An Efficient Route for Synthesis of 5,6-Diphenylimidazo-[2,1-*b*]thiazoles as Antibacterial Agents

Zeinab A. Hozien*, Abd El-Wareth A. O. Sarhan, Hassan A. H. El-Sherief and Abdalla M. Mahmoud

Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516, Egypt

Received November 20, 1999

This work is dedicated to the memory of Professor Raymond N. Castle

The reaction of 4,5-diphenylimidazol-2-thione (**1**) with aromatic ketones **2a-i** using the acidified acetic acid method afforded the 4,5-diphenyl(2-imidazolylthio)acetophenones **3a-h** in good yields. While, the cyclized product **4i** was obtained directly upon reaction of **1** with α-acetyl naphthalene. Compounds **3a-h** were cyclized directly to the corresponding 3-aryl-5,6-diphenylimidazo[2,1-*b*]thiazoles (**4a-c**) and (**4e-h**). In the same manner the reaction of **1** with aliphatic and/or alicyclic ketones gave the 3-(4,5-diphenyl-2-imidazolylthio)acetone derivatives **5a-d**, 2-(4,5-diphenylimidazolylthio)cycloalkanones **8a,d** and the tricyclic compounds **9b-c** respectively. The cyclized compounds **6a-d** and **9a,d** were obtained by cyclization of **5a-d** and **8a,b** respectively. Oxidation of **1** gives the corresponding bis(4,5-diphenyl-2-imidazolyl)-disulfide (**10**) in 90% yield. Some of the synthesized compounds were tested for antifungal and antibacterial activity.

J. Heterocyclic Chem., **37**, 943 (2000).

Introduction.

The synthesis of imidazo[2,1-*b*]thiazoles have been receiving attention during recent years as antitumor, anti-inflammatory, cardiotonic and diuretic agents [1]. The synthetic methods of imidazo[2,1-*b*]thiazoles have appeared in the literature using either 2-aminothiazoles [1-3] or 2-mercaptoimidazoles [4-13] as starting materials, reacting with the proper α-haloketones, followed by cyclization.

The disadvantages of these methods are the many steps, long reaction times, highly toxic substances like α-haloketones, and poor overall yields. In this paper, we wish to report the synthesis of 5,6-diphenylimidazo[2,1-*b*]thiazoles using our novel method [14] of reacting 4,5-diphenyl-2-mercaptoimidazol (**1**) with aromatic or aliphatic ketones in acetic acid containing catalytic amounts of concentrated sulphuric acid. This method has the advantages of an efficient high yielding synthesis, utilizing easily handled chemicals.

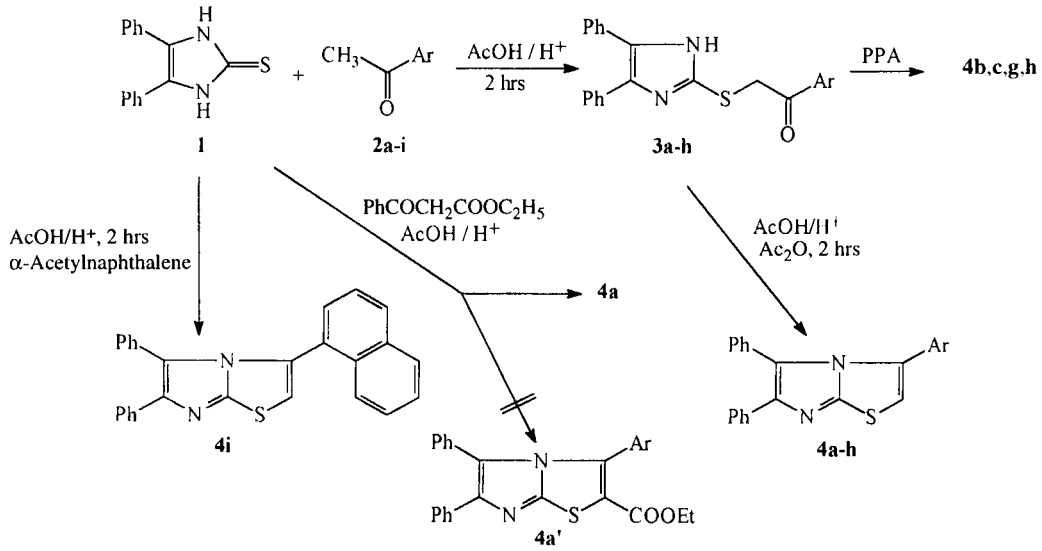
Results and Discussion.

In continuation of our studies of heteroaryl thioacetophenones and their cyclization to fused heterocycles [14], we report here that the interaction of 4,5-diphenylimidazol-2-thione (**1**) with aromatic ketones **2a-i** in boiling acetic acid, containing a few drops of concentrated sulfuric acid, for two hours afforded the 4,5-diphenylimidazolylthioacetophenone derivatives **3a-h** in very good yields. The cyclized product **4i** was obtained directly upon reaction of **1** with α-acetyl naphthalene. Compounds **3a-h** were cyclized directly to the corresponding 3-aryl-5,6-diphenylimidazo[2,1-*b*]thiazoles (**4a-c**, **4e-h**) on refluxing the reaction mixture for two hours in the presence of acetic anhydride as cyclizing agents. The cyclization of **3g** has been reported [7] using Ac_2O/AcONa as cyclizing agent. This resulted in the formation of 2-(*p*-bromobenzoyl)-3-methylimidazo[2,1-*b*]thiazole *via* *N*-acetylation followed by cyclization, Scheme 1.

