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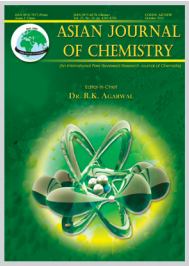

Amino Acid-Catalyzed Synthesis of Triarylimidazoles-A New Green Protocol

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A green and efficient solventless method using a variety of amino acids as catalysts at 100 ºC for a few minutes, were used for the synthesis of 2,4,5-triaryl-1*H*-imidazoles. Another mild method for the synthesis of triarylimidazoles using amino acid catalysts in ethanol solvent is also described. The yields are excellent in all cases.

Key Words: Triarylimidazoles, Benzil, Benzoin, Glycine, Leucine, Phenyl alanine, MCRs.

INTRODUCTION

Imidazoles play an important role in life processes and many imidazoles (including benzimidazoles) are known to form part of vitamins, enzymes and many pharmacologically important drugs[1,2]. Many triarylimidazoles have been tested as effective inhibitors of p38 MAP kinase[3] and B-Raf kinase[4], plant growth regulators[5], glucagon receptor antagonists[6], antibacterial[7], antifungal[8], antitumor[9], antithrombotic[10] and antihelmintic agents[11]. In addition, triarylimidazoles are also used in photography as photosensitive compounds[12]. The classical synthesis of triarylimidazoles involves the multicomponent condensation of 1,2-diketone, α-hydroxy ketone or α-ketooxime with an aldehyde and ammonia (or its salt) under pressure[13]. Review of literature has revealed a variety of catalysts used in these reactions, *e.g.*, ionic liquids[14], silica supported sulfuric acid[15], acetic acid[16], $NiCl_2.6H_2O/Al_2O_3$[17], iodine[18], sodium bisulphite[19], $Yb(OTf)_3$[20], *p*-toluenesulfonic acid[21], $InCl_3.3H_2O$[22], ceric ammonium nitrate[23], *etc*. However, to our best of knowledge, except for L-proline no other amino acid has been employed in these reactions[24,25]. We have tried to use various amino acids as catalysts for this protocol for the synthesis of triarylimidazoles with success and here we would like to report our findings.

EXPERIMENTAL

The chemicals used were commercially available from Merck or Fluka and were used as such. However when needed were purified using normal techniques. FTIR spectra were recorded on Bruker Tensor-27. Melting points were taken on a Gallen Kamp melting point apparatus and are uncorrected. The ^{1}H NMR spectra were taken on Bruker DPX instrument at 400 MHz. High resolution mass spectra were recorded on Finnigan MAT 312.

Synthesis of triarylimidazoles

Method 1: A mixture of benzil (0.525 g; 2.5 mmol), benzaldehyde (0.5 mL; 2.5 mmol), ammonium acetate (0.5 g; 6 mmol) and an amino acid (0.05 g) was stirred in ethanol (10 mL) for 48 h at room temperature. After completion of the reaction, the reaction mixture was filtered to get 2,4,5-triphenyl-1*H*-imidazole (off-white precipitates).

Method 2: A mixture of benzil (0.2625 g; 1.25 mmol), benzaldehyde (0.25 mL; 1.25 mmol), ammonium acetate (0.231 g; 3 mmol) and an amino acid (0.025 g) was heated on a boiling water-bath for 10-20 min. The reaction mixture was then poured into water; precipitates of 2,4,5-triaryl-1*H*-imidazole formed were filtered, washed with cold ethanol-water mixture and dried well.

2,4,5-Triphenyl-1*H*-imidazole (1a): m.p. > 250 ºC; Lit.[24] 276-277 ºC. FTIR (cm^{-1}): 3430, 2982, 1600, 1588, 1488, 1462, 1324; ESI MS (m/z): 296 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.59 (s, 1H), 7.9 (d, 2H, *J* = 7.6 Hz), 7.47 (d, 4H, *J* = 6.8 Hz), 7.38 (t, 2H, *J* = 7.4 Hz), 7.32-7.22 (m, 7H).

