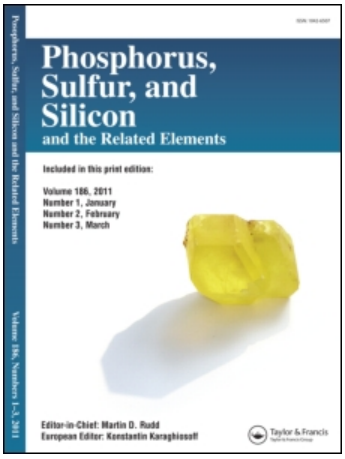
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

One-Pot Multi-Component Approach to the Synthesis of 1,4-Benzothiazines in Aqueous Media

Hassan Sheibani[a]; Mohammad Reza Islami[a]; Avid Hassanpour[a]; Kazem Saidi[a]
[a] Department of Chemistry, Shahid Bahonar University of Kerman, Kerman, Iran

To cite this Article Sheibani, Hassan , Islami, Mohammad Reza , Hassanpour, Avid and Saidi, Kazem(2008) 'One-Pot Multi-Component Approach to the Synthesis of 1,4-Benzothiazines in Aqueous Media', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 1, 13 — 20
To link to this Article: DOI: 10.1080/10426500701544599
URL: http://dx.doi.org/10.1080/10426500701544599

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 183:13–20, 2008
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701544599

Taylor & Francis
Taylor & Francis Group

One-Pot Multi-Component Approach to the Synthesis of 1,4-Benzothiazines in Aqueous Media

Hassan Sheibani, Mohammad Reza Islami, Avid Hassanpour, and Kazem Saidi
Department of Chemistry, Shahid Bahonar University of Kerman, Kerman, Iran

A new and rapid synthetic strategy for the oxidative cyclocondensation of 2-aminobenzenethiol and 1,3-dicarbonyls has been developed in order to obtain 2,3-disubstituted 1,4-benzothiazines at ambient temperature and in aqueous media. A mechanism is presented to account for the formation of the products.

Keywords 2-Aminobenzenethiol; 1,3-dicarbonyl; 1,4-benzothiazines; cyclocondensation

Downloaded At: 17:50 27 January 2011

INTRODUCTION

Increasing attention for environmental protection during the last decades has led both modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost while using non-toxic reagents, solvents and catalysts. One of the tools used to combine economic aspects with the environmental ones is the multi-component reaction (MCR) strategy; this process consists of two or more synthetic steps, which are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials.[1–3] The synthesis of heterocyclic systems is of continuing interest, at least in part as a result on the large number of biologically active molecules that contain heterocyclic rings.[4,5] A relatively unexplored heterocyclic ring system, with respect to both its synthesis and its biological activity, is 1,4-benzothiazines. These compounds possess a wide spectrum of biological and pharmacological activities due to the presence nitrogen and sulfur groups, which are considered to be responsible as

Received 5 May 2007; accepted 18 June 2007.
The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee for its support of this investigation.
Address correspondence to Hassan Sheibani, Department of Chemistry, Shahid Bahonar, University of Kerman, P.O. Box 76169-133, Kerman, Iran. E-mail: hassansheibani@yahoo.com

one of the structural features to impart their activities.[6] They are used as antihistaminics,antipsychotics,[7] antiemetics,[8] neuroleptics,[9] tranquilizers, [10] sedatives,[11]and so on.

The importance and utility of benzothiazine derivatives have led to the development of numerous synthetic routes. One of the most widely methods employed for the preparation of 1,4-benzothiazines involves the reaction of 2-aminobenzenethiols with alkynes,[12]α-haloketones or α-haloesters[13] and oxidative cyclocondensation of 2-aminobenzenethiols with 1,3-dicarbonyl compounds using dimethylsulfoxide (DMSO).[14,15] The former method requires the use of lachrymatory α-haloketones or α-haloesters as one of the reactants and the products isolated are in low yields (50–65%) and as isomeric mixtures. In the latter method, the yields are higher, and the amount of impurities of the products are much less. A dipolar aprotic solvent with several unfavorable properties such as dimethylsulfoxide, is necessary to act as both solvent and oxidant.

