Molecular iodine: a highly efficient catalyst in the synthesis of quinolines *via* Friedländer annulation

Jie Wu,* Hong-Guang Xia and Ke Gao

Received 17th October 2005, Accepted 3rd November 2005
First published as an Advance Article on the web 28th November 2005
DOI: 10.1039/b514635f

A mild and efficient route for the synthesis of quinolines and polycyclic quinolines *via* Friedländer annulation, utilizing molecular iodine (1 mol%) as a new catalyst, is described.

Introduction

Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize 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.[1,2] For instance, it shows high efficiency in the Hantzsch reaction[1a] as well as the cyanation of imines.[1b,1o] Recently, we found that it was also efficient as a catalyst in the synthesis of quinolines and polycyclic quinolines *via* Friedländer annulation, which is disclosed herein.

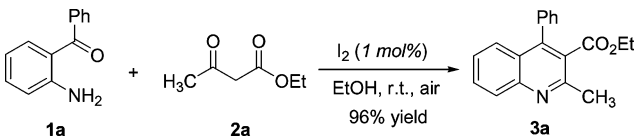
As a privileged fragment, quinoline is a ubiquitous subunit in many quinoline-containing natural products with remarkable biological activities.[3] Members of this family have wide applications in medicinal chemistry, being used as antimalarial, antiinflammatory, antiasthmatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[3] In addition, quinolines are valuable synthons, used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.[4] Because of their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed into the development of new quinoline-based structures[5] and new methods for their construction.[6]

As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[7] we became interested in the possibility of developing a novel and efficient method to construct the quinoline scaffold. Though some methods such as the Skraup, Doebner–von Miller, and Combes reactions[8] are available, the protocol reported by Friedländer is one of the most simple and straightforward methods for the synthesis of polysubstituted quinolines. The Friedländer annulation, that is, a condensation followed by a cyclodehydration between 2-aminoaryl ketones and α-methylene ketones, is catalyzed by both acids and bases. Brønsted acids like sulfamic acid, hydrochloric acid, sulfuric acid, *p*-toluene sulfonic acid and phosphoric acid were widely used as catalysts.[9] However, many of these methods require harsh reaction conditions and lead to several side reactions. Under base catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters.[9] Recently, Lewis acids such as $FeCl_3$, $Mg(ClO_4)_2$, $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, silver phosphotungstate, sodium fluoride, and $NaAuCl_4 \cdot 2H_2O$ have been reported to be effective for the synthesis of quinolines.[10] However, many of these procedures also suffered from harsh reaction conditions, low yields, difficulties in work-up, and the use of stoichiometric and/or relatively expensive reagents. And in some cases, high catalyst loading had to be employed in order to obtain respectable yields. Since quinoline derivatives are increasingly useful and important in pharmaceuticals and industry, the development of a simple, eco-benign, low cost protocol is still desirable.

Inspired by reports of continuation of interest in catalytic applications of elemental iodine for organic transformation,[1,2] we considered employing molecular iodine as a catalyst for Friedländer quinoline synthesis since most of the iodine-catalyzed transformations are acid-induced processes. As Friedländer annulations are among the most important acid-mediated reactions, development of a reaction that uses catalytic amounts of low toxic, economic, readily available iodine should greatly contribute to the creation of environmentally benign processes.

Results and discussion

An initial study was performed by the treatment of 2-aminobenzophenone **1a** with ethyl acetoacetate **2a** in EtOH in the presence of a catalytic amount of I_2 (10 mol%) at room temperature. To our delight, we observed the formation of ethyl-2-methyl-4-phenylquinoline-3-carboxylate **3a**. Complete conversion and 96% isolated yield were obtained after 16 hours. Further studies established that 1 mol% of catalyst was also efficient in this reaction (1 mol%: 16 hours, 96% yield). Moreover, it is noteworthy that this reaction could be run under air without loss of efficiency (Scheme 1).

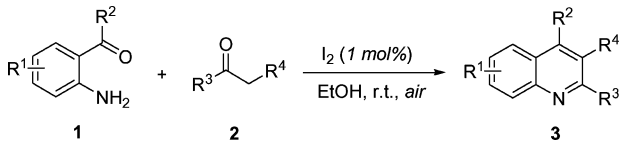


Scheme 1 Reaction of **1a** and **2a** catalyzed by I_2 (1 mol%) in EtOH at room temperature.