2-(Furan-2'-yl)-4,5-diphenyl-1*H*-imidazole (1b): m.p.188-189 ºC; Lit.[26] 199-201 ºC. FTIR (cm^{-1}): 3437, 2982, 1602, 1583, 1525, 1487, 1447, 1327; ESI MS (m/z): 286 (M^+);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.61 (bs, 1H), 7.45-7.24 (m, 10 H), 6.99 (d, 1H, J = 3.2 Hz), 6.52 (m, 1H).

2-(4'-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (1c): m.p. > 250 ºC; Lit.[24] 260-262 ºC. FTIR (cm^{-1}): 3476, 3012, 1602, 1588, 1485, 1461, 1323; ESI MS (m/z): 330 (100 %) and 332 (37 %) (M^+); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.74 (s, 1H), 8.09 (d, 2H, J = 8.8 Hz), 7.55-7.22 (m,12H).

2-(2'-Hydroxy)-4,5-diphenyl-1*H*-imidazole (1d): m.p. 191-193 ºC; Lit.[24] 202-203 ºC. FTIR (cm^{-1}): 3550, 3434, 3010, 1601, 1584, 1487, 1442, 1321; ESI MS (m/z): 312(M^+); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (s, 1H), 10.25 (s, 1H), 8.02 (d of d, 1H, J_1 = 1.4 Hz, J_2 = 7.8 Hz), 7.54-7.25 (m, 10H), 7.0-6.92 (m, 3H).

2-(4'-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (1e): m.p.222-224 ºC; Lit.[24] m.p. 232-233 ºC FTIR (cm^{-1}): 3390, 2994, 1599, 1581, 1484, 1441, 1509, 1332; ESI MS (m/z): 341 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 8.36-8.31 (m, 4H), 7.53-7.25 (m, 10H).

RESULTS AND DISCUSSION

Initially, condensation of 1:1 mixture of benzil and benzaldehyde with an excess of ammonium acetate in ethanol under reflux using catalytic amounts of glycine, resulted in excellent yield (96 %). Condensation at room temperature using glycine catalyst with stirring for 48 h (method 1) also gave 2,4,5-triphenyl-1*H*-imidazole (**1a**) in comparable excellent yields.

Keeping in view the successful results obtained from glycine, various other amino acids were used in the synthesis of 2,4,5-triphenyl-1*H*-imidazole (**1a**). The products were obtained in excellent (89 %) to almost quantitative yields (Table -1).

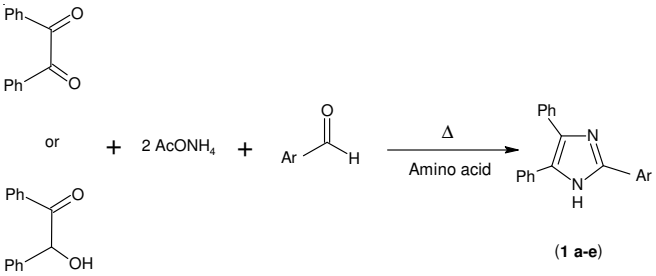
TABLE-1
AMINO ACID-CATALYZED SYNTHESIS OF 2,4,5-TRIPHENYL-1*H*-IMIDAZOLE (**1a**) FROM CONDENSATION OF BENZIL, BENZALDEHYDE AND AMMONIUM ACETATE IN ETHANOL AT ROOM TEMPERATURE

Amino acid used	Yield (%)
Glycine	99
Lysine	91
Methionine	89
Cysteine	98
Leucine	95
Phenyl alanine	99
Hippuric acid	98

The efficacy of amino acid catalysts was further tested in the synthesis of diverse 2,4,5-triaryl-1*H*-imidazoles with encouraging results. Once again, excellent yields were obtained **(Scheme-I**, Table-2). It was found that this condensation can be carried out in a solventless condition (green procedure) by just heating a mixture of benzil/benzoin, aromatic aldehyde and ammonium acetate with the amino acid catalyst for a few minutes on a water bath to give the respective triarylimidazoles in excellent yields (method 2[26], Table-2).

