Chinese Journal of Chemistry, **2009**, *27*, 1953—1956

Full Paper

One-pot Synthesis of 1,8-Dioxo-decahydroacridine Derivatives in Aqueous Media

BALALAIE, Saeed*[,a] CHADEGANI, Fatemeh[a] DARVICHE, Fatemeh[a]
BIJANZADEH, Hamid Reza[b]

[a] *Peptide Chemistry Research Group, K. N. Toosi University of Technology, 15875-4416, Tehran, Iran*
[b] *Department of Chemistry, Tarbiat Modares University, 14115-175, Tehran, Iran*

A new and efficient method for the synthesis of 1,8-dioxo-9-aryl-decahydroacridine derivatives was developed via a one-pot three component reaction of dimedone, aromatic aldehydes and ammonium acetate in the presence of ammonium chloride, or $Zn(OAc)_2•2H_2O$ or *L*-proline separately in water in the short period of time and high yields.

Keywords 1,8-dioxo-9-aryl-decahydro-acridine derivative, Domino Knoevenagel-Michael reaction, aqueous media, one-pot three component reaction, ammonium chloride, $Zn(OAc)_2•2H_2O$, *L*-proline

Introduction

Green chemistry involves the developing of chemical products and synthetic procedures, which are environmentally friendly and have reduced health risks followed by researching on more efficient methods by means of chemistry science. Water plays an essential role in human beings and other creatures and the use of it as a medium for organic reactions is one of the latest challenges for modern organic chemists. This field of study has grown steadily since Breslow demonstrated, in 1980, the use of the hydrophobic effect to promote Diels-Alder reaction,[1] and according to new work, a variety of organic reactions could be carried out in water.[2]

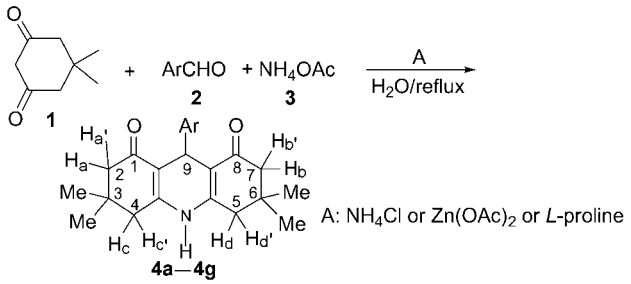
Acridinediones, the acridine derivatives having two keto functional groups at the 1st and 8th positions are found to be good anti-malarial agents. Substituted hexahydroacridine-1,8-dione, a novel dihydropyridine molecule, resembles K-channel openers, and relaxes KCl reconstructed urinary-bladder smooth muscle *in-vitro*.[3] These acridinediones were also found to act as laser dyes.[4] In acridine 1,8-diones, electron delocalization along a stretch of nine non-H atoms facilitate them to exhibit fluorescence and laser activity.[5] The effectiveness of lasing can be controlled by the substituents at C-9 and N-10 of the acridine chromophore. Apart from the above applications, acridinediones also possess other important photo-physical and electrochemical properties.[6] Acridine dyes reacting with nucleic acids have received increasing interest as mutagens in micro-organisms.[7]

Many procedures describe the synthesis of acridinedione derivatives by three component cyclocondensation between dimedone and benzaldehyde in the presence of nitrogen source like urea,[8] ammonium bicarbonate,[9a] ammonium acetate on basic alumina,[9b] ammonium hydroxide,[10] hydroxylamine[11] in different organic solvents at reflux or under a microwave irradiation condition. Dodecyl benzenesulfonic acid as phase transfer catalyst in aqueous media under reflux has been reported.[12] Condensation of dimedone, ammonium acetate with α-keto acid has also been reported.[13]

Each of these methods has its own merit, however, most of these reported procedures have disadvantages including low yields, prolonged reaction time, using the excess of reagents and catalysts, a microwave oven and toxic organic solvents, which necessitate the development of a new methodology for the synthesis of 1,8-dioxo-9-aryl-decahydroacridine derivatives.

Herein, we report a simple and convenient procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives in aqueous media via a one-pot three component reaction of dimedone, aromatic aldehydes, ammonium acetate in the presence of ammonium chloride or $Zn(OAc)_2•2H_2O$ or *L*-proline (Scheme 1).