To ascertain the role of AcOH/Ac_2O in the presence of H_2SO_4 as cyclizing agent, cyclization of **3b,c,g,h** were carried out using poly phosphoric acid as previously described [9]. The compounds **3b,c,g,h** and **4b,c,g,h** were found to be identical in all respects with those obtained using our reaction conditions. Interestingly enough, interaction of **1** with ethyl benzoylacetate under the same reaction conditions gave **4a** instead of the compound **4a'**. The formation of **4a** may be explained as a result of ester hydrolysis followed by decarboxylation of the expected product 2-ethoxycarbonyl-3,5,6-triphenylimidazo[2,1-*b*]-thiazole (**4a'**). This was confirmed by tlc, ir, mp and mixed mp, Scheme 1.

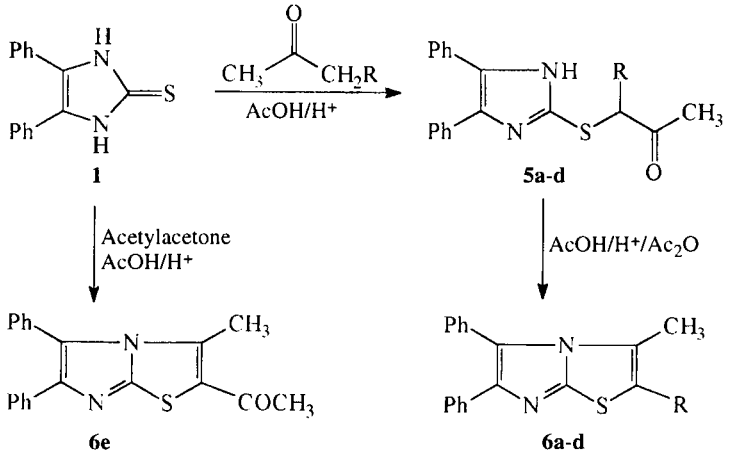
Similarly, reaction of 4,5-diphenylimidazole-2-thione (**1**) with aliphatic ketones such as acetone, butanone, pentan-2-one, phenylacetone, acetylacetone and ethyl acetoacetate using the acidified acetic acid method gave 3-(4,5-diphenylimidazolylthio)acetone derivatives (**5a-d**) in good yield. Addition of Ac_2O and refluxing the reaction mixture for two hours gave the cyclized products **6a-d** directly. The structure of compounds **6a-d** was confirmed by cyclization of **5a-d** using poly phosphoric acid as previously described [8]. While on reaction of **1** with acetylacetone using the same method, the cyclized product **6e** was obtained in 65% yield. Also, 3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**6a**) was obtained when ethyl acetoacetate reacted with **1** under the same reaction conditions, Scheme 2.

Scheme 1



Ar, **a**: C_6H_5; **b**: C_6H_4Cl-p; **c**: $C_6H_4CH_3$-p; **d**: $C_6H_4OCH_3$-p; **e**: C_6H_4OH-p; **f**: $C_6H_4NHCOCH_3$-p; **g**: C_6H_4Br-p; **h**: $C_6H_4NO_2$-p; **i**: α-$C_{10}H_7$.

Scheme 2

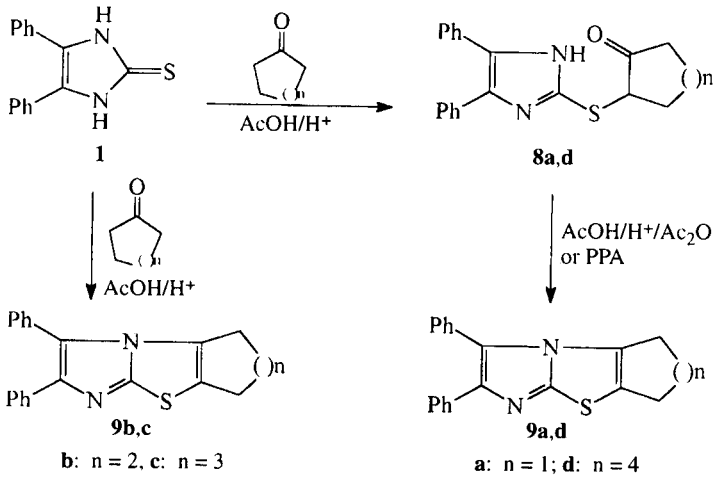


5,6a: R = H; **b**: R = CH_3; **c**: R = CH_2CH_3; **d**: R = C_6H_5

Alicyclic ketones like cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone (**7a-d**) were allowed to react with **1** in the same conditions ($AcOH/H_2SO_4$) afforded the 2-(4,5-diphenyl-2-imidazolylthio)cycloalkanone (**8a,d**) and the cyclized products 2,3-cycloalkano-5,6-diphenylimidazo[2,1-*b*]thiazoles (**9b,c**). Compounds **8a,d** were cyclized to the corresponding **9a,d** either by addition of Ac_2O to the reaction mixture or using poly phosphoric acid as the cyclizing agent, Scheme 3.

In our previous work [14] we thought that the mechanism of the formation of the title compounds can, therefore, be explained by the nucleophilic attack of α-aryl/alkyl-α-hydroxymethylene carboxylate [formed by esterification of the enol form] on the dimeric disulfide (**10**) to give the carbonium ion intermediate followed by oxygen-acetyl bond fission to give the title compounds (route a) or intramolecular cyclization to yield the cyclized compounds (route b) directly.

Scheme 3



The suggested mechanism of the reaction was confirmed chemically by refluxing **1** in AcOH/H+ for 30 minutes which gave the disulfide **10** in 90% yield. The disulfide **10** was established not only using elemental analysis but also with spectral data such as ir, nmr and ms. F. Freeman *et al.* [15] synthesized the disulfide **10** by electrochemical oxidation of **1** in 2 moles of ethanolic HCl as a dihydrochloride salt (72%). Here we present another explanation of the reaction mechanism as shown in Scheme 4.