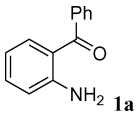
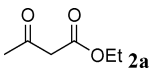
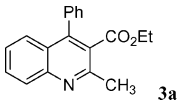
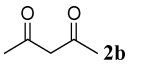
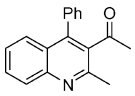
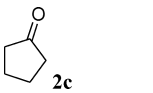
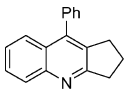
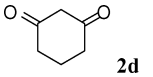
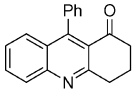
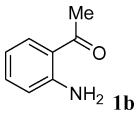
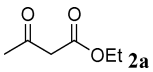
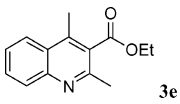
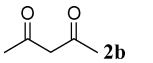
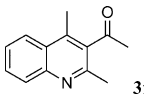
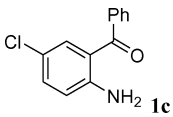
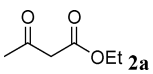
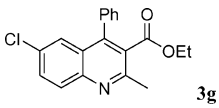
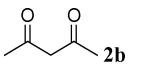
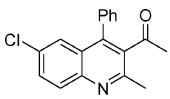
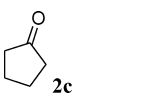
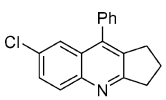
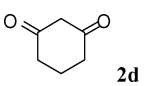
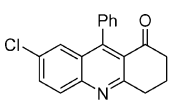
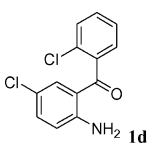
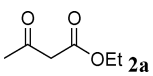
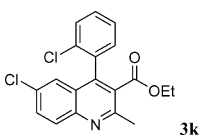
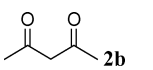
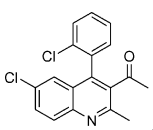
Among the solvents (EtOH, THF, H_2O, CH_3CN, toluene) screened, EtOH was demonstrated as the best solvent. Under solvent-free conditions, the reaction also proceeded smoothly to

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, China. E-mail: jie_wu@fudan.edu.cn; Fax: 86 21 6510 2412; Tel: 86 21 5566 4619

Table 1 Molecular iodine-catalyzed Friedländer synthesis of quinolines[a]



1 2 3

Entry	2-Aminoaryl ketone **1**	Ketone **2**	Product **3**	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	96
2		 **2b**	 **3b**	90
3		 **2c**	 **3c**	73
4		 **2d**	 **3d**	88
5	 **1b**	 **2a**	 **3e**	68
6		 **2b**	 **3f**	53
7	 **1c**	 **2a**	 **3g**	98
8		 **2b**	 **3h**	93
9		 **2c**	 **3i**	71
10		 **2d**	 **3j**	83
11	 **1d**	 **2a**	 **3k**	76
12		 **2b**	 **3l**	61

[a] Reaction conditions: 2-aminoaryl ketone **1** (0.5 mmol), α-methylene ketone **2** (0.6 mmol, 1.2 equiv.), iodine (1 mol%), EtOH (1.0 mL), r.t. [b] Isolated yield based on 2-aminoaryl ketone **1**.

afford the corresponding product although the yield was slightly lower (89%). To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions (EtOH, 1 mol% of iodine, r.t.) and the results are summarized in Table 1. As shown in Table 1, this method is equally effective for both cyclic and acyclic ketones. Various substituted 2-aminoaryl ketones **1** such as 2-aminobenzophenone, 2-aminoacetophenone, and 2-amino-5-chlorobenzophenone reacted smoothly with α-methylene ketones **2** to produce a range of quinoline derivatives. Complete conversion and good to excellent isolated yields were observed for all substrates employed. This reaction is very clean and free from side reactions, such as self-condensation of ketones, which are normally observed under basic conditions. Unlike reported methods, the present protocol does not require high temperature or drastic conditions to produce quinoline derivatives. In the absence of a catalyst, the reaction did not yield any product even after long reaction times. Interestingly, cyclic ketones such as cyclopentanone and cyclohexadione also underwent smooth condensation with 2-aminoaryl ketones to afford the respective tricyclic quinolines (for example: Table 1, entries 3 and 4).

Conclusions

In conclusion, we describe a mild and efficient route for the synthesis of quinolines and polycyclic quinolines utilizing molecular iodine as a novel catalyst *via* Friedländer annulation. This method not only provides an excellent complement to quinoline synthesis *via* Friedländer annulation, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents and catalyst under mild conditions, and experimental operational ease. Reactions employing iodine as a catalyst for other organic transformations are currently under investigation in our research group, and will be reported in due course.

