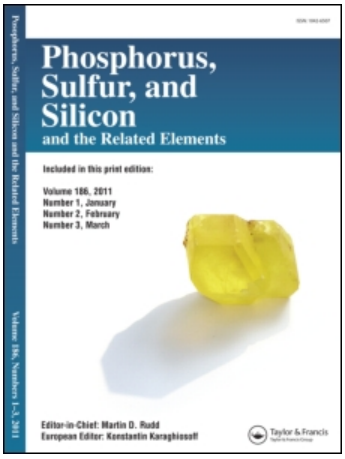

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Phase-Transfer Catalyzed Alkylation and Acylation of 2-Mercapto-5-Methyl-1*H*-Benzimidazole

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Phase-Transfer Catalyzed Alkylation and Acylation of 2-Mercapto-5-Methyl-1*H*-Benzimidazole

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Solid / liquid phase-transfer catalyzed alkylation and acylation of 2-mercaptobenzimidazole at 25°C by different organohalogen reagents in the presence of tetrabutylammonium bromide as a catalyst underwent, exclusively, S-monoalkylation and N-monoacylation or S- and N-dialkylation, cycloalkylation, and S- and N-diacylation depending on the nature of alkylating and acylating agents.

Keywords Acylation; alkylation; mercaptobenzimidazole; phase transfer catalysis; tetrabutylammonium bromide

INTRODUCTION

Phase Transfer Catalysis (PTC) is one of the promising methods in organic synthesis of specialty chemicals. In the last 20 years, a steadily increasing number of published papers and patents dealing with PTC topics and their applications have appeared. PTC is not merely important for substitutional reactions, but it is being extensively applied in polymer chemistry, heterocyclic chemistry, organometallic synthesis, agrochemicals, dyes, flavors, perfumes, and pharmaceutical manufactureing.[1–3]

The technique of PTC has extensively been applied in organic synthesis via substitution, displacement, condensation, elimination, Ylide-mediated reactions, redox, and polymerization processes. The advantages of using the PTC technique to synthesize organic chemicals are the enhancement of the reaction rate, carrying out the reaction at moderate conditions, and obtaining high selectivity of the main product with high conversion of the reactants.[4,5]

On the other hand, 2-mercaptobenzimidazoles are the most frequently encountered heterocycles in industrial and medicinal chemistry with wide applications including corrosion inhibition of steel;[6,7]

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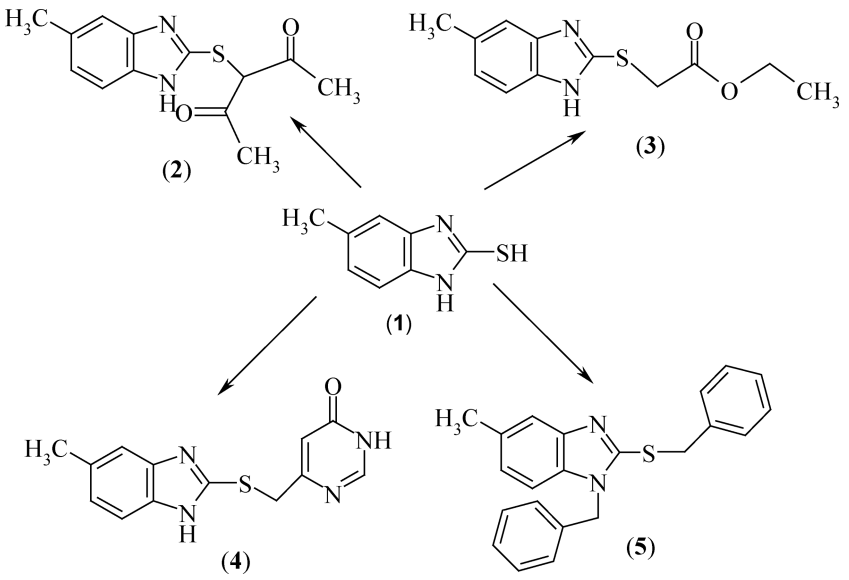
antioxidant and vulcanization agents of rubber and its products;[8,9] cyclooxygenase inhibitors;[10] antimycobacterial agents;[11] inhibitors of influenza B virus multiplication;[12] antihelicobacter pylori agents;[13] and goitrogenic[14] antihypercholesterolemic and antiatherosclerotic,[15] antiinflammatory,[16,17] antihypertensive,[18] antitrichinellosis,[19] analgesic,[20] and growth-regulating[21] activities.

