Nucleophilic substitution of 2,2'-disulfanediyldianiline by β-keto esters and 1,3-diketones in the presence of triethylamine

Hassan Sheibani*, Mohammad Reza Islami, Avid Hassanpour, and Fatemeh Alsadat Hosseininasab

Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169, Iran
E-mail: hsheibani@mail.uk.ac.ir

Abstract
The 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 in the presence of triethylamine is followed by cyclization providing 4*H*-benzo[*b*][1,4]thiazine derivatives.

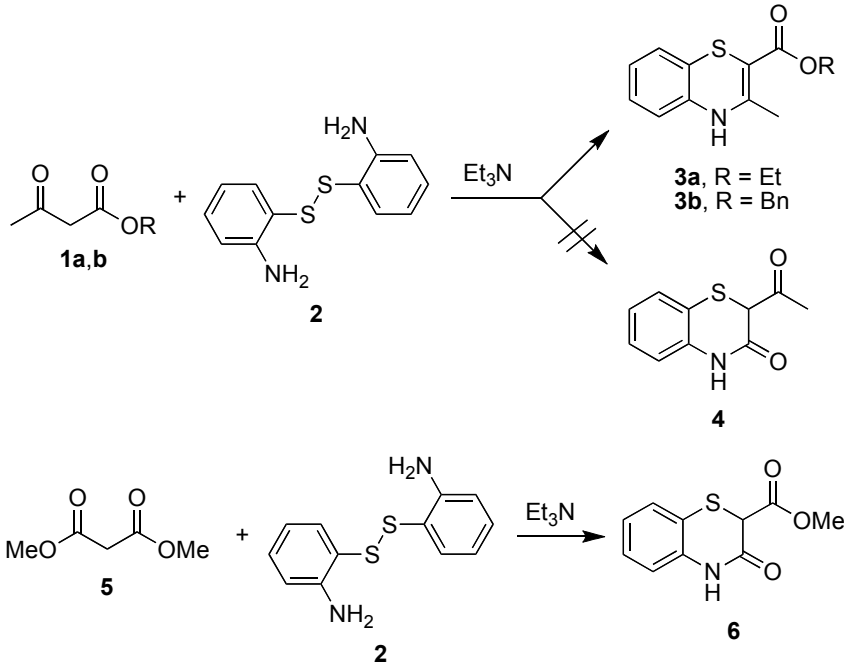
Keywords: Nucleophilic substitution, 2,2'-disulfanediyldianiline, 4*H*-benzo[*b*][1,4]thiazine

Introduction

For more than a century, 1,3-dicarbonyl compounds and their derivatives have been the most versatile and frequently employed C_3 synthons in organic synthesis, especially in heterocyclic synthesis.[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 4*H*-benzo[*b*][1,4]thiazine. Various benzothiazine derivatives have been patented as therapeutic agents having calcium-antagonistic properties[6,7] and anti inflammatory.[8] It has been long known that pheomelanins, the distinctive pigments of red hair and celtic skin, arise by the oxidative cyclization of cysteinyldopas via 1,4-benzothiazines.[9] Benzothiazines bearing a nitrooxyethyl group show anti-ischemic properties for heart diseases and for their control of hypertension.[10] 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-aminothiophenol with alkynes,[11] α-bromocarbonyl compounds,[12] and 1,3-ketones.[13, 14]