Experimental

General procedure

A mixture of the 2-aminoaryl ketone **1** (0.5 mmol), the α-methylene ketone **2** (0.6 mmol, 1.2 equiv.) and I_2 (1 mol%) in EtOH (1.0 mL) was stirred at r.t. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with EtOAc (2 × 10 mL). Evaporation of the solvent followed by purification on silica gel afforded pure quinoline. (All the products are known compounds. The characterizations of these compounds are identical with the literature reports.[10])

3a: ethyl-2-methyl-4-phenylquinoline-3-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.94 (t, $J = 7.1$ Hz, 3H), 2.79 (s, 3H), 4.04–4.09 (m, 2H), 7.36–7.72 (m, 8H), 8.07 (d, $J = 8.4$ Hz, 1H).

3b: 1-(2-methyl-4-phenylquinolin-3-yl)ethanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.00 (s, 3H), 2.71 (s, 3H), 7.36–8.11 (m, 9H).

3c: 9-phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.16–2.19 (m, 2H), 2.91 (t, $J = 7.3$ Hz, 2H), 3.25 (t, $J = 7.6$ Hz, 2H), 7.36–8.10 (m, 9H).

3d: 9-phenyl-3,4-dihydroacridin-1(2*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.24–2.27 (m, 2H), 2.69 (t, $J = 6.6$ Hz, 2H), 3.36 (t, $J = 6.4$ Hz, 2H), 7.17–7.19 (m, 2H), 7.40–7.46 (m, 6H), 8.05 (d, $J = 8.7$ Hz, 1H).

3e: ethyl-2,4-dimethylquinoline-3-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.41 (t, $J = 7.1$ Hz, 3H), 2.61 (s, 3H), 2.71 (s, 3H), 4.45–4.49 (m, 2H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.99 (d, $J = 8.4$ Hz, 1H).

3f: 1-(2,4-dimethylquinolin-3-yl)ethanone. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.54 (d, $J = 12.3$ Hz, 6H), 2.62 (s, 3H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.99 (d, $J = 8.4$ Hz, 1H).

3g: ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.94 (t, $J = 7.1$ Hz, 3H), 2.77 (s, 3H), 4.04–4.09 (m, 2H), 7.34–7.66 (m, 7H), 8.00 (d, $J = 9.0$ Hz, 1H).

3h: 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)ethanone. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.00 (s, 3H), 2.68 (s, 3H), 7.33–7.35 (m, 2H), 7.53–7.66 (m, 5H), 8.00 (d, $J = 8.9$ Hz, 1H).

3i: 7-chloro-9-phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.14–2.18 (m, 2H), 2.89 (t, $J =$ 7.3 Hz, 2H), 3.21 (t, $J = 7.8$ Hz, 2H), 7.32–7.34 (m, 2H), 7.52–7.53 (m, 5H), 7.98 (d, $J = 9.2$ Hz, 1H).

3j: 7-chloro-9-phenyl-3,4-dihydroacridin-1(2*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.22–2.27 (m, 2H), 2.69–2.72 (m, 2H), 3.34–3.37 (m, 2H), 7.15–8.00 (m, 8H).

3k: ethyl 6-chloro-4-(2-chlorophenyl)-2-methylquinoline-3-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.95–0.98 (m, 3H), 2.81 (s, 3H), 4.06–4.08 (m, 2H), 7.27–7.55 (m, 6H), 8.02 (d, $J = 9.3$ Hz, 1H).

3l: 1-(6-chloro-4-(2-chlorophenyl)-2-methylquinolin-3-yl)ethanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.15 (s, 3H), 2.71 (s, 3H), 7.23–7.28 (m, 2H), 7.40–7.67 (m, 4H), 8.01 (d, $J = 9.2$ Hz, 1H).