The structures of the synthesized compounds were confirmed by elemental analysis and spectral data. Some of these compounds with expected biological activity were tested againist bacteria and fungus and showed satisfactory effects.

Biological Activity.

The antimicrobial activities of the synthesized compounds were determined by the usual disc assay [16-17] at a concentrations of (10^{-3} mole) per disc. Nutrient agar media with the following composition in g/l: beef extract, 3; peptone, 5; NaCl, 5 and agar 20, were used for bacterial cultures. Fungi were grown on Sabovroud's dextrose agar containing (g/l): glucose 40; peptone 10 and agar 20. Inhibition zones (in mm) around filter paper discs (3 mm in diameter) were measured and the average of three readings was considered. Clotrimazol was used as standard reference, Table 1.

Scheme 4

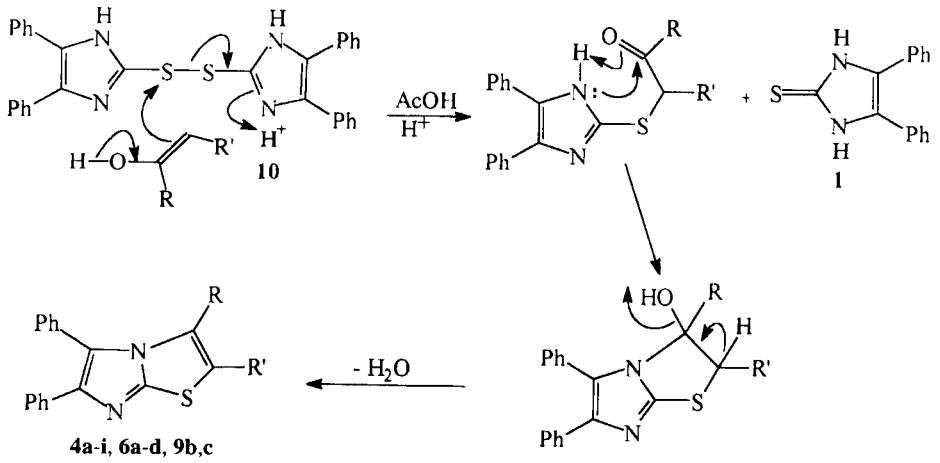


Table 1

Biological Screening of the Selected Compounds on Some Bacteria and Fungus

Compound No.	Staphylococus Auhrus (+ Ve)	Bacelleus Cereus (+ Ve)	Serraha (- Ve)	Pseudomones (- Ve)	Yeast (Fungi)
1	-	-	-	-	-
3a	-	-	-	-	0.7
3b	-	0.6	-	-	0.8
3c	-	-	-	-	1.0
3d	-	-	-	-	0.7
3e	-	-	-	-	1.1
3f	-	-	-	-	-
3g	-	0.7		-	1.1
3h	-		-	-	-
4a	-	-	-	-	0.7
4b	-	-	-	-	0.8
4c	-	-	-	-	0.8
4e	-	0.7	-	-	-
4f	-	-	-	-	-
4g	-		-	-	0.9
4h	-	-	-	-	-
4i	-	0.9	-		1.0
5a	-	0.7	-	-	0.7
5b	-	0.9	-	-	-
5c	-	-	-	-	-
5d	-	-	-	-	-
6a	-	0.7	-	-	0.7
6b	-	-	-	-	-
6c	-	-	-	-	-
6d	-	-	-	-	-
6e	-	-	-	-	-
8a	0.9	0.6	-	-	-
8d	-		-	-	-
9a	-	-	-	-	-
9b	-	-	-	-	-
9c	-	-	-	-	0.8
9d	-	-	-	-	-
10 DMF	-	-	-	-	-
Clotrimazol	3	2	1.9	1.8	1.5

EXPERIMENTAL

Melting points were uncorrected. The ir spectra were measured on a Shimatzu-470 spectrophotometer using KBr technique (ν cm^{-1}). Elemental analyses were performed using Perkin-Elmer elemental analyzer 240-C. The ^1H nmr were recorded on a Varian EM-390, 90 MHz spectrometer. TMS was used as an internal standard, δ ppm. Mass spectra were performed on Shimatzu-GC.MS-QP 1000EX spectrometer using the direct inlet system. The starting materials were commercially available, Aldrich and Merck Chemical Company, and the solvents were distilled and dried before using.

General Procedures for Synthesis of 4,5-Diphenylimidazolylthio Acetophenone Derivatives (**3a-h**) and **4i**.

A mixture of 4,5-diphenylimidazole-2-thione (**1**, 2.5 g, 10 mmoles) and *p*-substituted acetophenones (10 mmoles) was refluxed in acetic acid (20 ml) containing a few drops of concentrated H_2SO_4 for 2-3 hours. The reaction mixture was cooled and neutralized with NH_4OH solution. The resulting precipitate was collected by filtration, washed with water several times and dried under vacuum. The crude product was crystallized from the proper solvent to give the corresponding **3a-h** as colorless crystals and the cyclized product **4i** in 80% yield.

2-Benzoylmethylthio-4,5-diphenylimidazole (**3a**).

This compound was obtained as colorless crystals from ethanol, mp 194-196 °C, Lit. mp 180-181 °C [10], 80% yield; ir: ν 3400 (NH), 1670 (CO), 1590 (C=N), 1490 (C=C) cm^{-1}, ^1H nmr (DMSO-d_6): δ 4.8 (s, 2H, CH_2), 7.15-8.15 (m, 15H, Ar-H), 12.5 ppm (br, 1H, NH); ms: m/z 370.8 [M^+] (87.2), 371.8 [M^{+1}] (17.3), 369.8 [M^{-1}] (100).