Downloaded At: 17:50 27 January 2011

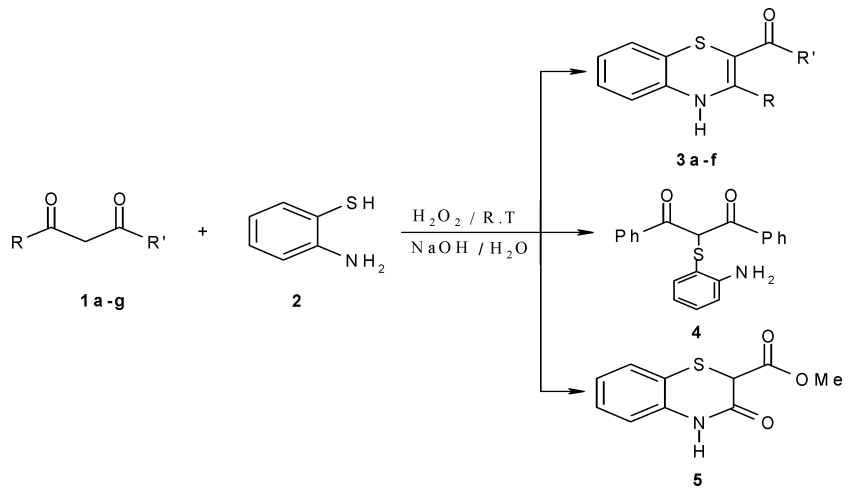
RESULTS AND DISCUSSION

Recently Munde et al.,[16] have reported an in-situ synthesis of 1,4-benzothiazines under solvent free conditions from 2-aminobenzenethiols and 1,3-dicarbonyls under oxidative conditions involving the formation of dimer of 2-aminobenzenethiols.[16]

In this method, 2-aminobenzethiols are oxidized to the corresponding disulfides in the presence of hydrazine hydrate and air, followed by condensation with the 1,3-dicarbonyls to yield 1,4-benzothiazines. The hydrazine hydrate catalyst acts as a base. Hydrazine—especially in anhydrous form—is highly toxic and dangerously unstable.

We have recently reported the synthesis of 1,4-benzothazines by using of 1,3-bielectrophiles and binucleoplies such as 1,3- dicarbonyl, enaminones and 2,2′-disulfanediyldianiline.[17,18] The chemical and pharmaceutical industries are under an accelerating pressure to find eco-friendly synthetic methodologies. With the aim of developing an efficient, economic, and clean procedure green chemistry) for preparation of 1,4-benzothiazines, we proceeded to condense equimolar quantities of 2-aminobenzenethiol **2** with 1,3-dicarbonyls **1a–g** in the presence of hydrogen peroxide in alkaline solution at ambient temperature (Scheme 1).

The complete process represents an example of a one-pot and sequential steps reaction (often referred to as tandem or cascade reaction), where reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade.[19,20]

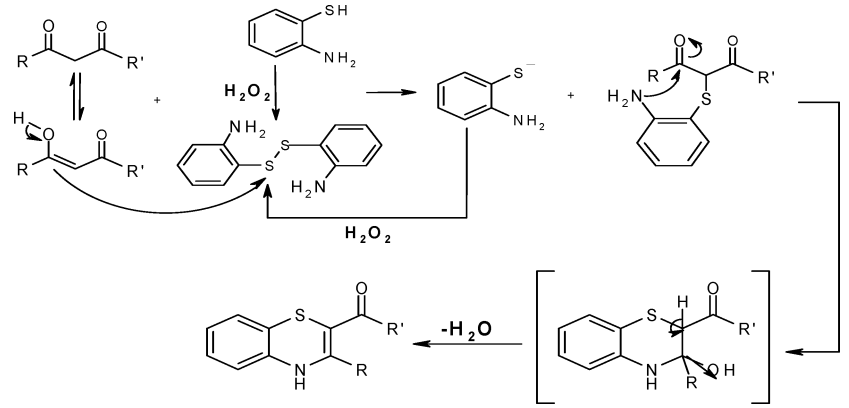


SCHEME 1

Downloaded At: 17:50 27 January 2011

Thus, the disulfide is quantitatively produced by fast oxidation of 2-aminobenzenethionl with hydrogen peroxide in the alkaline solution (Scheme 2)[12] proceeds through nucleophilic substitution at the S–S-bond of 2,2′-disulfanediyldianiline acting as an electrophile by β-keto esters, dimethyl malonate, and 1,3-diketones, followed by cyclization provides compounds **3a–f**, **4**, and **5** (Table I).

