A solvent-free synthesis of 1,2,4,5-tetrasubstituted imidazoles using molecular iodine as catalyst

Yi-Ming Ren[a]* and Chun Cai[b]

[a]*Department of Biochemical Engineering, Anhui University of Technology and Science, Wuhu, 241000, P. R. China*

[b]*Chemical Engineering College, Nanjing University of Science & Technology, Nanjing, 210094, P. R. China*

An efficient method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by three-component condensation of benzil, benzonitrile derivatives and primary amines under solvent-free conditions using molecular iodine as catalyst is described with high product yields. The significant features of the iodine-catalysed condensation are operational simplicity, inexpensive reagents, high yield of products and use of non-toxic reagents.

Keywords: molecular iodine, 1,2,4,5-tetrasubstituted imidazoles, solvent-free

Imidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Different substituted imidazole derivatives show variable biological activities such as antiulcer, antihypertensive, antiviral, antiallergic, antifungal, anticancer, and antihistaminic.[1–7] Due to their wide range of pharmacological activity and industrial and synthetic applications, a number of methods have been reported for the synthesis of highly substituted imidazoles, which include the condensation of β-carbonyl-*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing HOAc;[8] three-component condensation of benzil or benzoin with aldehydes and ammonium acetate;[9–11] four-component condensation of benzil or benzoin, aldehydes, amines and ammonium acetate;[12–15] 1,2-amino alcohols in the presence of PCl_5;[16] and conversion of N-(2-oxo)amides with ammonium trifluoroacetate under neutral conditions.[17] However, many of the synthetic protocols reported so far suffer from disadvantages, such as needing use of organic solvents, harsh reaction conditions, prolonged reaction times, use of metals and expensive reagents, *etc.* Previously, Balalaie, S. and co-workers had reported a novel one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles from three-component condensation of benzil, benzonitrile and primary amine on the surface of silica gel under solvent-free conditions and microwave irradiation.[18] But a microwave irradiation process was difficult to apply in the industrial process until now.

With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water and solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. Recently, solvent-free has been proven to be an efficient medium for synthesis of highly substituted imidazoles.[12,13,19]

In recent years, the usage of molecular iodine has drawn considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhances its usage in organic synthesis to realise several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.[20–28] Given the large number of similar condensation reactions that have been reported to proceed readily under solvent-free conditions,[19,29–31] we proceeded to examine the synthesis of 1,2,4,5-tetrasubstituted imidazoles by three-component condensation of benzil, benzonitrile derivatives and primary amines in the presence of a catalytic amount of molecular iodine under solvent-free conditions.

Initially, the synthesis of 1-benzyl-2,4,5-triphenylimidazole **4a** was explored in order to search for the optimal conditions. The reactions were carried out under solvent-free conditions (Table 1). Table 1 showed that the appropriate amount of I_2 for synthesis of 1-benzyl-2,4,5-triphenylimidazole was 10 mol% to benzil, A longer reaction time would be necessary and lower yield was obtained with less I_2. And the reaction yields and rates were not increased when a larger amount of I_2 was employed. However, in the absence of iodine, few products were synthesised even after 5h (Table 1, entry 1). The reaction temperature has also a great influence on the reaction. A low yield was obtained when it was carried out at room temperature. Increasing the reaction temperature could remarkably enhance both reaction yield and rate. The reaction could be completed within 1h with a high yield (85%) at 100 °C (Table 1, entry 3).

To generalise our reagent system, the products **4a–f** were synthesised from the three-component condensation of benzil, benzonitrile derivatives and primary amines (Table 2). It was found that primary aliphatic amines reacted efficiently with benzil and benzonitrile derivatives promoted by I_2 within 1h. However, the reaction failed to proceed with aniline derivatives under the same reaction conditions (Table 2, entries 7, 8 and 9), this may be due to the conjugated Schiff base formation by aniline and carbonyl derivatives making difficult further reaction with the benzonitrile derivatives. And a plausible reaction pathway for the reation is not clear.[18]

In conclusion, the present synthetic method is a simple, inexpensive, effective and green synthesis of 1,2,4,5-tetrasubstituted imidazoles. The advantages of the present method are the elimination of the metals, organic solvents and toxic reagents, operational simplicity and high yields of products. Further study on the synthetic application of the present reaction is now in progress.