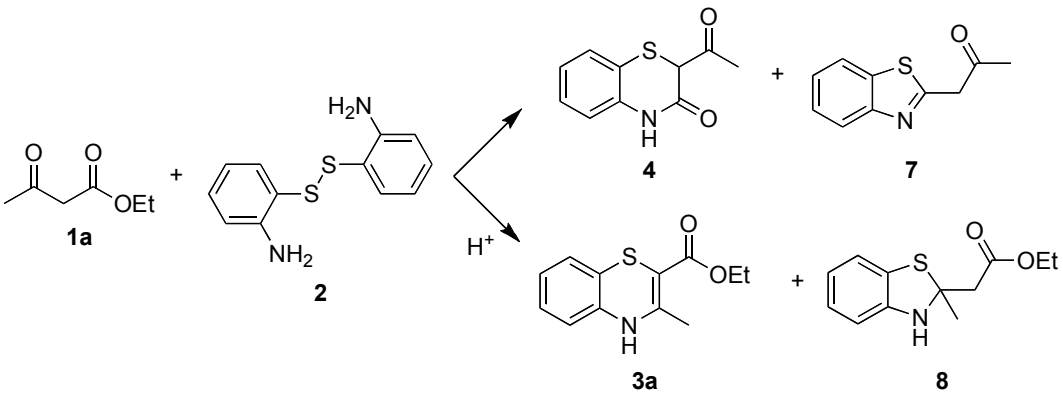
Results and Discussion

During the investigation of the synthesis of 1,3-thiazinones[15] and 1,4-benzothiazines[16] we anticipated that the nucleophilic substitution at the S–S-bond of 2,2'-disulfanediyldianiline (**2**) acting as electrophile by alkyl acetoacetates (**1a**,**b**) is followed by regioselective intramolecular condensation of the 2-amino group with the carbonyl group forming alkyl 3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carboxylates (**3a,b**).



Scheme 1

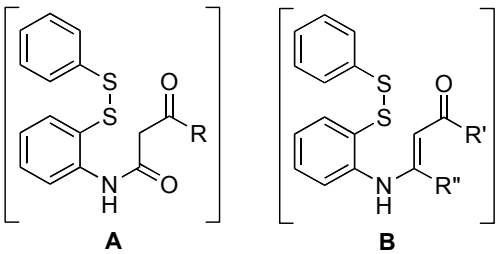
The reaction of alkyl acetoacetates (**1a**,**b**) with disulfide **2** in the presence of catalytic amounts of triethylamine was found to afford alkyl 3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carboxylates (**3a,b**) in a one step procedure with good to excellent yields (Scheme 1). Similarly, dimethyl malonate (**5**) is converted into methyl 3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-2-carboxylate (**6**) (Scheme 1). On the other hand, the reaction of ethyl acetoacetate (**1a**; R = Et) with disulfide **2** has been reported to afford a mixture of 2-acetyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (**4**) and 1-(benzo[*d*]thiazol-2-yl)propan-2-one **(7**) (Scheme 2).[17]