In fact, as clearly stated by R. A. Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it



SCHEME 2

TABLE I Reaction Time, Melting Points (°C) and Yields of Products

No.	R	R′	Time (min)	Yield (%)	M.P. (°C)
3a	CH_3	C_6H_5	15	92	183–184
3b	CH_3	CH_3	10	96	174–176
3c	—$CH_2CH_2CH_2$—		**25**	90	161(dec)
3d	—$CH_2C(CH_3)_2CH2$—		**20**	95	212(dec)
3e			20	90	188–190
3f	CH_3	CH_3CH_2O—	10	92	141–143
3g	CH_3	$PhCH_2O$—	15	88	155–157
4	C_6H_5	C_6H_5	30	95	132–133
5	CH_3O—	CH_3O—	30	95	169–170

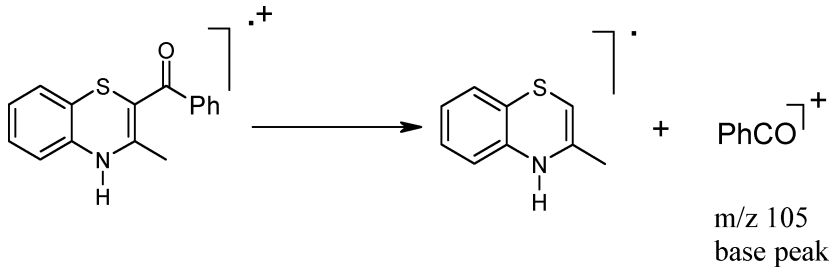
Downloaded At: 17:50 27 January 2011

should preferably be water."[22] The use of water as the reaction medium represents a remarkable benefit since this green solvent is highly polar, and therefore, immiscible with most organic compounds thus separation of the organic materials is easy. A further advantage is that many organic reactions like the aldol condensation, the benzoin condensation, the Diels-Alder cycloaddition, and cyclocondensation reactions exhibit rate enhancement in water.[23] In the present protocol as exhibited in (Scheme 1) the conversion of 1,3-diketones and 2-aminobenzenethionl in the presence of hydrogen peroxide to 1,4-benzothiazines has been efficiently performed in water as a "green" solvent. The easy purification of the products simply by crystallization, the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.

The structure of compounds **3a–g** and **4**, **5** were determined on the basis of their elemental analyses, mass spectrum, ^1H and ^{13}C NMR, and IR spectroscopic data. The infrared spectrum of compound **3a** revealed a band in the carbonyl region at 1640 cm^{-1} and a strong band at 3255 cm^{-1} which is due to the enaminone proton. The ^1H NMR spectrum of **3a** indicated three at different kinds of proton signals with a signal downfield (δ 9.09 ppm) which were identified as enaminone proton along with a multiplet (δ = 7.50–6.68) for the aromatic protons (9H), and a signal at δ 1.73 ppm were identified as methyl protons. The ^1H decoupled ^{13}C NMR spectrum of **3a** was measured in DMSO and it is in accord with the proposed structure.

β-Diketones and β-ketoesters exhibit keto-enol tautomerism. It can exist in two enolic forms. Hence, there is a possibility for the formation of two isomers, but **3a** is only obtained as revealed by mass spectrum which contain $PhCO^+$ ion at 105 as a base peak, and this is enough

evidence that the propose structure is **3a**. In addition, this compound did not give a positive iodoform test (Scheme 3).



