RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Iron/Acetic acid Mediated Intermolecular Tandem C-C and C-N Bond Formation: An Easy Access to Acridinone and Quinoline Derivatives

R. R. Rajawinslin, Sachin D. Gawande, Veerababurao Kavala, Yi-Hsiang Huang, Chun-Wei Kuo, Ting-Shen Kuo, Mei-Ling Chen, Chiu-Hui He, and Ching-Fa Yao*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An efficient Iron/Acetic acid mediated one pot reductive cyclization protocol was successfully developed for the synthesis of acridinone and quinoline derivatives. This highly efficient process proceeds under mild conditions, tolerates different functional groups, and provides various substituted acridinone and quinoline derivatives in good to excellent yields. In addition, biologically active compounds also accessed from this method.

The synthesis of nitrogen containing heterocyclic compounds such as acridinone, quinoline and their derivatives, is an important area of research in organic chemistry, because they are the building blocks of many biologically active compounds.[1-9] Acridinone and quinoline derivatives are well known structural scaffolds in medicinal chemistry and possess useful pharmacological and biological activities including antibacterial,[2] antiparasitic,[3] anticancer,[4] antiplasmodial,[5] antimalarial,[6] antiasthmatic,[7] antihypertensive,[8] and cholinesterase inhibiting agents[9] (Figure 1). For instance, compound **A** is a potential antibacterial agent against a panel of Gram-positive and Gram-negative bacteria.[2] Compound **B** (MC1626) is a Gcn5p inhibitor which represses cell growth, gene transcription and histone acetylation.[3] Compound **C** is an effective cholinesterase inhibiting agent.[9] Compounds **D**, **E** and **F** were proved for their cytotoxic effect in various human tumour cell lines[4] (chronic myeloid leukemia K562 cells, colon carcinoma Colo-205 cells, breast cancer MDA-MB 231 cells, neuroblastoma IMR32 cells).

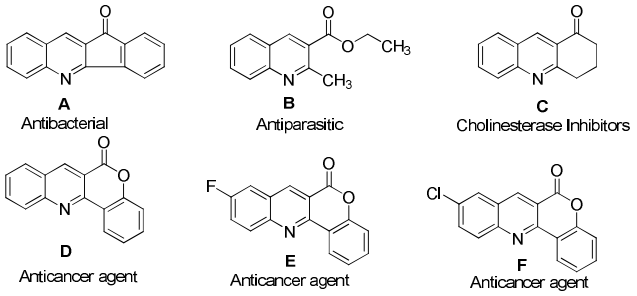


Figure 1. Fe/AcOH-mediated one pot synthesis of biologically active compounds.

The above described facts indicate that the synthesis of acridinone and quinoline derivatives is important and useful task in organic chemistry. Many methods are available in the literature that describes the synthesis of acridinone and quinoline derivatives[10] including skraup, Doebner-von Miller, Friedlander, Camps Combes, Conrad-Limpach-Knorr Gould-jacobs reaction[11] etc. Most of the known procedures are associated with several short comings with respective to the formation of side products, use of toxic solvents, tedious procedures of work-up and use of expensive catalysts. Hence, the development of a simple, convenient and environmentally benign method for the synthesis of acridinone and quinoline derivatives is still a welcoming topic in organic synthesis.

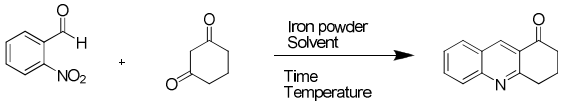
In 1993, Shutske et al., synthesized acridinone and quinoline derivatives from *N*-(2-(1,3-dioxolan-2-yl))phenylamine by using toluene-4-sulfonic acid,[9] and in 2009 Menéndez and co-workers reported the synthesis of same from *N*-(2-aminobenzylidene)-4-methylaniline by using cerium(IV) ammonium nitrate as a catalyst.[12] Very recently, Shi and co-workers developed a method for the synthesis of acridinone and quinoline derivatives from β-nitro olefins by using triphenylphosphine.[13] However, in these methods, the preparation of starting materials involved multiple steps. Similarly, Shen et al.,[14] and Boyd et al.,[15] reported the synthesis of same from 2-aminobenzaldehyde. Although the above mentioned two methods are exciting, the starting materials used in these strategies are much expensive and unstable. On the other hand, 2-nitrobenzaldehyde is a stable and inexpensive starting material which makes our protocol easy and attractive.