Scheme 1



Results and discussion

Three-component condensation of dimedone, aro-

* E-mail: balalaie@kntu.ac.ir; Fax: 0098-21-22853650
Received October 14, 2008; revised April 15, 2009; accepted May 20, 2009.
Project supported by the National Research Institute for Science Policy (NRISP) and the K. N. Toosi University of Technology Research Council.

matic aldehydes and ammonium acetate in the presence of ammonium chloride or $Zn(OAc)_2•2H_2O$ or *L*-proline led to hexahydroacridine-1,8-diones. In each case, we obtained the corresponding products after 2—3 h in good to excellent yields. In fact these additives play a crucial role in the success of the reaction in terms of yield and rate of reaction. For investigating the role of catalyst, by reaction of **1**, **2**, and **3** in water under a heating condition, even an extended reflux did give low yields of product **4** as expected. Most of substrates still remained and isolated yield of product was 30% after 14 h.

To study the generality of this process, several examples illustrating this method for the synthesis of products **4a**—**4g** were studied. The results are summarized in Table 1. The substituents on the aromatic ring did not show effects in terms of yields under these reaction conditions.

Table 1 Synthesis of 1,8-dioxo-decahydroacridine derivatives **4a**—**4g** in the presence of ammonium chloride or $Zn(OAc)_2•2H_2O$ or *L*-proline in water at reflux condition[a]

Product	Ar	Yield[b]/%		
		L-Proline	$Zn(OAc)_2$	NH_4Cl
4a	4-Br-C_6H_4-	82	84	86
4b	4-Cl-C_6H_4-	88	91	93
4c	4-CN-C_6H_4-	84	86	87
4d	4-MeCONH-C_6H_4-	97	94	95
4e	3-NO_2-C_6H_4-	96	93	96
4f	4-NO_2-C_6H_4-	89	90	93
4g	4-CF_3-C_6H_4-	96	93	96

[a] Reaction time in all reactions was between 2—3 h. [b] Isolated yield. The reactions were carried out in the presence of NH_4Cl or $Zn(OAc)_2•2H_2O$ or *L*-proline with molar ratio 0.65∶1∶035.

It has been established that dimedone **1** is stable as a conjugated enol rather than a diketone due to the delocalization which makes the counter ion more stable and less likely to regain the proton. In our proposed mechanism (Figure 1) we suggested the formation of enamine **9**, in the presence of ammonium acetate and **1** in water, which was a more active reactant toward unsaturated alkene **7** to make a domino Knoevenagel-Michael cyclization.

The three-component reaction was done in the presence of ammonium chloride, or $Zn(OAc)_2•2H_2O$ or *L*-proline separately. Ammonium chloride acts as a source of hydrochloric acid, which can protonate carbonyl group to create a more reactive species, and in the last step of reaction promote the cyclodehydration to give products **4a**—**4g**. $Zn(OAc)_2•2H_2O$ acts as a mild Lewis acid which has the same role as ammonium chloride to enhance the electrophilicity of the carbonyl group (Figure 1). *L*-Proline as a naturally occurring amino acid is non-toxic, non-metallic, readily available, cheap, and reactive at room temperature, water soluble and so easily removed at the end of the reaction. *L*-Proline converts the aldehydes into more reactive electrophilic iminium ions and helps the formation of intermediate olefin, which was readily prepared *in situ* from Knoevenagel condensation. It was proposed that *L*-proline could activate the olefin via formation of iminium form and then addition of enamine to form intermediate **10** and final cyclization led to product **4**[14,15] (Figure 1).

Formation of the 1,8-dioxo-decahydroacridines (**4a**—**4g**) structure was unambiguously supported by spectroscopic and analytical data. A singlet in the region δ 4.74—5.14 in the ^{1}H NMR spectra was assigned to H-9 of the acridinedione ring. In all cases for the products **4a**—**4g**, the axial protons of H-2 and H-7 appeared separately from equatorial protons as one doublet in the region δ 2.16—2.30 with J=16 Hz. The chemical shift of axial protons of H-4 and H-5 is the same but different from that of the equatorial protons. The mass spectra of these compounds detected the expected molecular ion signals.

In conclusion, our procedure has significant advantages over the existing ones such as general applicability, commercially available and safer reagents without use of any harmful organic solvent, thus hazardous pollution is minimized to achieve an eco-friendly process.

Experimental

Melting points were recorded on an Electrothermal 9100 melting point apparatus and IR spectra on an ABB FTLA-2000 spectrophotometer using KBr disks. ^{1}H-NMR spectra were recorded on a Bruker DRX 300 (300 MHz) Avance spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as the internal standard. Mass spectra were recorded by a GC-MS Hewlet Packard model 5973 instrument (Agilent Technology) using EI (20 eV).

General procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives

A mixture of dimedone (308 mg, 2.2 mmol), benzaldehyde derivatives (1 mmol), ammonium acetate (77 mg, 1 mmol), ammonium chloride (35 mg, 0.65 mmol) or *L*-proline (41 mg, 0.35 mmol) or $Zn(OAc)_2•2H_2O$ (220 mg, 1 mmol) was refluxed in water for 2—3 h. Completion of the reaction was confirmed by TLC [*V*(petroleum ether) ∶ *V*(ethyl acetate)=1∶4]. The mixture was filtered and then washed with water. The desired product was obtained with high purity (yields 82%—97%).

Selected data for the compounds 4a—4g

3,3,6,6-Tetra-methyl-9-(4-bromophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4a) m.p. 241—243 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97 (s, 6H, 2Me), 1.09 (s, 6H, 2Me), 2.16 (d, J=16 Hz, 2H, H-2a,7b), 2.26 (d, J=16 Hz, 2H, H-2a',7b'), 2.28 (d, J=16.5 Hz, H-4c,5d), 2.35 (d, J=16.5 Hz, H-4c',5d'), 5.06 (s, 1H, H-9), 7.08 (brs, 1H, N), 7.17 (d, J=8.3 Hz, 2H, ArH),

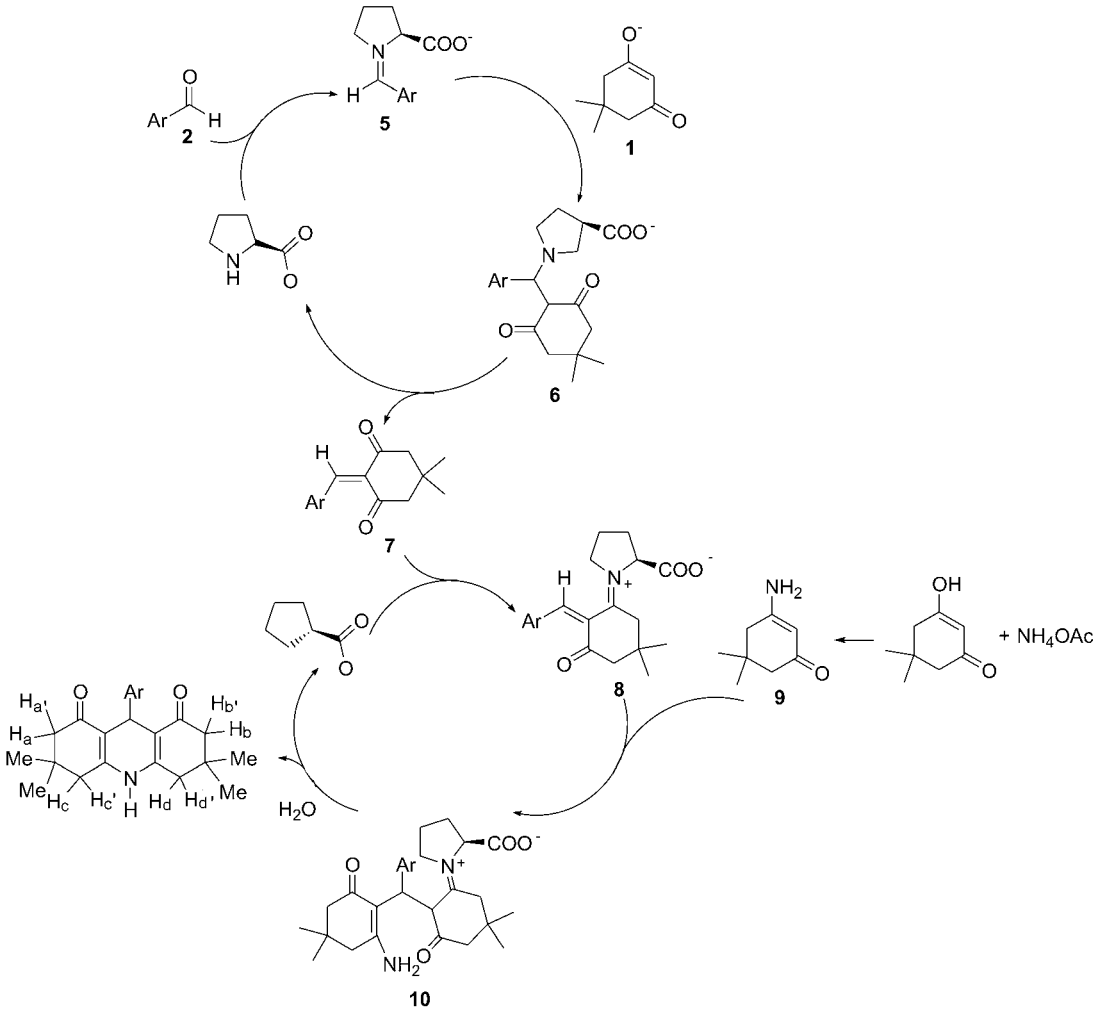


Figure 1 Proposed mechanism for the synthesis of 1,8-dioxo-decahydroacridines **4a**—**4g** in water at reflux condition in the presence of *L*-proline.

7.29 (d, 2H, J=8.3 Hz, ArH); IR (KBr) v: 3173, 2952, 1750, 1612 cm^{-1}; MS (20 eV) *m/z* (%): $C_{23}H_{26}O_2BrN$, 429 (M^++2, 9.1), 428 (M^++1, 3), 427 ($M^{\bullet+}$, 9.1), 272 ($M^{\bullet+}$−C_4H_8Br, 100), 188 ($M^{\bullet+}$−$C_{11}H_{12}BrO$, 2). Anal. calcd for $C_{23}H_{26}NO_2Br$: C 64.49, H 6.12, N 3.27; found C 64.40, H 6.08, N 3.30.

3,3,6,6-Tetra-methyl-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4b) m.p. 299—301 ℃ (lit.[9] 296—298 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (s, 6H, 2Me), 1.09 (s, 6H, 2Me), 2.16 (d, J=16 Hz, 2H, H-2a,7b), 2.27 (d, J=16 Hz, 2H, H-2a',7b'), 2.28 (d, J=16.5 Hz, H-4c,5d), 2.35 (d, J=16.5 Hz, H-4c',5d'), 5.06 (s, 1H, H-9), 7.07 (brs, 1H, NH), 7.17 (d, J=8.3 Hz, 2H, ArH), 7.29 (d, J=8.3 Hz, 2H, ArH); IR (KBr) v: 3282, 2957, 1659, 1606 cm^{-1}.