Anal. Calcd. for $C_{23}H_{18}N_2OS$ (370.5): C, 74.57, H, 4.9, N, 7.56; S, 8.65. Found: C, 74.50; H, 5.01; N, 7.63; S, 8.90.

2-*p*-Chlorobenzoylmethylthio-4,5-diphenylimidazole (**3b**).

This compound was obtained from the reaction of **1** and *p*-chloroacetophenone as faint yellow crystals after crystallization from ethanol, mp 207 °C, 92% yield; ir: ν 3400 (NH), 1660 (C=O), 1580 (C=N), 1480 (C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.6 (s, 2H, CH_2), 7.15-8.10 (m, 14H, Ar-H), 12.25 ppm (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{17}N_2ClOS$ (404.9): C, 68.23; H, 4.23; N, 6.92; S, 7.92; Cl, 8.76. Found: C, 68.50; H, 4.32, N, 6.73; S, 8.01; Cl, 8.80.

2-*p*-Methylbenzoylmethylthio-4,5-diphenylimidazole (**3c**).

This compound was obtained as colorless crystals after crystallization from ethanol, mp 189-191 °C, Lit. mp 185 °C [9], 87% yield; ir: ν 3500 (NH), 1660 (C=O), 1590 (C=N), 1490 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.20-7.95 ppm [m, 15H, (14H, Ar-H and 1H, NH)] after deuteration became (14H, Ar-H)

Anal. Calcd. for $C_{24}H_{20}N_2OS$ (384.5): C, 74.97; H, 5.24; N, 7.29; S, 8.34. Found: C, 75.02; H, 5.20; N, 7.36; S, 8.50.

2-*p*-Methoxylbenzoylmethylthio-4,5-diphenylimidazole (**3d**).

This compound was obtained as colorless crystals after crystallization from ethanol, mp 172 °C, 79% yield; ir: ν 3350 (NH), 1660 (C=O), 1590(C=N), 1500 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.9 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 7.00-8.2 (m, 14H, Ar-H), 9.0 ppm (br, 1H, NH).

Anal. Calcd. for $C_{24}H_{20}N_2O_2S$ (400.5): C, 71.98; H, 5.30; N, 6.99; S, 8.19. Found: C, 71.56, H, 5.37, N, 7.30; S, 8.19.

2-*p*-Hydroxybenzoylmethylthio-4,5-diphenylimidazole (**3e**).

This compound was obtained as colorless crystals from ethanol, 85% yield, mp 255 °C; ir: ν 3500 (br, OH), 3250 (NH), 1640 (C=O), 1590 (C=N), 1560 (C=C) cm^{-1}; ^1H nmr (DMSO): δ 4.5 (s, 2H, CH_2), 6.75-7.90 (m, 15H, 14H, Ar-H and 1H (OH)), 12.15 ppm (br, 1H, NH).

Anal. Calcd. for $C_{23}H_{18}N_2O_2S$ (386.5): C, 71.48; H, 4.69; N, 7.25; S, 8.30. Found: C, 71.42; H, 5.00; N, 7.20; S, 8.50.

2-*p*-*N*-Acetylaminobenzoylmethylthio-4,5-diphenylimidazole (**3f**).

This compound was obtained from the reaction of **1** with *p*-aminoacetophenone as pale brown crystals from ethanol, mp 229-230 °C, 83% yield; ir: ν 3555 (-NHCO-), 3250 (NH), 1720 (C=O), 1660 (-CONH), 1580 (C=N), 1520 (C=C) cm^{-1}, ^1H nmr (DMSO): δ 2.1 (s, 3H, $NHCOCH_3$), 4.6 (s, 2H, CH_2), 7.1-8.0 [m, 15H, (14H, Ar-H and 1H, NH)], 9.8 ppm (s, 1H, $NHCOCH_3$).

Anal. Calcd. for $C_{25}H_{21}N_3SO_2$ (427.5): C, 70.24; H, 4.95, N, 9.83; S, 7.50. Found: C, 70.17; H, 5.30; N, 10.00; S, 7.58.

2-*p*-Bromobenzoylmethylthio-4,5-diphenylimidazole (**3g**).

This compound was obtained as yellow crystals after crystallization from ethanol, mp 200 °C, Lit. mp 190 °C [9], 87% yield, ir: ν 3450 (NH), 1665 (C=O), 1580 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr (DMSO): δ 4.6 (s, 2H, CH_2), 7.25-8.00 (m, 14H, Ar-H); 12.3 ppm. (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{17}N_2BrOS$ (449.4): C, 61.48; H, 3.81; N, 6.23; S, 7.13; Br, 17.79. Found: C, 61.44; H, 4.05; N, 6.57; S, 7.23; Br, 18.00.

2-*p*-Nitrobenzoylmethylthio-4,5-diphenylimidazole (**3h**).

This compound was obtained as yellow crystals after crystallization from ethanol, mp 193 °C, Lit. mp 188 °C [9], 85% yield; ir: ν 3300 (NH), 1680 (C=O), 1590 (C=N), 1510 (C=C) cm^{-1}; ^1H nmr (DMSO): δ 4.6 (s, 2H, CH_2), 7.15-8.03 ppm [m, 15H, (14H, Ar-H and 1H, NH)]; ms m/z 415.7 [M^+] (3.6), 252 (22.3), 251.7 (100).

Anal. Calcd. for $C_{23}H_{17}N_3O_3S$ (415.5): C, 66.49; H, 4.12, N, 10.11; S, 7.72. Found: C, 66.70; H, 4.05; N, 10.30; S, 7.91.

3-α-Naphthyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**4i**).