Iron/acetic acid is an effective reagent that has been used for various reductive cyclization processes due to its easy availability, environmental safety and low cost.[16,17] For the past half a decade, our group has investigated the applications of conventional iron acetic acid system for the generation of versatile heterocyclic compounds.[17] In continuation to our work on iron/acetic acid mediated reductive cyclization of nitro derivatives, herein, we wish to investigate the one pot synthesis of acridinone and quinoline derivatives through intermolecular reductive cyclization of 2-nitrobenzaldehyde and various 1,3- diketones. To

the best of our knowledge, this transformation has not been reported in the literature.

To pursue our goal, we selected 2-nitrobenzaldehyde and 1,3-cyclohexanedione as model substrates. When these compounds were treated with iron/acetic acid at room temperature, the expected product was formed after 4 hours and the yield was 62%. The structure of the product was confirmed by ^{1}H, ^{13}C NMR spectroscopy, MS, HRMS, and single-crystal X-ray analysis (Figure 2). Aiming to increase the yield of the product and also to decrease the reaction time, we tested the reaction at different temperature. Interestingly, at 50°C, the expected acridinone was obtained as the sole product in 88% yield after 1h. However, when the reaction was conducted at 70°C and under reflux conditions, there was no increment in product yield as well as in the reaction time (Table 1).

Table 1. Optimization of the reaction conditions



Entry[a]	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	Acetic acid	r.t.	4	62
2	**Acetic acid**	**50**	1	**88**
3	Acetic acid	70	1	85
4	Acetic acid	Reflux	1	81

[a]All the reactions were performed on 1mmol scale by using 1.2 equiv of 1,3- diketone. [b]isolated yields.

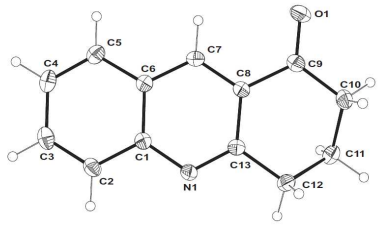
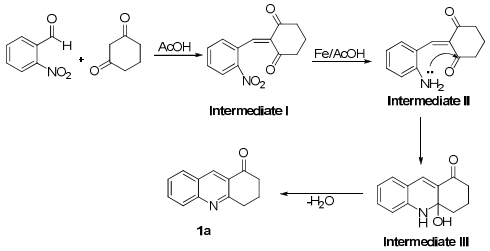


Figure 2. Crystal structure of compound **1a**[20]

A plausible mechanism for this reaction is shown in Scheme 1. We assume that, in this reaction knoevenagel condensation reaction[18] takes place between 2-nitrobenzaldehyde and 1,3-cyclohexanedione to form the intermediate **I**. The nitro group in intermediate **I** undergoes reduction in iron/acetic acid to form intermediate **II**. The nucleophilic attack of amino group on the carbonyl group[14] leads to the formation of intermediate **III** and the final product (**1a**) was formed by the dehydration of intermediate **III**. To confirm this reaction pathway, we conducted a reaction of 2-nitrobenzaldehyde and 1,3-cyclohexanedione in acetic acid at 50°C, in the absence of iron powder. Interestingly, the intermediate **I** was formed at a reaction time of 5h, which was isolated as brown solid and its structure was confirmed by ^{1}H, ^{13}C NMR spectroscopy, MS, HRMS, and single-crystal X-ray analysis (Figure 3).



Scheme 1. Plausible mechanism for the formation of acridinone and quinoline derivatives

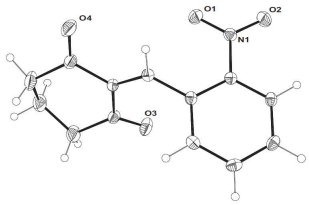
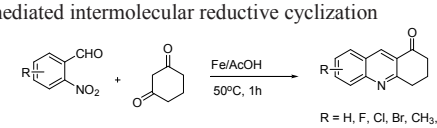
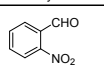
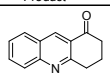
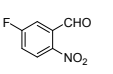
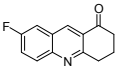
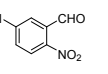
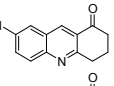
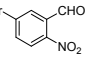
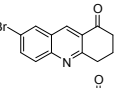
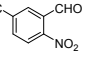
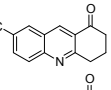
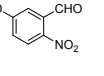
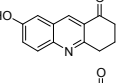
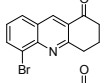
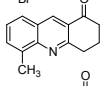
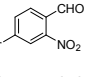
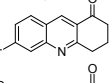
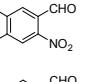
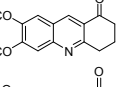
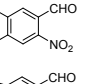
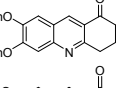
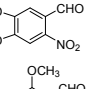