Table 1 Studies on the synthesis of 1-benzyl-2,4,5-triphenylimidazole[a]

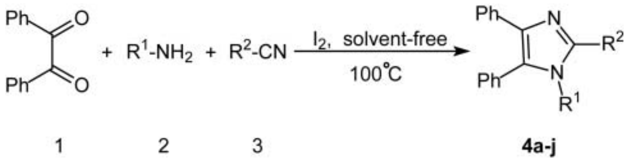
Entry	Iodine/mol%	T/°C	Time/min	Yield/%[b]
1	0	100	300	15
2	5	100	120	80
3	10	100	60	85
4	20	100	60	85
5	10	RT	300	10
6	10	80	120	53
7	10	90	120	67
8	10	100	60	85
9	10	110	60	85

[a]Product 1-benzyl-2,4,5-triphenylimidazole from 1 equiv benzil: 1.5 equiv benzyl amine: 1.5 equiv benzonitrile; The reactions were accomplished in 100 °C under solvent-free conditions.
[b]Isolated yields.

---

* Correspondent. E-mail: yimingren@auts.edu.cn

Table 2 I_2 catalysed solvent-free synthesis of 1,2,4,5-tetrasubstituted imidazoles[a]



Entry	R^1	R^2	Product	Time/h	Yield/%[b]
1	$C_6H_5CH_2$	C_6H_5	**4a**	1	85
2	$C_6H_5CH(CH_3)$	C_6H_5	**4b**	1	87
3	CH_3	4-$CH_3C_6H_4$	**4c**	1	80
4	C_2H_5	4-$CH_3C_6H_4$	**4d**	1	85
5	iso-C_4H_9	4-$CH_3C_6H_4$	**4e**	1	88
6	$C_6H_5CH_2$	4-$CH_3C_6H_4$	**4f**	1	87
7	C_6H_5	C_6H_5	**4g**	6	–
8	C_6H_5	4-$CH_3C_6H_4$	**4h**	6	–
9	4-ClC_6H_4	4-$CH_3C_6H_4$	**4i**	6	–

[a] Product **4a–f** from 1 equiv benzil: 1.5 equiv primary amine: 1.5 equiv benzonitrile derivatives.
[b] Isolated yields.

Experimental

Reagents were obtained from commercial resource. All products were known compounds and were identified by comparing of their IR, m.p. and ^1H NMR with those reported in the literature.[18]

Typical procedure of condensation of benzil with benzyl amine and benzonitrile: To a mixture of benzil (5 mmol), benzyl amine (7.5 mmol), benzonitrile (7.5 mmol) was added I_2 (0.5 mmol) at room temperature. Then the mixture was stirred at 100 °C. After 1h, the mixture was treated with $Na_2S_2O_3$ solution (5%). Then the solution was extracted with chloroform, and the solvent was removed by rotary evaporation. The crude product was subjected to further purification by column chromatography of silica gel using 25% ethylacetate in petroleum ether as eluent to yield 1-benzyl-2,4,5-triphenylimidazole in 85% yield. m.p. 160–162 °C (Lit[18]. m.p. 160–161 °C); IR (KBr, cm^{-1}): 2996, 1639, 1586, 1478, 770, 695. ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6, δ): 5.25 (s, 2H), 6.68–7.71 (m, 20H). All prepared products are known compounds and identified by IR, m.p. and ^1H NMR.

Received 25 December 2009; accepted 8 February 2010
Paper 090928 doi: 10.3184/030823410X12659021476402