This compound was obtained as colorless crystals from the reaction of **1** with α-acetylnaphthalene after crystallization from benzene/methanol mixture, mp 190 °C, 80% yield; ir: ν 1590 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.7 (s, 1H, CH), 6.8-7.9 ppm (m, 17H, Ar-H).

Anal. Calcd. for $C_{27}H_{18}N_2S$ (402.1): C, 80.57; H, 4.51, N, 6.96; S, 7.95. Found: C, 79.99; H, 4.35; N, 7.17; S, 8.05.

General Methods for Synthesis of 3-Aryl-5,6-diphenylimidazo-[2,1-*b*]thizoles (**4a-h**).

Method A.

A mixture of 4,5-diphenylimidazole-2-thione (**1**, 2.5 g, 10 mmoles) and *p*-substituted acetophenone (10 mmoles) was refluxed in acetic acid (20 ml) containing a few drops of concentrated H_2SO_4 for two hours. Then acetic anhydride (7 ml) was added to the reaction mixture and refluxing was continued further for two hours. The reaction mixture was cooled and worked up as described above.

Method B.

A mixture of **3a-h** (5 mmoles) and poly phosphoric acid (10 ml) was heated in an oil bath at 140 °C for 3 hours. The reaction mixture was cooled and worked up as described above.

3,5,6-Triphenylimidazo[2,1-*b*]thiazole (**4a**).

This material was obtained as colorless crystals from ethanol; mp 162 °C, (82%); ir: ν 1580 (C=N), 1480 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.56 (s, 1H, CH), 6.9-7.6 ppm (m, 15H, Ar-H).

Anal. Calcd. for $C_{23}H_{16}N_2S$ (352.5): C, 78.38; H, 4.58, N, 7.95; S, 9.10. Found: C, 78.31; H, 4.48; N, 8.05; S, 9.00.

3-(*p*-Chlorophenyl)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4b**).

This material was obtained as faint yellow crystals from ethanol; mp 154 °C, Lit. mp 156 °C [9], 88% yield; ir: ν 1590 (C=N), 1560 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.6 (s, 1H, CH), 6.9-7.7 ppm (m, 14H, Ar-H), ms m/z (%) = 387 [M^+] (13.7), 388 [M^{+1}] (32.7), 389 [M^{+2}] (34), 386 (100).

Anal. Calcd. for $C_{23}H_{15}N_2ClS$ (386.9): C, 71.40; H, 3.91, N, 7.24; S, 8.29; Cl, 9.16. Found: C, 71.49; H, 4.00; N, 7.22; S, 8.30; Cl, 9.14.

3-(*p*-Tolyl)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4c**).

This compound was obtained as colorless crystals from ethanol; mp 137 °C, Lit. mp 148 °C [9], 88% yield; ir: ν 1590 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 6.55 (s, 1H, CH), 6.8-7.6 ppm (m, 14H, Ar-H).

Anal. Calcd. for $C_{24}H_{18}N_2S$ (366.5): C, 78.66; H, 4.95, N, 7.64; S, 8.75. Found: C, 78.53; H, 5.01; N, 7.80; S, 8.63.

3-(*p*-Hydroxyphenyl)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4e**).

This compound was obtained as colorless crystals from ethanol; mp 150 °C, 76% yield; ir: ν 3400 (OH), 1590 (C=N), 1500 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.7 (s, 1H, CH), 7.00-7.75 ppm [m, 15H, (14H, Ar-H and 1H, OH)].

Anal. Calcd. for $C_{23}H_{16}N_2OS$ (368.5): C, 74.98; H, 4.38, N, 7.60; S, 8.70. Found: C, 74.49; H, 4.80; N, 7.80; S, 8.76.

3-(*p*-Acetanilido)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4f**).

This compound was obtained as colorless crystals from ethanol, mp 215 °C, 83% yield; ir: ν 3550 (*NH*CO), 1660

(*CO*NH), 1580 (C=N), 1520 (C=C) cm^{-1}, ^1H nmr ($CDCl_3$): δ 2.15 (s, 3H, CH,), 6.65 (s, 1H, CH), 6.9-7.6 (m, 14H, Ar-H), 9.45 ppm (s, 1H, NH); ms: m/z 409.8 [M^+] (34.1), 410.8 [M^{+1}] (9.4), 408.8 [M^{-2}] (100), 407.9 (24.9).

Anal. Calcd. for $C_{25}H_{19}N_3OS$ (409.5): C, 73.33; H, 4.68, N, 10.26; S, 7.83. Found: C, 73.00; H, 4.80; N, 10.40; S, 8.00.

3-(*p*-Bromophenyl)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4g**).

This compound was obtained as yellow crystals from ethanol, mp 170 °C, Lit. mp 167 °C [9], 79% yield; ir: ν 1590 (C=N), 1560 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.55 (s, 1H, CH), 6.75-7.65 ppm (m, 14H, Ar-H); ms: m/z (%) = 431.6 [M^+] (100), 432.6 [M^{+1}] (38), 433.6 [M^{+2}] (11.3), 429.6 (98.9).

Anal. Calcd. for $C_{23}H_{15}N_2BrS$ (431.4): C, 64.04; H, 3.51, N, 6.49; S, 7.43, Br, 18.52. Found: C, 64.00; H, 3.40; N, 6.30; S, 7.33, Br, 18.59.

3-(*p*-Nitrophenyl)-5,6-diphenylimidazo[2,1-*b*]thiazole (**4h**).

This compound was obtained as yellow crystals from ethanol, mp 220-222 °C, Lit. mp 220° [9], 73% yield; ir: ν 1590 (C=N), 1500 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.75 (s, 1H, CH), 7.7-8.0 (m, 14H, Ar-H).