Figure 3. Crystal structure of Intermediate **I**[20]

Table 2. Synthesis of various substituted acridinones by Fe/AcOH-mediated intermolecular reductive cyclization

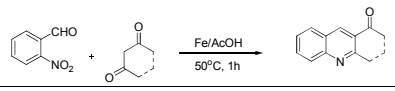


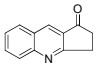
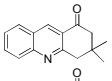
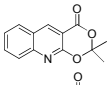
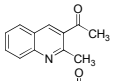
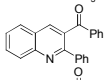
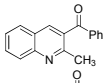
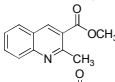
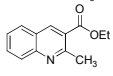
Entry[a]	Aldehyde	Diketone	Product		Yield(%)[b]
1				**1a**	88
2				**2a**	92
3				**3a**	86
4				**4a**	85
5				**5a**	79
6				**6a**	72
7				**7a**	86
8				**8a**	78
9				**9a**	75
10				**10a**	81
11				**11a**	80
12				**12a**	89
13				**13a**	75

[a]All the reactions were performed on 1mmol scale by using 1.2 equiv of 1,3-cyclohexanedione. [b]Isolated yields.

Encouraged by this interesting result, we applied the same reaction conditions to a range of substituted 2-nitrobenzaldehydes. The results are summarized in Table 2. The experimental results revealed that the nature of substituents on the benzene ring of the substrates did affect the product yields. Substrates bearing electron withdrawing groups (fluoro, chloro and bromo) produced the desired products in 85-92% yields (Table 2, entries 2-4). On the other hand, substrates bearing electron donating groups (CH_3 and OH) gave the products in good yields (entries 5 and 6). Further, we tested the substrates such as 3-bromo and 3-methyl-2-nitrobenzaldehydes. The yield was excellent for the former (entry 7) and good for the latter (entry 8). In the case of 4-bromo substituted 2-nitrobenzaldehyde, the product yield was 75% (entry 9). Then, we tested the reaction with disubstituted 2-nitrobenzaldehydes which gave good to excellent yields of the desired products (entries 10-13).

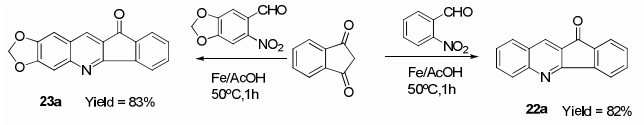
Table 3. Substrate scope of Fe/AcOH-mediated intermolecular reductive cyclization



Entry[a]	Aldehyde	Diketone	Product	Yield(%)[b]
1		 **1b**	 **14a**	85
2		 **2b**	 **15a**	90
3		 **3b**	 **16a**	78
4		 **4b**	 **17a**	90
5		 **5b**	 **18a**	91
6		 **6b**	 **19a**	80
7		 **7b**	 **20a**	75
8		 **8b**	 **21a**	79

[a]All the reactions were performed on 1mmol scale by using 1.2 equiv of 1,3- diketone. [b]Isolated yields.

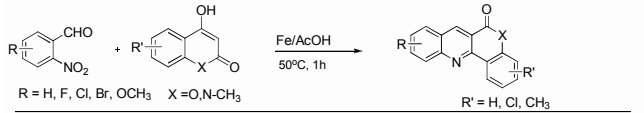
To explore the scope of our protocol, we applied the method to various cyclic and acyclic 1,3-diketones. The cyclic 1,3-diketones such as 1,3-cyclopentanedione (**1b**), 5,5 dimethyl cyclohexane-1 3-dione (**2b**), 2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**), and acyclic 1,3-diketones such as acetylacetone (**4b**), dibenzoylmethane (**5b**), benzoylacetone (**6b**), methyl acetoacetate (**7b**), ethyl acetoacetate (**8b**) were tested and the results are summarized in Table 3. Overall, the reaction proceeded smoothly and the product yields were good to excellent for all the cases (Table 3, entries 1-8).The compounds **14a** and **16a** have not been reported before.