3,3,6,6-Tetra-methyl-9-(4-cyanophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4c) m.p. 324—326 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (s, 6H, 2Me), 1.12 (s, 6H, 2Me), 2.17 (d, J=16.5 Hz, 2H, H-2a,7b), 2.26 (d, J=16.5 Hz, 2H, H-2a,7b'), 2.28 (d, J=16.5 Hz, 2H, H-4c,5d, 2CH), 2.43 (d, J=16.5 Hz, 2H, H-4c',5d'), 5.11 (s, 1H, H-9), 5.91 (brs, 1H, NH), 7.46 (d, J=8.3 Hz, 2H, ArH), 7.52 (d, J=8.3 Hz, 2H, ArH); IR (KBr) v: 3322, 2958, 2223, 1637, 1488 cm^{-1}; MS (20 eV) *m/z* (%): $C_{24}H_{26}N_2O_2$, 374 ($M^{\bullet+}$, 0.3), 348 (6), 321 (8), 273 (72), 272 ($M^{\bullet+}$−C_7H_4N, 100). Anal. calcd for $C_{24}H_{26}N_2O_2$: C 76.97, H 6.99, N 7.48; found C 76.84, H 6.90, N 7.43.

3,3,6,6-Tetra-methyl-9-(4-*N*-acetylphenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4d) m.p. 331—333 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.86 (s, 6H, 2Me), 1.00 (s, 6H, 2Me), 1.95 (d, J=16.5 Hz, 2H, H-2a,7b), 2.15 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.33 (d, J=16.5 Hz, 2H, H-4c,5d), 2.40 (d, J=16.5 Hz, 2H, H-4c',5d'), 2.54 (s, 3H, $COCH_3$), 4.74 (s, 1H, H-9), 7.03 (d, J=8.3 Hz, 2H, ArH), 7.31 (d, J=8.3 Hz, 2H, ArH), 9.26 (s, 1H, NH), 9.74 (brs, 1H, NH); IR (KBr) v: 3316, 3034, 2956, 1740, 1650, 1627 cm^{-1}; MS (20 eV) *m/z* (%): $C_{25}H_{30}N_2O_3$, 406 ($M^{\bullet+}$, 9.3), 405 ($M^{\bullet+}$−1, 15), 404 ($M^{\bullet+}$−2, 77), 377 (27), 363 ($M^{\bullet+}$−43, 29), 362 (100), 272 ($M^{\bullet+}$−C_8H_8NO, 22). Anal. calcd for $C_{25}H_{30}N_2O_3$: C 73.86, H 7.44, N 6.89; found 73.72, H 7.38, N 6.81.