Anal. Calcd. for $C_{23}H_{15}N_3O_2S$ (397.5): C, 69.51; H, 3.80; N, 10.05; S, 8.07. Found: C, 69.05; H, 3.80; N, 10.05; S, 8.17.

General Procedure for Synthesis of 3-(4,5-Diphenyl-2-imidazolylthio)acetone Derivatives (**5a-d**) and (**8a,d**) and the Cyclized Compounds **6e** and **9b,c**.

A mixture of 4,5-diphenylimidazole-2-thione (**1**, 2.5 g, 10 mmoles) and aliphatic or alicyclic ketones (10 mmoles) was refluxed in acetic acid (20 ml) containing a few drops of concentrated H_2SO_4 for 2-3 hours. The reaction mixture was cooled and neutralized with iced NH_4OH and extracted with chloroform. The combined extract was dried over molecular sieve. The chloroform was removed using rotatory evaporator and the resulting solid product was crystallized from the proper solvent to give the corresponding **5a-d, 6e, 8a,d and 9b,c** respectively.

2-Acetylmethylthio-4,5-diphenylimidazole (**5a**).

This compound was obtained as pale brown crystals from (benzene/pet. ether), mp 142-145 °C, Lit. mp 147 °C [10], 78% yield; ir: ν 3400 (NH), 1720 (C=O), 1590 (C=N), 1480 (C=C) cm^{-1}; ^1H nmr (DMSO): δ 2.4 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.2-7.7 (m, 10H, Ar- H), 12.25 ppm (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_2OS$ (308.4): C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 70.10; H, 5.38; N, 9.48; S, 10.43.

3-(4,5-Diphenyl-2-imidazolylthio)-2-butanone (**5b**).

This compound was obtained as colorless crystals from benzene/hexane mixture, mp 128-130 °C, 79% yield; ir: ν 3400 (NH), 1700 (C=O), 1595 (C=N), 1480 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.45 (d, 3H, CH_3CH), 2.3 (s, 3H, CH_3CO), 4.05 (q, $CHCH_3$), 7.1-7.6 (m, 10H, Ar-H), 10.2 ppm (br, 1H, NH).

Anal. Calcd. for $C_{19}H_{18}N_2OS$ (322.4): C, 70.78; H, 5.63; N, 8.69; S, 9.99. Found: C, 70.37; H, 5.49; N, 8.26; S, 10.01.

3-(4,5-Diphenyl-2-imidazolylthio)-2-pentanone (**5c**).

This compound was obtained as colorless crystals from benzene/hexane mixture, mp 133-135 °C, 80% yield; ir: ν 3400 (NH), 1700 (C=O), 1590 (C=N), 1490 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.95 (t, 3H, CH_2CH_3), 1.8 (m, 2H, $CHCH_2CH_3$), 2.25 (s, 3H, CH_3CO), 3.85 (t, 1H, $CHCH_2CH_3$), 7.2-7.6 (m, 10H, Ar-H), 10.8 ppm (br, 1H, NH).

Anal. Calcd. for $C_{20}H_{20}N_2OS$ (336.5): C, 71.40; H, 5.99; N, 8.33; S, 9.53. Found: C, 71.47; H, 6.00; N, 8.05; S, 9.68.

3-(4,5-Diphenyl-2-imidazolylthio)-2-pentanone (**5d**).

This compound was obtained as pale brown crystals from benzene/hexane mixture, mp 100-102 °C, 82% yield; ir: ν 3400 (NH), 1700 (C=O), 1590 (C=N), 1490 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 5.55 (s, 1H, CH), 7.1-7.7 (m, 15H, Ar-H), 10.6 ppm (br, 1H, NH).

Anal. Calcd. for $C_{24}H_{20}N_2OS$ (384.5): C, 74.97; H, 5.24; N, 7.29; S, 8.34. Found: C, 75.02; H, 5.20; N, 7.33; S, 8.32.

2-Acetyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**6e**).

The cyclized compound **6e** was obtained as colorless crystals from benzene after reaction of **1** with acetylacetone, mp 185-186 °C, 65% yield, Lit. mp 190 °C [8,10]; ir: ν 1680 (C=O), 1580 (C=N), 1520 (C=C), cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.45 (s, 3H, $COCH_3$), 7.15-7.75 (m, 10H, Ar-H); ms: m/z 332.8 [M^+] (14.9), 333.5 [M^{+1}] (28.1), 334.4 [M^{+2}] (12), 331.8 [M^{-1}] (100).

Anal. Calcd. for $C_{20}H_{16}N_2OS$ (332.4): C, 72.26; H, 4.85; N, 8.43; S, 9.64. Found: C, 72.00; H, 4.85; N, 8.82; S, 9.53.

2-(4,5-Diphenyl-2-imidazolylthio)-2-cyclopentanone (**8a**).

This compound was obtained as brown crystals from benzene/methanol mixture, mp 175 °C, 60% yield; ir: ν 3400 (NH), 1710 (C=O), 1660 (C=N), 1590 (C=C) cm^{-1}; ^1H nmr (DMSO): δ 1.8 (m, 2H, CH_2), 2.1 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.80 (t, 1H, SCH), 7.0- 7.7 (m, 10H, Ar-H), 10.8 ppm (br, 1H, NH).

Anal. Calcd. For $C_{20}H_{18}N_2OS$ (334.4): C, 71.82; H, 5.42; N, 8.38; S, 9.59. Found: C, 71.86; H, 5.40; N, 8.38; S, 9.65.

2-(4,5-Diphenyl-2-imidazolylthio)-2-cyclooctanone (**8d**).