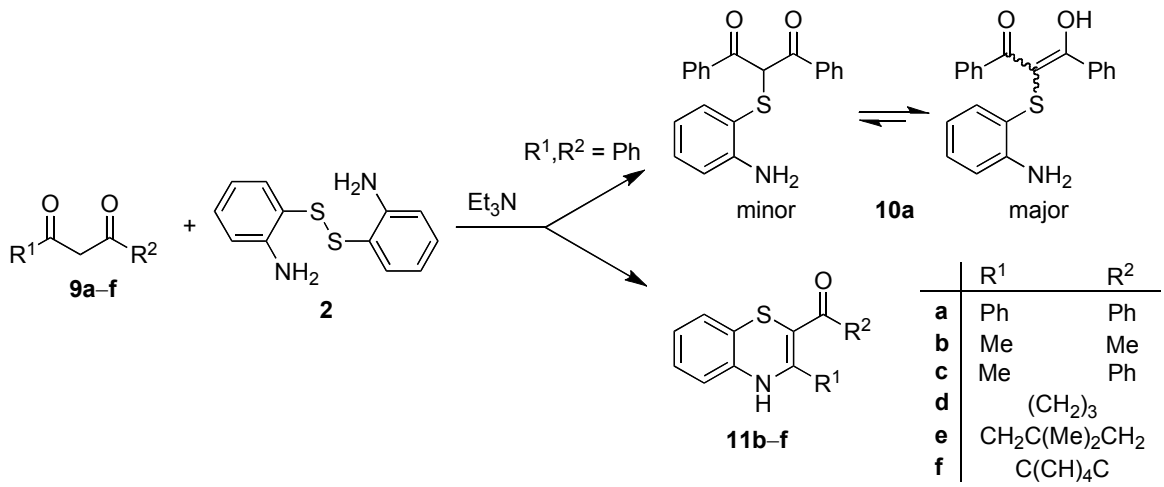
Scheme 2

In this context it should be noted that in the presence of a trace of *p*-toluenesulfonic acid the reaction of ethyl acetoacetate (**1a**; R = Et) with disulfide **2** leads to the formation of ethyl 3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carboxylates **(3a**) and ethyl 2-(2-methyl-2,3-dihydrobenzo [*d*]thiazol-2-yl)acetate (**8**) in about equal amounts (Scheme 2).[18]

Many useful and interesting reactions of disulfides are known.[19, 20] Disulfides, especially diaryl disulfides, are commonly used as electrophiles in the sulfenylation of enolates anions;[21, 22] sulfenamides and sulfenylimines have been prepared by nucleophilic substitution of the S–S-bond of disulfides with amines[23] and ketimines,[24] respectively. Recently, Munde *et al.* have reported an *in situ* synthesis of 1,4-benzothiazines from 2-aminobenzenethiols and 1,3-dicarbonyl compounds under oxidative conditions involving the formation of disulfide **2** under solvent free conditions.[25] Although the mechanism of these reactions have not yet been established, Trapani and his colleagues have reported an intermediate **A**, which was formed from the initial attack of amine at the ester group.[17] Munde *et al.* proposed a possible pathway with **B** as the suggested intermediate. Neither of these intermediates have been trapped or characterized.



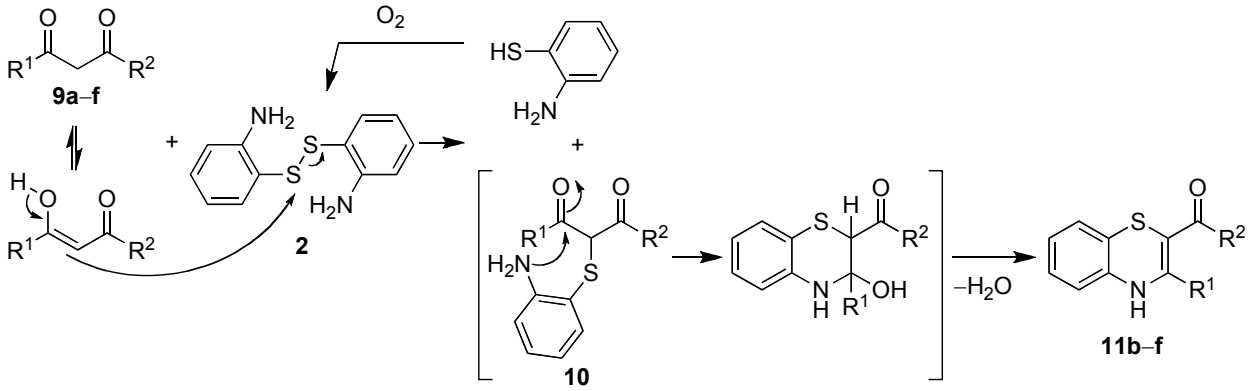
In this investigation, the reaction of 1,3-diketones **9a**–**f** with disulfide **2** was carried out in boiling ethanol in the presence of triethylamine, and products **10a** and **11b**–**f** were isolated in high yields and characterized spectroscopically (Scheme 3).