References

1 J.W. Blank, G.J. Durant, J.C. Emmett and C.R. Ganellin, *Nature*, 1974, **248**, 65.
2 P.W. Erhardt, *J. Med. Chem.*, 1987, **30**, 231.
3 B.E. Tomczuk, C.R.Jr. Taylor, L.M. Moses, D.B. Sutherland, Y.S. Lo, D.N. Johnson, W.B. Kinnier and B.F. Kilpatrick, *J. Med. Chem.*, 1991, **34**, 2993.
4 J.S. Kim, B. Gatto, C. Yu, A. Liu, L.F. Liu and E.J. LaVoie, *J. Med. Chem.*, 1996, **39**, 992.
5 T. Roth, M.L. Morningstar, P.L. Boyer, S.H. Hughes, R.W.Jr. Buckheit and C.J. Michejda, *J. Med. Chem.*, 1997, **40**, 4199.
6 M. Misono, *Chem. Commun.*, 2001, 1141.
7 U. Ucucu, N.G. Karaburun and I. Iskdag, *Il Farmaco*, 2001, **56**, 285.
8 D.A. Evans and K.M. Lundy, *J. Am. Chem. Soc.*, 1992, **114**, 1495.
9 A. Shaabani and A. Rahamati, *J. Mol. Catal. A: Chem.*, 2006, **249**, 246.
10 M.M. Heravi, K. Bakhtiari, H.A. Oskooie and S. Taheri, *J. Mol. Catal. A: Chem.*, 2007, **263**, 279.
11 M. Kidwai, P. Mothsra, V. Bansal, R.K. Somvanshi, A.S. Ethayathulla, S. Dey and T.P. Singh, *J. Mol. Catal. A: Chem.*, 2007, **265**, 177.
12 A.R. Karimi, Z. Alimohammadi, J. Azizian, A.A. Mohammadi and M.R. Mohammadizadeh, *Catal. Commun.*, 2006, **7**, 728.
13 M. Kidwai and P.A. Mothsra, *Tetrahedron Lett.*, 2006, **47**, 5029.
14 L. Nagarapu, S. Apuri and S. Kantevari, *J. Mol. Catal. A: Chem.*, 2007, **266**, 104.
15 M.M. Heravi, F. Derikvand and F.F. Bamoharram, *J. Mol. Catal. A: Chem.*, 2007, **263**, 112.
16 B.K. M.leicher, F. Gerbe, Y. Wuthrich, A. Alanine and A. Caprella, *Tetrahedron Lett.*, 2002, **43**, 7687.
17 C.F. Claiborne, N.J. Liverton and K.T. Nguyen, *Tetrahedron Lett.*, 1998, **39**, 8939.
18 S. Balalaie, M.M. Hashemi and M. Akhbari, *Tetrahedron Lett.*, 2003, **44**, 1709.
19 S. Kantevari, S.V.N. Vuppalapati, O. Biradar and L. Nagarapu, *J. Mol. Catal. A: Chem.*, 2007, **266**, 109.
20 B.K. Banik, O. Zegrocka, I. Banik, L. Hackfeld and F.F. Becker, *Tetrahedron Lett.*, 1999, **40**, 6731.
21 H. Firouzabadi, N. Iranpoor and H. Hazarkhani, *J. Org. Chem.*, 2001, **66**, 7527.
22 J.S. Yadav, B.V.S. Reddy, G. Sabitha and G.S.K.K. Reddy, *Synthesis*, 2000, 1532.
23 M.K. Basu, M.K. Samajdar, F.F. Becker and B.K. Banik, *Synlett*, 2002, 319.
24 J.S. Yadav, B.V.S. Reddy, C. Rao, V. Sabitha and M.J. Reddy, *Synthesis*, 2003, 247.
25 M. Ishihara and H. Togo, *Synlett*, 2006, 227.
26 B. Das, N. Chowdhury and K. Damodar, *Tetrahedron Lett.*, 2007, **48**, 2867.
27 M. Ishihara and H. Togo, *Tetrahedron*, 2007, **63**, 1474.
28 W. Rao, A.H.L. Tay, P.J. Goh, J.M.L. Choy, J.K. Ke, P.W.H. Chan, *Tetrahedron Lett.*, 2008, **49**, 122.
29 F. Toda and K. Tanaka, *Chem. Rev.*, 2000, **100**, 1025.
30 S. Chandrasekhar, C. Narsihmulu, S. S. Sultana, B. Saritha and S.J. Prakash, *Synlett*, 2003, 505.
31 A.R. Karimi, Z. Alimohammadi, J. Azizian, A.A. Mohammadi and M.R. Mohammadizadeh, *Catal. Commun.*, 2006, **7**, 728.