arnold, P. L.; Liddle, S. T. *Chem. Commun.* **2006**, 3959. (c) Ku¨ hl, O. *Chem. Soc. Rev.* **2007**, *36*, 592.
13. (a) Radziszewski, B. *Chem. Ber.* **1882**, *15*, 1493. (b) Japp, F. R.; Robinson, H. H. *Chem. Ber.* **1882**, *15*, 1268.
14. Radziszewski, B. *Chem. Ber.* **1882**, *15*, 1493.
15. Japp, F. R.; Robinson, H. H. *Chem. Ber.* **1882**, *15*, 1268.
16. Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; p 77.
17. Balalaie, S.; Arabanian, A.; Hashtroudi, M. S. *Monatsh. Chem.* **2000**, *131*, 945.
18. Sharma, G. V. M.; Jyothi, Y.; Lakshmi, P. S. *Synth. Commun.* **2006**, *36*, 2991.
19. Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A.; Taheri, S. *J. Mol. Catal. A: Chem.* **2007**, *263*, 279.
20. Kidwai, M.; Mothsra, P.; Bansal, V.; Goyal, R. *Monatsh. Chem.* **2006**, *137*, 1189.
21. Sangshetti, J. N.; Kokare, N. D.; Kothakar, S. A.; Shinde, D. B. *Monatsh. Chem.* **2008**, *139*, 125.
22. Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031.
23. Wolkenberg, S. E.; Winoski, D. D.; Leister, W. H.; Wang, Y.; Zhoa, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
24. Kidwai, M.; Saxena, S.; Rastogi, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 2051.
25. (a) Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal. A: Chem*. **2007**, *263*, 112. (b) Sadeghi, B.; Mirjalili, B. B. F.; Hashemi, M. M. *Tetrahedron Lett*. **2008**, *49*, 2575. (c) Karimi, A. R.; Alimohammadi, Z.; Azizian, J.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Catal. Commun.* **2006**, *7*, 728. (d) Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L.

J. Mol. Catal. A: Chem. **2007**, *266*, 109.
26. Samai, S.; Chandra Nandi, G.; Singh, P.; Singh, M. S. *Tetrahedron* **2009**, *65*, 10155.
27. Niknam, K.; Deris, A.; Naeimi, F.; Majleci, F. *Tetrahedron Lett*. **2011**, *52*, 4642.
28. Salehi, J., Khodaei, M. M.; Khosropour, A. R. *Synthesis* **2011**, 459.
29. Wang, L. M.; Wang, Y. H.; Tian, H.; Yao, Y. F.; Shao, J. H.; Liu, B. *J. Fluorine Chem.* **2006**, *127*, 1570.
30. (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772. (b) Khodaei, M. M.; Khosropour, A. R.; Kookhazadeh, M. *Can. J. Chem.* **2005**, *83*, 209.
31. (a) Veisi, H. *Synlett* **2007**, 2607. (b) Veisi, H. *Synthesis* **2010**, 2631. (c) Veisi, H. *Tetrahedron Lett.* **2010**, 2109. (d) Veisi, H.; Ghorbani-Vaghei, R. *Tetrahedron* **2010**, 7445.
32. (a) Khazaei, A; Rahmati, S.; Rostami, A. *Helv Chem. Acta* **2009**, *92*, 1434. (b) Rostami, A.; Rahmati, S.; Khazaei, A. *Monatsh Chem*. **2009**, *140*, 663. (c) Khazaei, A.; Zolfigol, M. A.; Rostami, A.; Ghorbani Choghamarani, A. *Catal. commun*. **2007**, *8*, 543. (d) Khazaei, A.; Zolfigol, M. A.; Tanbakouchian, Z.; Shiri, M.; Niknam, K.; Saien, J. *Catal. Commun*. **2007**, *8*, 917.
33. Veisi, H. *Curr. Org. Chem.* **2011**, *15*, 2438.
34. Uchida, H.; Shimizu, T.; Reddy, P. Y.; Nakamura, S.; Toru, T. *Synthesis* **2003**, 1236.