Scheme 3

Since β-diketone **9c** is capable of forming two isomeric enol tautomers both reacting as nucleophiles, the formation of **11c** (R^1 = Me, R^2 = Ph) and/or the isomeric 1-(3-phenyl-4*H*-benzo[*b*][1,4]thiazin-2-yl)ethanone (**11**; R^1 = Ph, R^2 = Me) has to be considered. However, only one product was isolated; its mass spectrum exhibiting the base peak at 105 ($PhCO^+$) is taken as evidence for structure **11c**. In addition, the isolated product **11c** did not give a positive iodoform test as would be expected for the isomer product with an acetyl group.

Attempts to clarify the mechanism of the reaction by isolation of an intermediate were unsuccessful. The isolated product of the reaction of 1,3-diphenyl-1,3-propandione (**9a**) with disulfide **2** was characterized as 2-[(2-aminophenyl)sulfanyl]-1,3-diphenyl-1,3-propanedione (**10a**). On the basis of the formation of **10a** we assume that products **11b–f** result from the initial attack of the nucleophilic β-carbon atom of the enol tautomer of 1,3-diketones **9** at the electrophilic S–S-bond of disulfide **2**, followed by intramolecular nucleophilic addition of the 2-amino group to the carbonyl group of intermediate **10**. Similarly, enol tautomers of β-keto esters **1** and dimethyl malonate (**5**) give rise to the formation of products **3a,b** and **6**, respectively. Since the by-product 2-aminobenzenethiol is easily oxidized by oxygen (air) and reverted to disulfide **2**, only 0.5 equivalents of disulfide **2** is needed (Scheme 4).



Scheme 4

Experimental Section

General Procedures

Melting points were measured on a calibrated Gallenkamp melting point apparatus. IR spectra were measured with a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

General preparative method

A solution of disulfide **2** (0.24 g, 1 mmol) and β-keto ester **1a**,**b**, dimethyl malonate **5**, or 1,3-dicarbonyl compound **9a**–**f** (2 mmol) in ethanol (50 mL) containing triethylamine (3–4 drops) was refluxed with stirring. The progress of the reaction was monitored by TLC; upon cooling the respective product **3a,b**, **6**, **10a**, or **11b**–**f** was precipitated, filtered off and recrystallized from ethanol.

Ethyl 3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carboxylate (3a). Yellow crystals (0.40g, 91%); mp 141–143 °C. IR (KBr): $\tilde{\nu}$ 3329, 1641, 1592 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.63 (1H, s, NH), 6.90–6.57 (4H, m, H_{ar}), 4.03 (2H, q, ^{3}J = 6.75 Hz, CH_2), 2.18 (3H, s, CH_3), 1.17 (3H, t, ^{3}J = 6.78 Hz, CH_3). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 163.04 (C=O), 152.9 (3-C), 139.20 (C), 127.01, 125.71, 124.15 (3CH), 119.58 (C), 114.72 (CH), 86.00 (2-C), 59.61 (CH_2), 19.73 (CH_3), 14.21 (CH_3). MS *m/z* (%): 235 (100, M^+), 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-4*H*-benzo[*b*][1,4]thiazine-2-carboxylate (3b). Yellow crystals (0.31g, 81%); mp 157–158 °C. IR (KBr): $\tilde{\nu}$ 3255, 1691, 1617 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (1H, s, NH), 7.37–6.61 (9H, m, H_{ar}), 5.10 (2H, s, CH_2), 2.21 (3H, s, CH_3). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 163.73 (C=O), 154.58 (3-C), 139.93, 137.50, 129.30, 128.70, 128.54,

128.02, 126.71, 125.25, 120.46, 115.79 (C_{ar}), 86.33 (2-C), 66.06 (CH_2), 20.81 (CH_3). MS *m/z* (%): 297 (83, M^+), 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.