3,3,6,6-Tetra-methyl-9-(3-nitrophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4e) m.p. 288—290 ℃ (lit.[9] 285—286 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.99 (s, 6H, 2Me) ,1.12 (s, 6H, 2Me), 2.16 (d,

J=16.5 Hz, 2H, H-2a,7b), 2.26 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.32 (d, J=16.5 Hz, 2H, H-4c,5d), 2.43 (d, J=16.5 Hz, 2H, H-4c',5d'), 5.19 (s, 1H, H-9), 6.36 (brs, 1H, NH), 7.39 (t, J=7.9 Hz, 1H, ArH), 7.90 (d, J=7.9 Hz, 1H, ArH), 7.97 (d, J=8.1 Hz, 1H, ArH), 8.06 (brs, 1H, ArH); IR (KBr) v: 3251, 3189, 3066, 2947, 1745, 1660, 1645, 1540, 1350 cm^{-1}.

3,3,6,6-Tetra-methyl-9-(4-nitrophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4f) m.p. 286—288 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.85 (s, 6H, 2Me), 1.01 (s, 6H, 2Me), 1.96 (d, J=16.5 Hz, 2H, H-2a,7b), 2.23 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.33 (d, J=16.5 Hz, 2H, H-4c,5d), 2.52 (d, J=16.5 Hz, 2H, H-4c',5d'), 4.90 (s, 1H, H-9), 7.41 (d, J=8.5 Hz, 2H, ArH), 8.07 (d, J=8.5 Hz, 2H, ArH), 9.47 (brs, 1H, NH); IR (KBr) v: 3378, 2957, 1647, 1600, 1511, 1339 cm^{-1}; MS (20 eV) m/z (%): $C_{23}H_{26}N_2O_4$, 394 ($M^{\bullet+}$, 98.7), 377 (14), 347 (M^+-NO_2, 5), 347 (10), 273 (97), 272 ($M^+-C_6H_4NO_2$, 100), 216 ($M^{\bullet+}-C_{10}H_{12}NO_2$, 28), 188 ($M^+-C_{11}H_{12}NO_3$, 26), 83 (10). Anal. calcd for $C_{23}H_{26}N_2O_4$: C 70.03, H 6.64, N 7.10; found C 69.92, H 6.58, N 7.02.

3,3,6,6-Tetra-methyl-9-(4-trifluoromethylphenyl)-1,2,3,4,5,67,8-octahydroacridine-1,8-dione (4g) m.p. 241—243 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.99 (s, 6H, 2Me), 1.12 (s, 6H, 2Me), 2.16 (d, J=16.5 Hz, 2H, H-2a,7b), 2.26 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.28 (d, J=16.5 Hz, 2H, H-4c,5d), 2.42 (d, J=16.5 Hz, 2H, H-4c',5d'), 5.14 (s, 1H ,H-9), 6.93 (s, 2H, ArH), 7.28 (brs, 1H, NH), 7.63 (s, 2H, ArH); IR (KBr) v: 3275, 2973, 1715, 1612 cm^{-1}; MS (20 eV) m/z (%): $C_{24}H_{26}NO_2F_3$, 417 ($M^{\bullet+}$, 50), 402 (M^+-Me, 3), 398 (M^+-F, 4), 273 (55), 272 ($M^+-C_7H_4F_3$, 100), 262 (15), 216 ($M^+-C_{11}H_{12}F_3$, 15), 188 ($M^+-C_{12}H_{12}F_3O$, 16). Anal. calcd for $C_{24}H_{26}NO_2F_3$: C 69.05, H 6.27, N 3.35; found C 68.91, H 6.20, N 3.30.

References

1 (a) Breslow, R.; Riseout, D. C. *J. Am. Chem. Soc*. **1980**, *102*, 7816.
(b) Grieco, P. A. *Organic Synthesis in Water*, Thomson Science, Glascow, **1998**, pp. 1—80, p. 250.
(c) Li, C.-J. *Chem. Rev*. **2005**, *105*, 3095.