SCHEME 3

Downloaded At: 17:50 27 January 2011

EXPERIMENTAL

General Procedures

2-Aminobenzenethiol, 1,3-dicarbonyls, and hydrogen peroxide were obtained from Merck Chemical Company and were used without further purification. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed by using a Heracus CHN-O-Rapid analyzer.

(3-Methyl-4H-1,4-benzothiazin-2-yl)(phenyl)methanone (3a)

The procedure for the preparation of 1-(3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-yl)ethanone 3a is described as an example. To a magnetically stirred solution of 1.00 g acetylacetone (2 mmol), 0.25 g 2-aminobenzenethiol (2 mmol) and 0.12 g NaOH in 10 mL water were mixed; then 5 mL hydrogen peroxide (30%) at 0°C was added to the reaction mixture for a period of 2 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 10 min. The solid product was collected and recrystallized from ethanol.

Red crystals, m.p. 182–184°C. IR (KBr): 3255, 1640,1590 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.09 (1H, s, NH), 7.50–6.68 (9H, m, arm), 1.73 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): 188.97 (C=O), 154.13 (C3), 140.86, 138.69, 131.02, 128.41, 127.86, 127.06, 126.07, 124.73, 120.31, 115.07, 97.33 (C_2), 21.03 (CH_3). MS *m/z* (relative intensity) 267 (M^+, 25), 162 (18),

105 (100), 77 (60), 51 (15). Anal. Calcd. For $C_{16}H_{113}NOS$: C, 71.88; H, 4.90; N, 5.24%. Found: C, 71.70; H. 4.92; N; 4.96%.

1-(3-Methel-4H-1,4-benzothiazin-2-yl)-1-ethenone (3b)

Red crystal, m.p. 173–176°C. IR (KBr) (ν_{max}/cm^{-1}): 3280, 1617, 1592.^{1}H NMR (500 MHz, DMSO-d_6): 8.85 (1H, s, NH), 6.91–6.63 (4H, m, arm), 2.22 (3H, s, CH_3), 2.18 (3H, s, CH_3).^{13}C NMR (DMSO $-d_6$): 190.68 (C=O), 153.41 (C_3), 139.36 (C), 127.44, 126.36, 124.99 (3CH), 120.49 (C), 115.43 (CH), 98.15(C_2), 30.24, 21.41 ($2CH_3$). MS *m/z* (relative intensity) 205 (M^+, 90), 162 (100), 130 (55), 118 (40), 109 (35), 77(18), 65 (20), 43 (32). Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82%. Found: C, 64..39; H. 5.33; N; 6.81%.

2,3-Dihydro-1H-phenothiazin-4(10H)-one (3c)

Dark yellow crystals. IR (KBr): 3280, 1592, 1567 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.89 (1H, s, NH), 7.08–6.40 (4H, m, arm), 2.31 (2H, t,$^3J_{HH}$ = 5.93 Hz, CH_2), 2.3 (2H, t, $^3J_{HH}$ = 6.34 Hz, CH_2), 1.80 (2H, m, CH_2).^{13}C NMR (DMSO-d_6): 188.91 (C=O), 155.90 (C_3), 136.59, 126.75, 126.32, 124.39, 119.87, 115.56 (arm), 97.83 (C_2), 36.08, 27.92, 20.06 ($3CH_2$). MS, m/z (%): 217 (100 parent and base peak), 162 (82), 118 (11), 94 (15), 80 (10), 69 (10), 45 (9).

2,2-Dimethyl-2,3,10,10a-tetrahydro-1H-phenothiazin-4(4aH)-one (3d)

Orange crystals. IR (KBr): 3255, 1617, 1592 cm^{-1}.^{1}H NMR (DMSO-d_6): δ 8.83 (1H, s, NH), 6.84–6.51 (4H, m, arm), 2.18 (2H, s, CH_2), 2.13 (2H, s, CH_2), 0.97 (6H, s, $2CH_3$). ^{13}C NMR (DMSO-d_6): δ 188.64 (C=0), 153.98 (C_3), 136.61, 126.90, 126.47, 124.60, 119.84, 115.67 (arm), 96.59 (C_2), 49.75 (CH_2), 41.21 (C), 31.51(CH_2), 27.61 ($2CH_3$). MS, m/z (%):245 (86, M^+),186 (95), 160 (100), 118 (27), 83 (71), 39 (68) . Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71%. Found: C, 68.20; H, 6.06; N, 5.61%.