Methyl 3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-2-carboxylate (6). White crystals (0.40 g, 90%); mp 169–171 °C. IR (KBr): $\tilde{\nu}$ 3205, 1741, 1691 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.95(1H, s, NH), 7.37–6.98 (4H, m, H_{ar}), 4.74 (1H, s, CH), 3.62 (3H, s, OCH_3). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 168.38, 162.78 (2C=O), 137.54, 128.34, 128.32, 124.15, 117.98, 117.17 (C_{ar}), 53.92 (OCH_3), 44.77 (2-C). MS *m/z* (%): 223 (51, M^+), 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.

2-[(2-Aminophenyl)sulfanyl]-1,3-diphenyl-1,3-propanedione (10a). White crystals (0.35 g, 85%); mp 133–135 °C. IR (KBr): $\tilde{\nu}$ 3329, 3056, 1691, 1666, cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.98 (1H, s, OH, enol form, major tautomer), 7.96–7.21 (14H, m, H_{ar}), 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 (125.77 MHz, DMSO-d_6): δ 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 (C_{ar}). MS *m/z* (%): 347 (8, M^+), 225 (13), 196 (11), 105 (100), 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.

1-(3-Methyl-4*H*-benzo[*b*][1,4]thiazine-2-yl)ethanone (11b). Red crystals (0.35 g, 82%); mp 174–176 °C. IR (KBr): $\tilde{\nu}$ 3280, 1617, 1592 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.85 (1H, s, NH), 6.91–6.63 (4H, m, H_{ar}), 2.22 (3H, s, CH_3), 2.18 (3H, s, CH_3). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 190.68 (C=O), 153.41 (3-C), 139.36 (C), 127.44, 126.36, 124.99 (3CH), 120.49 (C), 115.43 (CH), 98.15 (2-C), 30.24, 21.41 ($2CH_3$). MS *m/z* (%): 205 (90, M^+), 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.

(3-Methyl-4*H*-benzo[*b*][1,4]thiazine-2-yl)(phenyl)methanone (11c). Red crystals (0.35 g, 72%); mp 183–184 °C. IR (KBr): $\tilde{\nu}$ 3255, 1590 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.09 (1H, s, NH), 7.50–6.68 (9H, m, H_{ar}), 1.73 (3H, s, CH_3). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 188.97 (C=O), 154.13 (3-C), 140.86, 138.69, 131.02, 128.41, 127.86, 127.06, 126.07, 124.73, 120.31, 115.07, 97.33 (2-C), 21.03 (CH_3). MS *m/z* (%): 267 (25, M^+), 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.

2,3-Dihydro-1*H*-phenothiazin-4(10*H*)-one (11d). Dark yellow crystals (0.28 g, 72%); mp (decomp) 161 °C. IR (KBr): $\tilde{\nu}$ 3280, 1592, 1567 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.89 (1H, s, NH), 7.08–6.40 (4H, m, H_{ar}), 2.31 (2H, t, ^3J = 5.93 Hz, CH_2), 2.3 (2H, t, ^3J = 6.34 Hz, CH_2), 1.80 (2H, m, CH_2). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 188.91 (C=O), 155.90 (3-C), 136.59, 126.75, 126.32, 124.39, 119.87, 115.56 (C_{ar}), 97.83 (2-C), 36.08, 27.92, 20.06 ($3CH_2$). MS *m/z* (%): 217 (100, M^+), 162 (82), 118 (11), 94 (15), 80 (10), 69 (10), 45 (9).

2,2-Dimethyl-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one (11e). Orange crystals (0.45 g, 92%); mp (decomp) 212–214 °C. IR (KBr): $\tilde{\nu}$ 3255, 1617, 1592 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.83 (1H, s, NH), 6.84–6.51 (4H, m, Har), 2.18 (2H, s, CH2), 2.13 (2H, s, CH_2), 0.97 (6H, s, $2CH_3$). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 188.64 (C=O), 153.98 (3-C), 136.61, 126.90, 126.47, 124.60, 119.84, 115.67 (C_{ar}), 96.59 (2-C), 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(5*H*)-one (11f). Black crystals (0.45 g, 89%); mp 189–191 °C. IR (KBr): $\tilde{\nu}$ 3230, 3056, 1666, 1617, 1592, cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.8 (1H, s, NH), 7.5–6.86 (8H, m, H_{ar}). ^{13}C NMR (125.77 MHz, DMSO-d_6): δ 184.83 (C=O), 156.06 (3-C), 135.70, 135.51, 133.75, 130.58, 130.08, 127.61, 125.73, 119.14, 118.16, 118.11, 117.88 (C_{ar}), 92.29 (2-C). 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.