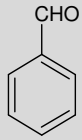
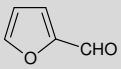
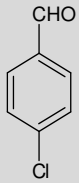
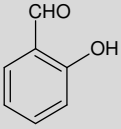
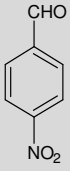
One of the major advantages of using amino acids as catalysts is in the isolation and purification of the desired product. The amino acids are usually soluble in water and are eliminated during work-up and purification.

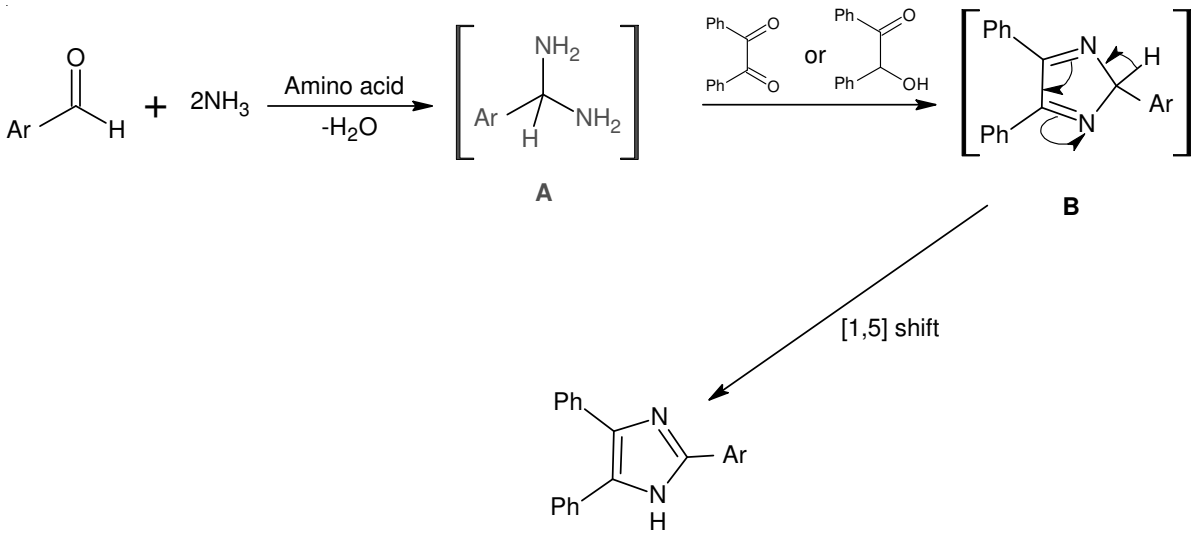
A plausible mechanistic explanation for the amino acid-catalyzed synthesis of 2,4,5-triaryl-1*H*-imidazoles has been depicted in **Scheme-II**, which is somewhat similar to the one proposed for the L-proline catalyzed reaction. An intermediate 'A' is probably formed by the condensation of an aromatic aldehyde with two molecules of ammonia facilitated by amino acid catalyst. This diamine intermediate 'A' then condenses with benzil/ benzoin followed by dehydration to give imino intermediate 'B'. A rearrangement would occur to afford the formation of the desired 2,4,5-triaryl-1*H*-imidazole.



Scheme-I: Synthesis of 2,4,5-triaryl-1*H*-imidazoles (**1 a-e**) from benzil/ benzoin, ammonium acetate, and an aryl aldehyde using various amino acids catalyst under solventless conditions

TABLE-2
AMINO ACID CATALYZED SYNTHESIS OF 2,4,5-TRIARYL -1*H*-IMIDAZOLES (**1 a-e**) FROM BENZIL OR BENZOIN, RESPECTIVE AROMATIC ALDEHYDE AND AMMONIUM ACETATE UNDER SOLVENTLESS CONDITIONS