This compound was obtained as colorless crystals from benzene/hexane mixture, mp 170-172 °C, 70% yield; ir: ν 3400 (NH), 1695 (C=O), 1590 (C=N), 1495 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.4-2.15 (m, 10H, cyclooctanyl-H), 2.4 (t, 2H, CH_2CO), 4.1 (t, 1H, SCH), 7.1-7.6 (m, 10H, Ar-H), 10.6 ppm (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{24}N_2OS$ (376.5): C, 73.37; H, 6.42; N, 7.44; S, 8.51. Found: C, 73.86; H, 6.36; N, 7.76; S, 8.39.

2,3-Diphenyl-5,6,7,8-tetrahydrobenzo[*d*]imidazo[2,1-*b*]thiazole (**9b**).

The cyclized compound **9b** was obtained as colorless crystals from benzene/pet. ether mixture, mp 183-185 °C, 60% yield; ir: ν 1590 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.7 (m, 4H, $2CH_2$), 2.05 (t, 2H, CH_2), 2.65 (t, 2H, CH_2), 7.1-7.7 ppm (m, 10H, Ar-H), ms: m/z 330.7 [M^+] (100), 333 [M^{+2}] (51), 328.5 [M^{-2}] (32).

Anal. Calcd. for $C_{21}H_{18}N_2S$ (330.5): C, 76.33; H, 5.49; N, 8.48; S, 9.70. Found: C, 76.00; H, 5.40; N, 8.82; S, 10.01.

2,3-Diphenyl-5,6,7,8-tetrahydro-5*H*-cyclohepta[*d*]imidazo[2,1-*b*]-thiazole (**9c**).

The cyclized compound **9c** was obtained as colorless crystals from benzene/hexane mixture, mp 150 °C, 50% yield; ir: ν 1590 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.5-1.7 (m, 6H, $3CH_2$), 2.2 (t, 2H, CH_2), 2.6 (t, 2H, CH_2), 7.0-7.7 ppm (m, 10H,

Ar-H); ms: m/z 344.8 [M+] (76.7), 345.9 [M+1] (19.5), 343.7 [M-1] (100).

Anal. Calcd. for $C_{22}H_{20}N_2S$ (344.5): C, 76.71; H, 5.85; N, 8.13; S, 9.31. Found: C, 76.95; H, 5.92; N, 7.88; S, 9.23.

General Procedure for Synthesis of 5,6-Diphenyl-3-methyl-2-substituted Imidazo[2,1-*b*]thiazoles (**6a-d**) and 5,6-Diphenyl-cycloalka[*d*]imidazo[2,1-*b*]thiazoles (**9a,d**).

According to the general procedures described above, method A and B, the compounds **6a-d** and **9a,d** were obtained in good yield.

5,6-Diphenyl-3-methylimidazo[2,1-*b*]thiazole (**6a**).

The cyclized compound **6a** was obtained as colorless crystals from benzene/methanol mixture, mp 180 °C, 40% yield: ir: ν 1590 (C=N), 1490 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.9 (s, 3H, CH_3), 6.3 (s, 1H, CH), 7.15-7.7 ppm (m, 10H, Ar-H).

Anal. Calcd. for $C_{18}H_{14}N_2S$ (290.4): C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 74.40; H, 4.92; N, 9.56; S, 11.08.

2,3-Dimethyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**6b**).

The cyclized compound **6b** was obtained as colorless crystals from benzene/hexane mixture, mp 160-162 °C, 70% yield; ir: ν 1590 (C=N), 1520 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$); δ 1.75 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 7.1-7.6 ppm (m, 10H, Ar-H); ms: m/z 304 [M+] (100), 305 [M+1] (44), 306 [M+2] (17.7), 303 [M-1] (35).

Anal. Calcd. for $C_{19}H_{16}N_2S$ (304.4): C, 74.97; H, 5.30; N, 9.20; S, 10.53. Found: C, 74.60; H, 5.08; N, 8.89; S, 10.80.

2-Ethyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**6c**).

The cyclized compound **6c** was obtained as colorless crystals from benzene/hexane mixture, mp 118 °C, 63% yield; ir: ν 1590 (C=N),1490(C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.2 (t, 3H, CH_2CH_3), 1.7 (s, 3H, CH_3), 2.6 (q, 2H, CH_2CH_3), 7.0-7.6 ppm (m, 10H, Ar-H), ms: m/z 318.8 [M+] (44.9), 319.8 [M+1] (12.3), 317.8 [M-1] (100), 316.6 [M-2] (15.3).

Anal. Calcd. for $C_{20}H_{18}N_2S$ (318.4): C, 75.44; H, 5.70; N, 8.80; S, 10.07. Found: C, 75.80; H, 5.80; N, 8.54; S, 10.00.

3-Methyl-2,5,6-triphenylimidazo[2,1-*b*]thiazole (**6d**).

The cyclized compound **6d** was obtained as pale brown crystals from benzene/hexane mixture, mp 182 °C, 71% yield; ir: ν 1590 (C=N), 1490 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.9 (s, 3H, CH_3), 7.1-7.6 ppm (m, 15H, Ar-H).

Anal. Calcd. for $C_{21}H_{18}N_2S$ (366.5): C, 78.66; H, 4.95; N, 7.64; S, 8.75. Found: C, 78.66; H, 5.05; N, 7.59; S, 8.81.

2,3-Diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]imidazo[2,1-*b*]thiazole (**9a**).

The cyclized compound **9a** was obtained as brown crystals from benzene/pet. ether mixture, mp 160 °C, 40% yield; ir: ν 1660 (C=N), 1590 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.45 (m, 2H, CH_2), 2.9 (m, 2H, CH_2), 3.4 (m, 2H, CH_2), 7.1-7.9 ppm (m, 10H, Ar-H).