Acknowledgements

The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee Fund for its support of this investigation.

References and Footnotes

1. Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.
2. Sheibani, H.; Islami, M. R.; Khabazzadeh, H.; Saidi, K. *Tetrahedron* **2004**, *60*, 5932.
3. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2006,** 435.
4. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449.
5. Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195.
6. Lerch, U.; Henning, R. U.S. Patent 4,831,028, 1989. *Chem. Abstr.* **1988**, *108*, 37851c.
7. Henning, R.; Lerch, U.; Kaiser, J. U.S. Patent 4,595,685, 1986. *Chem. Abstr.* **1986**, *104*, 88571m.
8. Krapcho J. (E. R. Squibb and Sons Inc.) U.S. Patent Application B 348.433 (1976). *Chem. Abstr*. **1976**, *84*, 180247b.
9. Napolitano, A.; Memoli, S.; Prota, G. *J. Org. Chem.* **1999**, *64*, 3009.
10. Benedini, F.; Bertolini, G.; Ferrario, F.; Guindani, R.; Sala, A. *J. Heterocycl. Chem.* **1994**, *31*, 1589.
11. Liso, G.; Trapani, G.; Berardi, V.; Latrofa, A.; Marchini, P. *J. Heterocycl. Chem.* **1980**, 793.
12. Unger, O. *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 607.
13. Miyano, S.; Abe, N; Sumoto, K. Teramoto, K. *J. Chem. Soc., Perkin Trans.* 1 **1976**, 1146.
14. Jain, M. L.; Soni, R. P. *Synthesis* **1983**, 933.

15. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Foroughi, H.; Saidi, K. *Arkivoc* **2005**, (*xv*), 88.
16. Islami, M. R.; Mollazehi, F.; Badiei, A.; Sheibani, H. *Arkivoc* **2005**, *15*, 25.
17. Trapani, G.; Latrofa, A.; Reho, A.; Franco, M.; Liso, G. *J. Heterocycl. Chem.* **1992**, *29*, 1155.
18. Marchini, P.; Trapani, G.; Liso, G.; Berardi, V.; Liberatore, F.; Micheletti, F.; Moracci. *Phosphorus Sulfur* **1977**, *3*, 309.
19. Nishiyama, Y.; Maehira, K.; Nakase, J.; Sonoda, N. *Tetrahedron Lett*. **2005**, *46*, 7415.
20. Arisama, M.; Tetsuta, O.; Yamaguchi, M. *Tetrahedron Lett*. **2005**, *46*, 5669.
21. Trost, B.; Salzmann, T. N. *J. Am. Chem. Soc*. **1973**, *95*, 6840.
22. Schnell, B.; Georgieva, K.; Kappe, T. *J. Heterocycl. Chem.* **1998**, *35*, 157.
23. Davis, F. A.; Friedman, A. J.; Kluger, E. W.; Skibo, E. B.; Fretz, E. R.; Milicia, A. P.; LeMasters, W. C. *J. Org. Chem*. **1977**, *42*, 967.
24. Fronza, G.; Fuganiti, C.; Grasselli, P.; Pedrocci, F. G. *Tetrahedron Lett*. **1981**, *22*, 5073.
25. Munde, S. B.; Bondge, S.P.; Bhingolikar, V. E.; Mane, R. A. *Green Chem.* **2003**, *5*, 278.