References

1 (*a*) S. Ko, M. N. V. Sastry, C. Lin and C.-F. Yao, *Tetrahedron Lett.*, 2005, **46**, 5771; (*b*) J. S. Yadav, B. V. S. Reddy, M. Srinivas and K. Sathaiah, *Tetrahedron Lett.*, 2005, **46**, 3489; (*c*) C.-M. Chu, S. Gao, M. N. V. Sastry and C.-F. Yao, *Tetrahedron Lett.*, 2005, **46**, 4971; (*d*) W.-Y. Chen and J. Lu, *Synlett*, 2005, 1337; (*e*) B. S. Lee, S. Mahajan and K. D. Janda, *Synlett*, 2005, 1325; (*f*) M. C. Bagley, C. Glover and D. Chevis, *Synlett*, 2005, 649; (*g*) B. K. Banik, M. Fernandez and C. Alvarez, *Tetrahedron Lett.*, 2005, **46**, 2479; (*h*) B. K. Banik, M. Chapa, J. Marquez and M. Cardona, *Tetrahedron Lett.*, 2005, **46**, 2341; (*i*) P. D. Lokhande, S. S. Sakate, K. N. Taksande and B. Navghare, *Tetrahedron Lett.*, 2005, **46**, 1573; (*j*) P. Gogoi, P. Hazarika and D. Konwar, *J. Org. Chem.*, 2005, **70**, 1934; (*k*) J. Sun, Y. Dong, L. Cao, X. Wang, S. Wang and Y. Hu, *J. Org. Chem.*, 2004, **69**, 8932; (*l*) K. V. N. S. Srinivas and B. Das, *Synthesis*, 2004, 2091; (*m*) R. S. Bhosale, S. V. Bhosale, T. Wang and P. K. Zubaidha, *Tetrahedron Lett.*, 2004, **45**, 7187; (*n*) B. P. Bandgar and S. V. Bettigeri, *J. Chem. Res.*, 2004, 389; (*o*) L. Royer, S. K. De and R. A. Gibbs, *Tetrahedron Lett.*, 2005, **46**, 4595.

2 (*a*) K. K. Rana, C. Guin, B. Banerjee and S. C. Roy, *J. Indian Chem. Soc.*, 2003, **80**, 1005; (*b*) J. S. Yadav, B. V. S. Reddy, K. V. Rao, K. S. Raj, P. P. Rao, A. R. Prasad and D. Gunasekar, *Tetrahedron Lett.*, 2004, **45**, 6505; (*c*) P. Phukan, *J. Org. Chem.*, 2004, **69**, 4005; (*d*) B. P. Bandgar, S. V. Bettigeri and N. S. Joshi, *Synth. Commun.*, 2004, **34**,

1447; (*e*) X. Gang, Y. Zhu, H. Birch, H. A. Hjuler and N. J. Bjerrum, *Appl. Catal., A*, 2004, **261**, 91; (*f*) P. Phukan, *Synth. Commun.*, 2004, **34**, 1065; (*g*) J. S. Yadav, B. V. S. Reddy and M. S. Reddy, *Synlett*, **2003**, 1722; (*h*) B. Karimi and D. Zareyee, *Synthesis*, 2003, 1875; (*i*) C.-S. Liu, C.-F. Zhao and G.-X. Luo, *Hecheng Huaxue*, 2003, **11**, 254; (*j*) R. Saeeng, U. Sirion, P. Sahakitpichan and M. Isobe, *Tetrahedron Lett.*, 2003, **44**, 6211; (*k*) J. S. Yadav, B. V. S. Reddy, C. V. Rao and M. S. Reddy, *Synthesis*, 2003, 247; (*l*) B. P. Bandgar and K. A. Shaikh, *Tetrahedron Lett.*, 2003, **44**, 1959; (*m*) J. S. Yadav, B. V. S. Reddy, M. S. Reddy and A. R. Prasad, *Tetrahedron Lett.*, 2002, **43**, 9703; (*n*) J. S. Yadav, B. V. S. Reddy, K. Sadasiv and G. Satheesh, *Tetrahedron Lett.*, 2002, **43**, 9695; (*o*) J. S. Yadav, B. V. S. Reddy, C. V. Rao and K. V. Rao, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1401; (*p*) B. Karimi and B. Golshani, *Synthesis*, 2002, 784; (*q*) J. S. Yadav, P. K. Chand and S. Anjaneyulu, *Tetrahedron Lett.*, 2002, **43**, 3783; (*r*) M. K. Basu, S. Samajdar, F. F. Becker and B. K. Banik, *Synlett*, 2002, 319; (*s*) J. S. Yadav, B. V. S. Reddy, C. V. Rao, P. K. Chand and A. R. Prasad, *Synlett*, 2001, 1638; (*t*) S. Samajdar, M. K. Basu, F. F. Becker and B. K. Banik, *Tetrahedron Lett.*, 2001, **42**, 4425; (*u*) C. Mukhopadhyay, F. F. Becker and B. K. Banik, *J. Chem. Res., Synop.*, 2001, 28; (*v*) N. Deka and J. C. Sarma, *J. Org. Chem.*, 2001, **66**, 1947; (*w*) H. M. S. Kumar, B. V. S. Reddy, E. J. Reddy and J. S. Yadav, *Chem. Lett.*, 1999, 857; (*x*) K. M. Kim, D. J. Jeon and E. K. Ryu, *Synthesis*, 1998, 835; (*y*) N. Deka, D. J. Kalita, R. Borah and J. C. Sarma, *J. Org. Chem.*, 1997, **62**, 1563.