Indeno[2,1-b][1,4]benzothiazin-11(5H)-one (3e)

Black crystals. IR (KBr): 3230, 3056, 1666, 1617, 1592 cm^{-1}.^{1}H NMR (DMSO-d_6): 10.8 (1H, s, NH), 7.5–6.86 (8H, m, arm).^{13}C NMR (DMSO-d_6): 184.83 (C=O), 156.06 (C_3), 135.70, 135.51, 133.75, 130.58, 130.08, 127.61, 125.73, 119.14, 118.16, 118.11, 117.88 (arm), 92.29 (C_2). MS, m/z (%):251 (81, M^+), 219 (89), 146 (40), 121 (100), 69 (28), 45 (47). Anal. Calcd. for $C_{15}H_9NOS$: C, 71.69; H, 3.61; N, 5.57%. Found: C, 71.40; H, 3.50; N, 5.34%.

Downloaded At: 17:50 27 January 2011

Downloaded At: 17:50 27 January 2011

Ethyl 3-Methyl-4H-1,4-benzothiazine-2-carboxylate (3g)

Yellow crystals. IR(KBr): 3329, 1641, 1592 cm^{-1}.^{1}HNMR (DMSO-d_6): δ 8.63 (1H, s, NH), 6.90–6.57 (4H, m, arm), 4.03 (2H, q, $^3J_{HH}$ 6.75 HZ, CH_2), 2.18 (3H, s, CH_3), 1.17 (3H, t, $^3J_{HH}$ 6.78 HZ, CH_3). ^{13}C NMR (DMSO-d_6): 163.04(C=O), 152.9 (C_3), 139.20 (C), 127.01, 125.71, 124.15 (3CH), 119.58 (C), 114.72 (CH), 86.00 (C_2), 59.61 (CH_2), 19.73 (CH_3), 14.21 (CH_3). MS *m/z* (relative intensity) 235 (M^+, 100), 207 (20), 162 (98), 130 (25), 118 (24), 109 (23), 77 (14), 65 (15), 45 (15). Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95%. Found: C, 60.95; H. 5.46; N; 5.92%.

Benzyl 3-Methyl-4H-1,4-benzothiazine-2-carboxylate (3h)

Yellow crystals. IR (KBr): 3255, 1691, 1617 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.74 (1H, s, NH), 7.37–6.61 (9H, m, arm), 5.10 (2H, s, CH_2), 2.21 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): 163.73 (C=O), 154.58 (C_3), 139.93, 137.50, 129.30, 128.70, 128.54, 128.02, 126.71, 125.25, 120.46, 115.79 (arm), 86.33 (C_2), 66.06 (CH_2), 20.81 (CH_3). MS *m/z* (relative intensity) 297 (M^+, 83), 188 (40), 171 (75), 162 (100), 136 (55), 109 (95), 91(93), 65 (82), 39 (78). Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71%. Found: C, 68.39; H, 5.06; N, 4.69%.

2-[(2-Aminophenyl)sulfanyl]-1,3-diphenyl-1,3-propanedione (4)

White crystals. IR (KBr): 3329, 3056, 1691, 1666, cm^{-1}.^{1}H NMR (DMSO-d_6): δ 9.98 (1H, s, OH, enol form, major tautomer), 7.96–7.21 (14H, m, arm), 4.55 (1H, s, CH, keto form, minor tautomer), 3.41(2H, s, NH_2, minor tautomer) 3.38 (2H, s, NH_2, major tautomer). ^{13}C NMR (DMSO-d_6): 194.77 (C=O), 165.14, 165.05, 137.66, 135.17, 134.19, 133.65, 131.96, 131.83, 128.75, 128.60, 128.55, 127.76, 127.41, 126.12, 125.21,125.06 (arm). MS, m/z(%): 347 (8), 225 (13), 196 (11), 105 (100, base peak), 91 (10),77 (62), 69 (17), 43 (32), 41 (13). Anal. Calcd. for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03%. Found: C, 72..39; H. 4.72; N; 3.96%.