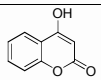
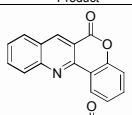
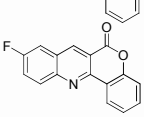
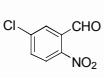
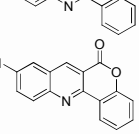
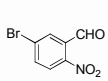
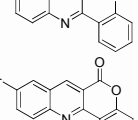
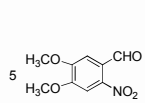


Scheme 2. Fe/AcOH-mediated one pot synthesis of polycyclic compounds

Then, we successfully extended this method for the synthesis of various biologically active compounds. When 2-nitrobenzaldehyde was treated with 1,3-indanedione, the expected product (**22a**) was formed in good yield. This compound is a well known antibacterial agent[2]. Similar result was obtained when 6-nitropiperonal treated with 1,3-indanedione (Scheme 2).

Table 4. Fe/AcOH-mediated one pot synthesis of various biologically active compounds.



Entry[a]	Aldehyde	Diketone	Product		Yield (%)[b]
1				**24a**	77
2				**25a**	72
3				**26a**	68
4				**27a**	70
5				**28a**	75
6				**29a**	68
7				**30a**	63
8				**31a**	81

[a]All the reactions were performed on 1mmol scale by using 1.2 equiv of 1,3-diketone. [b]Isolated yields.

On the other hand, when 4-hydroxycoumarin was treated with different substituted 2-nitrobenzaldehydes, the respective products were formed in moderate to good yields (Table 4, entries 1-6) and those compounds were proved for their anti-cancer activity.[4] When substituted 4-hydroxycoumarins such as 4-hydroxy-6-methylcoumarin and 6-chloro-4-hydroxycoumarin were treated with 2-nitrobenzaldehyde, the desired products were formed in moderate yields. The present methodology was also amenable for the synthesis of dibenzonaphthyridinones. When 4-

hydroxy-1-methyl-2-quinolone was treated with 2-nitrobenzaldehyde, dibenzonaphthyridinone (**31a**) was formed in good yield, The structure of the product was confirmed by ^{1}H, ^{13}C NMR spectroscopy, MS, HRMS, and single-crystal X-ray analysis (Figure 4). Dibenzonaphthyridinones are known as antimicrobial alkaloids, anticancer agents, and compounds that can reverse multidrug resistance.[19]

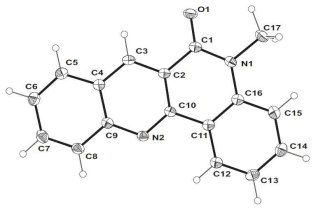
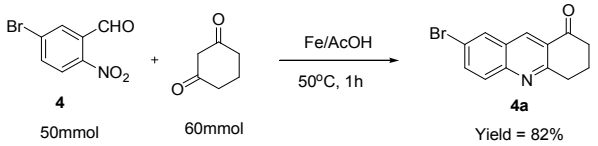


Figure 4. Crystal structure of compound **31a**[20]



Scheme 3. Large-scale synthesis of 7-bromo-3,4-dihydroacridin-1(2H)-one (**4a**)

Finally, to illustrate the scalability of our protocol, we performed the reductive cyclization reaction in gram scale. 11.5g (50 mmol) of 5-bromo-2-nitrobenzaldehyde (**4**) and 6.72g of 1,3-cyclohexanedione were treated with 14g of iron powder and 80 ml acetic acid at 50°C. The desired product 7-bromo-3,4-dihydroacridin-1(2H)-one (**4a**) was obtained in 82% yield. From this result, it is confirmed that, this protocol is applicable in milligram scale to multigram scale and thereby suitable for industrial level.

Conclusions

In conclusion, we have developed a simple, straightforward and effective iron/ acetic acid mediated protocol for the synthesis of various acridinone and quinoline derivatives. Also, we successfully extended this method for the synthesis of various biologically active compounds. Short reaction time, high yield, economical viability and ready availability of starting materials are the salient features of this method. Once the reaction was completed, the product can be obtained simply by filtering the resulting precipitate and, significantly, no work up involving a base is required to remove the acetic acid. This new protocol could substitute the existing methods for the synthesis of acridinone and quinoline derivatives which makes it very interesting for industrial purposes.

Experimental Section

General Remarks: Reagents and solvents were purchased from commercial suppliers and were used directly without any further purification unless otherwise stated. Column chromatography was performed on 63–200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) on the δ scale by using $CDCl_3$ as an internal standard, and coupling constants are expressed in Hertz (Hz). IR spectra were recorded with an FTIR spectrometer, and data are reported in cm^{-1}. Melting points were recorded by using an Electro Thermal capillary melting point apparatus.