2 (a) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett*. **2005**, *46*, 4473.
(b) Zha, Z.; Hui, A.; Zhou, Y.; Miao, Q.; Wang, Z.; Zhang, H. *Org. Lett*. **2005**, *7*, 1903.
(c) Gogoi, P.; Hazarika, P.; Konwar, D. *J. Org. Chem*. **2005**, *70*, 1934.
(d) Botella, L.; Najera, C. *J. Org. Chem*. **2005**, *70*, 4360.
(e) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 7768.
(f) Chen, L.; Li, C.-J. A. *Org. Lett*. **2004**, *6*, 3151.
(g) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc*. **2002**, *124*, 5640.
(h) Hikaru, Y.; Akio, S.; Takeo, T. *Tetrahedron* **2005**, *61*, 7087.
(i) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev*. **2004**, *104*, 199.
(j) Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem*., *Int. Ed*. **2005**, *44*, 3407.
(k) Biondini, D.; Brinchi, L.; Germani, R.; Goracci, L.; Savelli, G. *Eur. J. Org. Chem*. **2005**, 3060.

3 (a) Li, J. H.; Yasay, G. D.; Kan, S. T.; Ohnmacht, C. J.; Trainor, D. A.; Boney, A. D.; Heppner, T. J.; Nelson, M. T. *Arzneimittelforschung* **1996**, *46*, 525.
(b) Shout, D. M.; Meyers, A. I. *Chem. Rev*. **1982**, *82*, 223.

4 (a) Murugan, P.; Shanmugasundaram, P.; Ramakrishnan, V. T.; Venkatachalapathy, B.; Srividya, N.; Ramamurthy, P.; Gunasekaran, K.; Velmurugan, D. *J. Chem. Soc*., *Perkin Trans 2* **1998**, 999.
(b) Prabahar, K. J.; Ramakrishnan, V. T.; Sastikumar, D.; Selladurai, D.; Masilamani, V. *Indian J. Pure Appl. Phys*. **1991**, *29*, 382.
(c) Islam, A.; Murugan, P.; Hwang, K. C.; Cheng, C.-H.; *Synth. Metals* **2003**, *139*, 347.

5 (a) Shanmugasundaram, P.; Prabahar, K. J.; Ramakrishnan, V. T. *J. Heterocyclic Chem*. **1993**, *30*, 1003.
(b) Shanmugasundaram, P.; Murugan, P.; Ramakrishnan, V. T.; Srividya, N.; Ramamurthy, P. *Heteroatom Chem*. **1996**, *7*, 17.

6 Mohan, H.; Srividya, N.; Ramamurthy, P.; Mittal, J. P. *J. Chem. Soc*., *Faraday Trans*. **1996**, *92*, 2353.

7 Sivaraman, J.; Subramanian, K.; Velmurugan, D.; Subramanian, E.; Shanmugasunda-ram, P. S. *Acta Crystallogr*. **1996**, *C52*, 481.

8 Bakibaev, A. A.; Fillimonov, V. D.; Nevgodova, E. S. *Zh. Org. Khim*. **1991**, *27*(7), 1519.

9 (a) Tu, S.-J.; Lu, Z.; Shi, D.; Yao, C.; Gao, Y.; Guo, C. *Synth. Commun*. **2002**, *32*, 2181.
(b) Suárez, M.; Loupy, A.; Salfrán, E.; Morán, L.; Rolando, E. *Heterocycles* **1999**, *51*, 21.

10 Mora, A.; Suarez, M.; Ochoa, E.; Morales, A. *J. Heterocyclic Chem*. **1995**, *32*, 235.

11 Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhuang, Q. *J. Heterocyclic Chem*. **2004**, *41*, 767.

12 Jin, T.-S.; Zhang, J.-S. Guo, T.-T.; Wang, A.-Q.; Li, T.-S. *Synthesis* **2004**, 2001.

13 Viswanathan, N.; Sidhaye, A. R.; Goward, D. H. *Indin J. Chem*. **1986**, *25B*, 347.

14 (a) Balalaie, S.; Bararjanian, M.; Amani, M. A.; Movassagh, B. *Synlett* **2006**, 263.
(b) Abdolmohammadi, S.; Balalaie, S. *Tetrahedron Lett*. **2007**, *48*, 3299.
(c) Balalaie, S.; Abdolmohammadi, S.; Bijanzadeh, H. R.; Amani, A. M. *Mol. Diversity* **2008**, *12*, 85.

15 (a) List, B. *Tetrahedron* **2002**, *58*, 5573 and references cited therein.
(b) Jayasree, S.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.

(E0810144 Lu, Y.)