Methyl 3-Oxo-3,4-dihydro-2H-1,4-benzothiazin-2-carboxylate (5)

White crystals. IR (KBr): 3205, 1741, 1691 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.95(1H, s, NH), 7.37–6.98 (4H, m, arm), 4.74 (1H, s, CH), 3.62 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6): 168.38, 162.78 (2C=O), 137.54, 128.34, 128.32, 124.15, 117.98, 117.17 (arm), 53.92 (OCH_3), 44.77(C_2). MS *m/z* (relative intensity) 223 (M^+, 51), 164 (85), 136 (100), 109 (38),

69 (30). Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27%. Found: C, 53.91; H, 3.90 ; N, 6.26%.

REFERENCES

[1] N. Hall, *Science*, **32,** 266 (1994).
[2] P. G. Jessop, T. Ikariya, and R. Noyori, *Chem. Rev*., **99,** 475 (999).
[3] I. P. Beletsksya and A. V. Cheprakov, *Chem. Rev*., **100,** 3009 (2000).
[4] H. Sheibani, P. V. Bernhardt, and C. Wentrup, *J. Org. Chem*., **70,** 5859 (2005).
[5] H. Sheibani, M. R. Islami, H. Khabazzadeh, and K. Saidi, *Tetrahedron*., **60,** 5932 (2004).
[6] R. R. Gupta, Ed., Phenothiazines and 1,4-Benzothiazines, In *Chemical and Biomedical Aspects* (Elsevier, Amsterdam, 1988).
[7] Y. Sugimoto, T. Tarumi, Q.E. Zhao, Y. Fujii, and C. Kamei, *Methods Find Exp. Clin. Pharmaco*., **20,** 457 (1998).
[8] J. David and E. Wager, *J. Psychopharmacol.*, **12,** 283 (1998).
[9] I. A. Platonov, Vop. *Med. Khim*., **41,** 27 (1995).
[10] M. K. El-said, *Pharmazie*., **36,** 678, 12 (1981).
[11] H. V. Petts and B. J. Br. Pleuvry, *J. Anaesthesiol*., **55,** 437 (1983).
[12] G. Liso, G. Trapani, V. Berardi, A. Latrofa, and P. Marchini, *J. Heterocycl. Chem*., 793 (1980).
[13] A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Comprehensive Heterocyclic Chemistry II (Elsevier, Amsterdam., 1996).
[14] B. S. Rathore and M. Kumar, *Bioorg. Med. Chem*., **14,** 5678 (2006).
[15] P. R. Sharma, V. Gupta, D. C. Gautam, and R. R. Gupta, *Phosph. Sulfur, and Silicon.*, **178,** 1483 (2003).
[16] S. B. Munde, S. P. Bondge, V. E. Bhingolikar, and R. A. Mane, *Green Chemistry*, **5,** 278 (2003).
[17] H. Sheibani, M. R. Islami, A. Hassanpour, and F. A. Hosseininasab, *ARKIVOC*., **15,** 68 (2006).
[18] H. Sheibani, M. R. Islami, F. A. Hosseininasab, and A. Hassanpour, *ARKIVOC*., **15,** 175 (2006).
[19] C. O. Kappe, *Tetrahedron.*, **49,** 6937 (1993).
[20] L. Weber, F. Illgen, and K. Conforti, M. Almstetter, *Synlett*., 366 (1999).
[21] B. J. Evans, J. T. Doi, and W. K. Musker, *J. Org. Chem*., **55,** 2337 (1990).
[22] R. A. Sheldon, *J. Mol. Catal. A*., **7,** 75 (1996).
[23] P. A. Grieco, Ed., *Organic Synthesis in Water* (Blackie Academic and Professional: London, 1998).
[24] A. Meijer, S. Otto, and J. B. F. N. J. Engberts, *J. Org. Chem*., **63,** 8989 (1998).

Downloaded At: 17:50 27 January 2011