3 (*a*) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. Zamboni, *J. Org. Chem.*, 1996, **61**, 3398; (*b*) Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu and C. C. Tzeng, *J. Med. Chem.*, 2001, **44**, 2374; (*c*) G. Roma, M. D. Braccio, G. Grossi and M. Chia, *Eur. J. Med. Chem.*, 2000, **35**, 1021; (*d*) D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J. P. Falgueyeret, R. W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari and R. N. Yong, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1255; (*e*) M. P. Maguire, K. R. Sheets, K. Mcvety, A. P. Spada and A. Zilberstein, *J. Med. Chem.*, 1994, **37**, 2129; (*f*) O. Bilker, V. Lindo, M. Panico, A. E. Etiene, T. Paxton, A. Dell, M. Rogers, R. E. Sinden and H. R. Morris, *Nature*, 1998, 289.

4 (*a*) A. K. Aggarwal and S. A. Jenekhe, *Macromolecules*, 1991, **24**, 6806; (*b*) X. Zhang, A. S. Shetty and S. A. Jenekhe, *Macromolecules*, 1999, **32**, 7422; (*c*) S. A. Jenekhe, L. Lu and M. M. Alam, *Macromolecules*, 2001, **34**, 7315.

5 M. Z. Hoemann, G. Kumaravel, R. L. Xie, R. F. Rossi, S. Meyer, A. Sidhu, G. D. Cuny and J. R. Hauske, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2675.

6 A subset of recent work in this area includes: (*a*) W. Du and D. P. Curran, *Org. Lett.*, 2003, **5**, 1765; (*b*) D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp and P. Knochel, *Org. Lett.*, 2002, **4**, 1819; (*c*) M. Matsugi, F. Tabusa and J. Minamikawa, *Tetrahedron Lett.*, 2000, **41**, 8523; (*d*) P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey, J. C. McWilliams, P. J. Reider, J. W. Sager and R. P. Volante, *J. Org. Chem.*, 2003, **68**, 467.

7 (*a*) J. Wu, L. Zhang and X. Sun, *Chem. Lett.*, 2005, **34**, 796; (*b*) J. Wu, X. Sun and L. Zhang, *Chem. Lett.*, 2005, **34**, 550.

8 (*a*) C. S. Cho, B. H. Oh, J. S. Kim, T.-J. Kim and S. C. Shim, *Chem. Commun.*, 2000, 1885; (*b*) B. Jiang and Y. C. Si, *J. Org. Chem.*, 2002, **67**, 9449; (*c*) H. Skraup, *Chem. Ber.*, 1880, **13**, 2086; (*d*) P. Friedländer, *Chem. Ber.*, 1882, **15**, 2572; (*e*) R. H. Mansake and M. Kulka, *Org. React.*, 1953, **7**, 59; (*f*) R. J. Linderman and S. K. Kirollos, *Tetrahedron Lett.*, 1990, **31**, 2689; (*g*) M. E. Theclitou and L. A. Robinson, *Tetrahedron Lett.*, 2002, **43**, 3907.

9 E. A. Fehnel, *J. Heterocycl. Chem.*, 1966, **31**, 2899.

10 (*a*) L. Strekowski and A. Czamy, *J. Fluorine Chem.*, 2000, **104**, 281; (*b*) Y. Z. Hu, G. Zang and R. P. Thummel, *Org. Lett.*, 2003, **5**, 2251; (*c*) A. Arcadi, M. Chiarini, S. Di Giuseppe and F. Marinelli, *Synlett*, 2003, 203; (*d*) B. R. McNaughton and B. L. Miller, *Org. Lett.*, 2003, **5**, 4257; (*e*) J. S. Yadav, B. V. S. Reddy and K. Premlatha, *Synlett*, 2004, 963; (*f*) J. S. Yadav, B. V. S. Reddy, P. Sreedhar, R. S. Rao and K. Nagaiah, *Synthesis*, 2004, 2381; (*g*) K. Mogilaih and C. S. Reddy, *Synth. Commun.*, 2003, 3131; (*h*) A. Walser, T. Flyll and R. I. Fryer, *J. Heterocycl. Chem.*, 1975, **12**, 737; (*i*) S. K. De and R. A. Gibbs, *Tetrahedron Lett.*, 2005, **46**, 1647; (*j*) P. Arumugam, G. Karthikeyan, R. Atchudan, D. Muralidharan and P. T. Perumal, *Chem. Lett.*, 2005, **34**, 314; (*k*) J. Wu, L. Zhang and T.-N. Diao, *Synlett*, 2005, 2653.