General Procedure for the synthesis of acridinone and quinoline derivatives (1a-31a)

Iron powder (5mmol) was added to a stirred solution of substrate (1mmol) and 1,3-diketone (1.2mmol) in acetic acid (5mL). This mixture was heated to 50°C for 1h. After the completion of reaction (TLC), the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The resulting mixture was dissolved in EtOAc and then filtered to remove the iron impurities. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography to obtain the pure product.

(**Note:** Because of solubility problem, for the compounds **22a-31a**, the mixture were diluted with CH_2Cl_2 instead of EtOAc, then filtered.)

Acknowledgments

Financial support for this work by the Ministry of Science and Technology of the Republic of China, National Taiwan Normal University (99T3030-2, 99-D, 100-D-06) and Instrumentation Centre at National Taiwan Normal University are gratefully acknowledged.

Notes and references

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei-116, Taiwan, R.O.C.

E-mail: cheyaocf@ntnu.edu.tw, cheyaocf@yahoo.com.tw

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. (a) G. M. Shutske and J. D. Tomer IV, *J. Heterocycl. Chem.*, 1993, **30**, 23; (b) L. Paloque , P. Verhaeghe, M. Casanova, C. C. Ducros, A. Dumètre, L. Mbatchi, S. Hutter, M. K. Rabet, M. Laget, V. Remusat, S. Rault, P. Rathelot, N. Azas and P.Vanelle, *Euro. J. Med. Chem.*, 2012, **54**, 75; (c) A. Mai, D. Rotili, D. Tarantino, P. Ornaghi, F. Tosi, C. Vicidomini, G. Sbardella, A. Nebbioso, M. Miceli, L. Altucci, P. Filetici, *J. Med. Chem.*, 2006, **49**, 6897; (d) L. E. Korhonen, M. Turpeinen, M. Rahnasto, C. Wittekindt, A. Poso, O. Pelkonen, H. Raunio and R.O. Juvonen, *Br. J. Pharmacol.*, 2007, **150**, 932.

2. N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, V. Dorcet, A. L. Gagez, S. Sable, L. Picot, V. Thiery, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron*, 2013, **69**, 10123.

3. (a) P. Ornaghi, D. Rotili, G. Sbardella, A. Mai and P. Filetici, *Biochem. Pharm.*, 2005,**70**, 911; (b) A. T. Smith, M. R. Livingston, A. Mai, P. Filetici, S. F. Queener and W. J. Sullivan, *Antimicrob. Agents Chemother.*, 2007, **51**, 1109.

4.(a) N. Mulakayala, D. Rambabu, M. R. Raja, M. Chaitanya, C. S. Kumar, A. M. Kalle, G. R. Krishna, C. M. Reddy, M. V. Basaveswararao and M. Pal, *Bioorg.Med.Chem.*, 2012, **20**, 759; (b) J. V. Prasad, J. S. Reddy, N. Ravikumar, K. A. Solomon and G. Gopikrishna , *J. Chem. Sci.*, 2011, **123**, 673.

5. A. D. Yapi, N. Desbois, J. M. Chezal, O. Chavignon, J. C. Teulade, A. Valentin and Y. Blache, *Euro. J. Med. Chem.,* 2010, **45**, 2854.