Product	Aldehyde	Amino acid used	Time (min)	Yields (%)	
				Benzil	Benzoin
1a		Glycine	20	93	92
		Lysine		86	84
		Methionine		81	78
		Cysteine		94	92
		Leucine		86	84
		Phenyl alanine		92	89
		Hippuric acid		92	85
1b		Glycine	10	97	90
		Lysine		89	83
		Methionine		87	82
		Cysteine		94	92
		Leucine		91	89
		Phenyl alanine		95	90
		Hippuric acid		95	91
1c		Glycine	20	96	90
		Lysine		89	82
		Methionine		82	81
		Cysteine		92	89
		Leucine		86	78
		Phenyl alanine		89	81
		Hippuric acid		89	79
1d		Glycine	20	92	91
		Lysine		84	82
		Methionine		85	79
		Cysteine		92	89
		Leucine		92	89
		Phenyl alanine		93	91
		Hippuric acid		95	92
1e		Glycine	20	94	90
		Lysine		85	80
		Methionine		85	82
		Cysteine		91	88
		Leucine		90	85
		Phenyl alanine		89	84
		Hippuric acid		90	84



Scheme-II

For the present work, only a few representative aromatic aldehydes were used to check the feasibility of amino acid catalysis in these reactions. The yields in all five cases were comparable and these catalysts can be extended using other diketones and aldehydes.

In conclusion, an efficient and another green method for the synthesis of triarylimidazoles from benzil/benzoin, mediated by amino acids is presented. Seven representative amino acids have been used but the list is not exhaustive.