Anal. Calcd. for $C_{20}H_{16}N_2S$ (316.4): C, 75.92; H, 5.10; N, 8.85; S, 10.13. Found: C, 76.00; H, 5.15, N, 8.79; S, 10.13.

2,3-Diphenyl-5,6,7,8,9,10-hexahydrocycloocta[*d*]imidazo[2,1-*b*]-thiazole (**9d**).

The cyclized compound **9d** was obtained as colorless crystals from benzene/methanol mixture, mp 160 °C, 69% yield; ir: ν 1590 (C=N), 1510 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.7-2.8 (m, 12H, cyclooctenyl-H), 6.9-7.5 ppm (m, 10H, Ar-H); ms: m/z 358.8 [M+] (25.8), 359.8 [M+1] (10), 357.7 [M-1] (85.2), 352.8 (18.3), 351.8 (100).

Anal. Calcd. for $C_{23}H_{22}N_2S$ (358.5): C, 77.06; H, 6.19; N, 7.81; S, 8.94. Found: C, 77.26; H, 6.50; N, 7.80; S, 9.10.

Bis-(4,5-diphenyl-2-imidazolyl)disulfide (**10**).

4,5-Diphenylimidazole-2-thione (**1**, 2.5 g, 10 mmoles) was refluxed in acetic acid (20 ml) containing a few drops of concentrated H_2SO_4 for 30 minutes. The reaction mixture was cooled and neutralized by NH_4OH solution. The resulting precipitate was crystallized from chloroform to give the corresponding disulfide 10 in 90% yield, mp 175 °C; ^1H nmr (DMSO): δ 7.0-7.75 [m, 22H (20H, Ar-H and 2NH)]; ms: m/z 502.8 [M+] (12.17), 470 (90.29), 438 (32.35), 218.1 (100).

Anal. Calcd. for $C_{30}H_{22}N_4S_2$ (502.7): C, 71.69; H, 4.41; N, 11.15; S, 12.76. Found: C, 71.87; H, 4.14; N, 11.31, S, 12.74. The dihydrochloride was separated by adding concentrated HCl to the disulfide solution in chloroform, mp 220 °C, Lit. mp 220-222 °C [15].

Anal. Calcd. for $C_{30}H_{24}N_4Cl_2S_2$ (575.6): C, 62.60; H, 4.20; N, 9.73; S, 11.14; Cl, 12.32. Found: C, 62.68; H, 4.18; N, 9.65; S, 11.15; Cl, 12.68.

REFERENCES AND NOTES

[*] Author to whom correspondence should be address: E-mail: hozien@aun.eun.eg.

[1] A. Andereani, M. Ramboldi, A. Locatelli and A. M. Isetta, *Eur. J. Med. Chem.*, **26**, 335 (1991), and references cited therein.

[2] P. E. Bender, D. T. Hill, P. H. Offen, K. Razgaitis, P. Lavanchy, O. D. Stringer, B. M. Sutton, D. E. Griswold, M. Dimatino, D. T. Walz, I. Landos and C. B. Ladd, *J. Med. Chem.*, **28**, 1169, (1985).

[3] I. Landos, B. E. Bender, K. A. Razgaitis, B. M. Sutton, M. J. Diamortino, D. E. Griswold and D. T. Wolz, *J. Med. Chem.*, **27**, 72 (1984).

[4] A. A. Mahfouz and F. M. Elhabashy, *Arch. Pharmacol. Res.*, **13** (1), 9 (1990).

[5] J. Mohan, G. S. R. Anjaneyulu and (Ms) Kiran, *Ind. J. Chem.*, **27B**, 570 (1988).

[6] V. R. Rao and T. V. P. Rao, *Sulfur Lett.*, **9**, 167 (1989).

[7] I. A. Mazur, P. M. Kochergin and V. G. Tromsa, *Chem. Heterocycl. Compds., Engl. Transl.*, **7**, 359 (1971).

[8] A. M. Abdel-Fattah, H. A. Daboun and S. M. Hussein, *Egypt. J. Chem.*, **26**, 409 (1983); *Chem. Abstr.*, **101**, 230419b (1984).

[9] J. Mohan, V. K. Chadha and H. K. Pujari, *Ind. J. Chem.*, **11**, 747 (1973).

[10] I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, 508 (1970), *ibid*; 512 (1970); *Chem. Abstr.*, **73**, 87855m (1970).

[11] I. A. Mazur, P. M. Kochergin and G. S. Tkachenko, *Khim. Geterotsikl. Soedin*, 824 (1970); *Chem. Abstr.*, **73**, 120565s (1970).

[12] P. M. Kochergin, *Zh. Obshch. Khim.*, 1956, **26**, 2493; *Chem. Abstr.*, **51**, 5050 (1957); *ibid*, 2916, (1956); *Chem. Abstr.*, **51**, 8078 (1957).

[13] P. M. Kochergin and M. N. Shchukina, *Zh. Obshch. Khim.*, **26**, 458 (1956); *Chem. Abstr.*, **50**, 1388b (1956), *ibid*, 1723 (1956); *Chem. Abstr.*, **51**, 1942 (1957).

[14] A. A. O. Sarhan, H. A. H. El-Sherif and A. M. Mahmoud, *Tetrahedron*, **52** (31), 10485 (1996).

[15] F. Freeman, M. C. Keindl, H. N. Po, E. Brinkman and J. Masse, *Synthesis*, 714 (1989).

[16] British Pharmacopeia, Pharmaceutical Press, London, 1953, pp 796.

[17] K. K. Chaturvedi, N. K. Jain, J. Praduddha and R. Kaushal, *Indian Drugs*, **15**, 57 (1978); *Chem. Abstr.*, **90**, 12208 (1979).