6. A. A. Joshi, S. S. Narkhede and C. L. Viswanathan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 73.
7. D. Dube, M. Blouin, C. Brideau, C. C. Chan, S. Desmarais, D. Ethier, J. P. Falgueyret, R. W. Friesen, M. Girard, Y. Girard, J. Guay, D. Riendeau, P. Tagari and R. N. Young, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1255.
8. (a) N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, *Bio. Pharm. Bull.*, 2004, **27**, 1683; (b) A. R. Martirosyan, R. R. Bata, A. B. Freeman, C. D. Clarke, R. L. Howard and J. S. Strobl, *Biochem. Pharmacol.,* 2004, **68**, 1729.
9. G. M. Shutske and J. D. Tomer, *J. Heterocycl. Chem.*, 1993, **30**, 23.
10. (a) J. M. Contelles, E. P. Mayoral, A. Samadi, M. C. Carreiras and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652; (b) C. S. Jia, Z. Zhang, S. J. Tub and G.W. Wang, *Org. Biomol. Chem.,* 2006, **4**, 104; (c) H. Zheng, J. Liu, Y. J. Mei, Q.Y. Shi and P. F. Zhang, *Catal Lett.*, 2012, **142**, 573; (d) R. G. Xing, Y. N. Li, Q. Liu, Y. F. Han, X. Wei, J. Li and B. Zhou, Synthesis., 2011, **13**, 2066; (e) S. D. Edmondson, A. Mastracchio and E. R. Parmee, *Org. Lett.*, 2000, **2**, 1109; (f) J. L. Asherson, O. Bilgic. and D. W. Young. *J. Chem. Soc., Perkin Trans. 1*, 1981, 3041;
11. (a) R. Camps, *Arch. Pharm.* 1899, **237**, 659; (b) H. Skraup, *Ber. Dtsch. Chem. Ges.*, 1880, **13**, 2086; (c) P. Friedlander, *Ber. Dtsch. Chem. Ges.,* 1882, **15**, 2572; (d) R. H. F. Manske and M. Kulka, *Org. React.,* 1953, **7**, 59; (e) E. A. Fehnel, *J. Heterocycl. Chem.,* 1967, **4**, 565; (f) C.-C. Cheng and S.-J. Yan, *Org. React.*, 1982, **28**, 37.
12. V. Sridharan, P. Ribelles, M. T. Ramos and J. C. Menendez, *J. Org. Chem.*, 2009, **74**, 5715.
13. Z. H. Yu, H. F. Zheng, W. Yuan, Z. L. Tang, A.D. Zhang and D.Q. Shi, *Tetrahedron*, 2013, **69**, 8137.
14. Q. Shen, L.Wang, J. Yu, M. Liu, J. Qiu, L. Fang, F. Guo and J. Tang, *Synthesis,* 2012, **44**, 389.
15. D. R. Boyd, J. H. Davies, L. Hamilton, J. J. McCullough, J. F. Malone, H. P. Porter and A. Smith, *J. Org. Chem.*, 1994, **59**, 984.
16. (a) C. Bolm, J. Legros, J. L. Paih and L. Zani, *Chem. Rev.,* 2004, **104**, 6217; (b) L. D. S. Yadav and A. Rai, *Synlett.*, 2009, 1067; (c) T.Erker, M. E. Schreder, and C. Studenik, *Arch. Pharm. Pharm. Med. Chem.*, 2000, **333**, 58; (d) S. Jonsson, C. S. Arribas, O. F. Wendt, J. S. Siegel and K.Warnmark, *Org. Biomol. Chem.,* 2005, **3**, 996; (e) J. K. Mishra, and G. Panda, *Synlett.*, 2005, 1881; (f) A. Kamal, B. S. P. Reddy and B. S. N. Reddy, *Tetrahedron Lett.,* 1996, **37**, 2281; (g) D. Basavaiah and J. S. Rao, *Tetrahedron Lett.,* 2004, **45**, 1621; (h) K. Y. Lee, Y. Lee and J. N. Kim, *Bull. Korean Chem.* Soc., 2007, **28**, 143.
17. (a) C. Ramesh, P. M. Lei, D. Janreddy, V. Kavala, C.-W. Kuo and C.-F. Yao, *J. Org. Chem.,* 2012, **77**, 8451; (b) D. Janreddy, V. Kavala, J. W. Bosco, C.-W. Kuo and C.-F. Yao, *Eur. J. Org. Chem.,* 2011, 2360; c) C. Ramesh, V. Kavala, B. R. Raju, C.-W. Kuo and C.-F. Yao, *Tetrahedron Lett.*, 2010, **51**, 5234; (d) C. Ramesh, B. R. Raju, V. Kavala, C.-W. Kuo and C.-F. Yao, *Tetrahedron,* 2011, **67**, 1187; (e) C. Ramesh, V. Kavala, B. R. Raju, C.-W. Kuo and C.-F. Yao, *Tetrahedron Lett.*, 2009, **50**, 4037.
18. (a) G. W. Wang and C. B. Miao, *Green Chem.,* 2006, **8**, 1080; (b) R. Miri, R. Motamedi, M. R. Rezaei, O. Firuzi1, A. Javidnia, and A. Shafiee, *Arch. Pharm. Chem. Life Sci.,* 2011, **2**, 111; (c) K. M. Clarke, J. J. Clair, and M. D. Burkart, *J. Org. Chem.*, 2005, **70**, 3709.
19. (a) Y. Fang, and R. C. Larock, *Tetrahedron,* 2012, **68**, 2819. (b) E. Kiselev, T. S. Dexheimer, Y. Pommier and M. Cushman, *J. Med. Chem.,* 2010, **53**, 8716.
20. CCDC- 998617 (**1a**), CCDC- 998615 (**31a**) and CCDC- 998616 (**I**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.