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REFERENCES

1. M.R. Grimmett, in eds: A.R. Katritzki and E.F.V. Seriven, Comprehensive Heterocyclic Chemistry II, Pergamon: Oxford, Vol. 3, p. 77 (1996).
2. J.G. Lambardino and E.H. Wiseman, *J. Med. Chem.*, **17**, 1182 (1974).
3. J.C. Lee, J.T. Laydon, P.C. McDonnell, T.F. Gallagher, S. Kumar, D. Green, D. McNulty, M.J. Blumenthal, J.R. Keys, S.W.L. Vatter, J.E. Strickler, M.M. McLaughlin, I.R. Siemens, S.M. Fisher, G.P. Livi, J.R. White, J.L. Adams and P.R. Young, *Nature*, **372**, 739 (1994).
4. A.K. Takle, M.J.B. Brown, S. Davies, D.K. Dean, G. Francis, A. Gaiba, A.W. Hird, F.D. King, P.J. Lovell, A. Naylor, A.D. Reith, J.G. Steadman and D.M. Wilson, *Bioorg. Med. Chem. Lett.*, **16**, 378 (2006).
5. (a) R. Schmierer, H. Mildenberger and H. Buerstell, German Patent 361464 (1987); *Chem. Abstr.*, **108**, 37838 (1988); (b) N.J. Laping, E. Grygielko, A. Mathur, S. Butter, J. Bomberger, C. Tweed, W. Martin, J. Fornwald, R. Lehr, J. Harling, L. Gaster, J.F. Callahan and B.A. Olson, *Mol. Pharmacol.*, **62**, 58 (2002).
6. L.L. Chang, K.L. Sidler, M.A. Cascieri, S. de Laszlo, G. Koch, B. Li, M. MacCoss, N. Mantlo, S. O'Keefe, M. Pang, A. Rolando and W.K. Hagmann, *Bioorg. Med. Chem. Lett.*, **11**, 2549 (2001).
7. (a) M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi and A. Ursini, *Bioorg. Med. Chem. Lett.*, **9**, 1023 (1999); (b) R.N. Brogden, R.C. Heel, T.M. Speight and G.S. Avery, *Drugs*, **16**, 387 (1978).
8. (a) A.F. Pozharskii, A.T. Soldatenkov and A.R. Katritzky, Heterocycles in Life and Society; Wiley, New York, p. 179 (1997); (b) J. Heeres, L.J.J. Backx, J.H. Mostmans and J. Van Cutsem, *J. Med. Chem.*, **22**, 1003 (1979).
9. A.P. Philips, H.L. White and S. Rosen, European Patent Appl. EP, 58,890 (1982).
10. L. Wang, K.W. Woods, Q. Li, K.J. Barr, R.W. McCroskey, S.M. Hannick, L. Gherke, R.B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J.Y. Lee, N. Zielinsky-Mozng, D. Frost, S.H. Rosenberg and H.L. Sham, *J. Med. Chem.*, **45**, 1697 (2002).
11. J. Hazelton, B. Iddon, A.D. Redhouse and H. Suschitzky, *Tetrahedron*, **51**, 5597 (1995).
12. (a) H. Sensui, J. Ichikawa and S. Sato, Jpn. Kokai Tokyo Koho JP 62, 94, 841; *Chem. Abstr.*, **107**, 187436 (1987); (b) I. Satoru, Japanese Patent, 01 117867, *Chem. Abstr.*, **111**, 214482 (1989).
13. B. Radziszewski, *Chem. Ber.*, **15**, 1493 (1882).
14. S.A. Siddiqui, U.G. Narkhede, S.S. Palimkar, T. Daniel, R.J. Lahoti and K.V. Srinivasan, *Tetrahedron*, **61**, 3539 (2005).
15. A. Shaabani and A. Rahmati, *J. Mol. Catal. A: Chem.*, **249**, 246 (2006).
16. (a) J. Wang, R. Mason, D.V. Derveer, K. Feng and X.R. Bu, *J. Org. Chem.*, **68**, 5415 (2003); (b) T.F. Gallagher, G.L. Seibel, S. Kassis, J.T. Laydon, M.J. Blumenthal, J.C. Lee, D. Lee, J.C. Boehm, S.M. Fier-Thompson, J.W. Abt, M.E. Soreson, J.M. Smietana, R.F. Hall, R.S. Garigipati, P.E. Bender, K.F. Erhard, A.J. Krog, G.A. Hofmann, P.L. Sheldrake, P.C. McDonnell, S. Kumar, P. R. Young and J.L. Adams, *Bioorg. Med. Chem.*, **5**, 49 (1997); (c) S.E. Wolkenberg, D.D. Winoski, W.H. Leister, Y. Wang, Z. Zhao and C.W. Lindsley, *Org. Lett.*, **6**, 1453 (2004).
17. M.M. Heravi, K. Bakhtiari, H.A. Oskooie and S. Taheri, *J. Mol. Catal. A: Chem.*, **263**, 279 (2007).
18. M. Kidwai, P. Mothsra, V. Bansal and R. Goyal, *Monatsh. Chem.*, **137**, 1189 (2006).
19. J.N. Sangshetti, N.D. Kokare, S.A. Kothakar and D.B. Shinde, *Monatsh. Chem.*, **139**, 125 (2008).
20. L.W. Wang, Y.H. Wang, H. Tian, Y.F. Yao, J.H. Shao and B. Liu, *J. Fluorine Chem.*, **127**, 1570 (2006).
21. M.M. Khodaei, K. Bahrami and I.J. Kavianinia, *J. Chin. Chem. Soc.*, **54**, 829 (2007).
22. S.D. Sharma, P. Hazarika and D. Konwar, *Tetrahedron Lett.*, **49**, 2216 (2008).
23. J.N. Sangshetti, N.D. Kokare, S.A. Kothrkara and D.B. Shinde, *J. Chem. Sci.*, **120**, 463 (2008).
24. S. Samai, G.C. Nandi, P. Singh and M.S. Singh, *Tetrahedron*, **65**, 10155 (2009).
25. N.V. Shitole, K.F. Shelke, S.S. Sonar, S.A. Sadaphal, B.B. Shingate and M.S. Shingare, *Bull. Korean Chem. Soc.*, **30**, 1963 (2009).
26. J.N. Sangshetti, N.D. Kokare, S.A. Kothrkara and D.B. Shinde, *Chin. Chem. Lett.*, **19**, 762 (2008).