RESULTS AND DISCUSSION

The approach reported here is an extension and continuation of our interest in alkylation of some heterocycles under PTC conditions.[22–25] This work is aiming to study the reactivity of S-versus N-alkylation and acylation of 2-mercapto-1*H*-benzimidazole (**1**) via solid/liquid PTC reaction conditions using some mono- and dihalogen organic reagents as an efficient recent alkylation technique. Also, it is expected that the alkylated products might have biological and medicinal activities in analogy to the well-known biologically active 2-mercaptobenzimidazole derivatives.[6–21]

It is reported that base-catalyzed mono-alkylation of 2-mercaptobenzimidazoles occurs predominantly at the more acidic SH, that is, via S-alkylation,[26–29] while mono-acylation occurs at the less acidic NH, that is, via N-acylation.[30] After extensive studies, it was found that the optimized reaction conditions of PTC-alkylation and acylation are by the treatment of 2-mercapto-benzimidazole (**1**) with haloorganic reagents in acetonitrile/anhydrous potassium carbonate as liquid/solid phases in the presence of Tetrabutylammonium Bromide (TBAB) as the catalyst with efficient stirring for 4–8 h at 25°C. Treatment of 2-mercaptobenzimidazole (**1**) with bromoacetylacetone, ethyl bromoacetate, and/or 6-(chloromethyl)pyrimidin-4(3*H*)-one in a 1:3 molar ratio, respectively, under the optimized PTC reaction conditions afforded, exclusively, S-monoalkylation to give 3-[(5-methyl-1*H*-benzimidazol-2-yl)thio]pentane-2,4-dione (**2**), ethyl [(5-methyl)-1*H*-benzimidazol-2-yl)thio]acetate (**3**), and/or 6-{[(5-methyl -1*H*-benz- imidazol-2-yl)thio]-methyl}pyrimidin-4(3*H*)-one (**4**), respectively. Moreover, PTC-alkylation of 2-mercaptobenzimidazole (**1**) with benzyl bromide underwent simultaneous S- and N-dialkylation to give 1-benzyl-2-(benzylthio)-5-methyl-1*H*-benzimidazole (**5**) (Scheme 1).

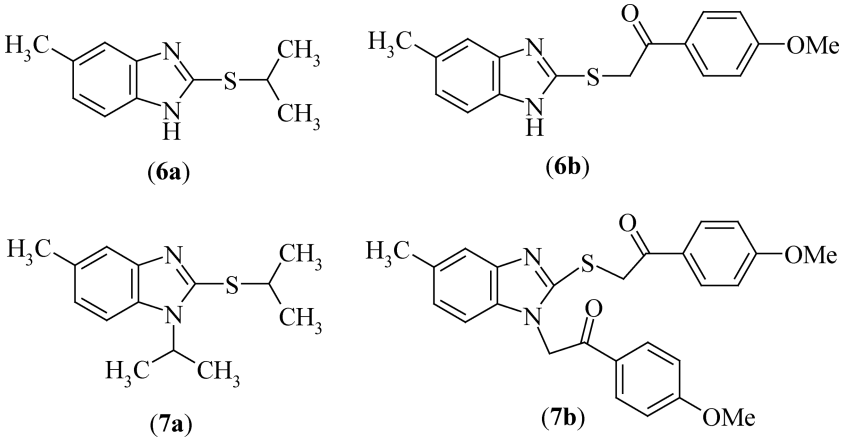
Treatment of either isopropyl bromide or ω-bromo-4-methoxyacetophenone with 2-mercaptobenzimidazole (**1**) in a 3:1 molar ratio, respectively, under the same PTC-reaction conditions afforded a mixture of S-monoalkylated products (**6a**,**b**) as major products and S- and



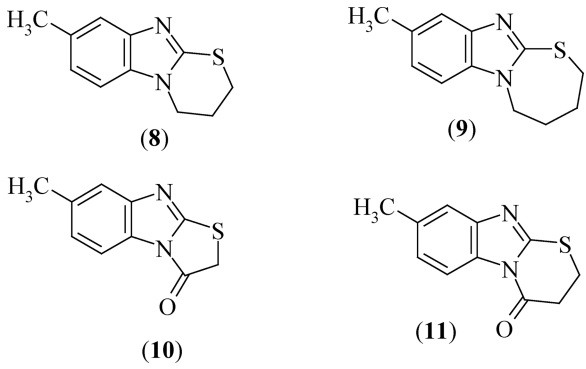
SCHEME 1

N-dialkylated products (**7a**,**b**), which were separated by column chromatography using silica gel and ether:petroleum ether (1:5) as an eluent (Scheme 2).

A mixture of equimolar amounts of 2-mercaptobenzimidazole (**1**) and 1,3-dibromopropane, 1,4-dibromobutane, chloroacetyl chloride, and/or



SCHEME 2



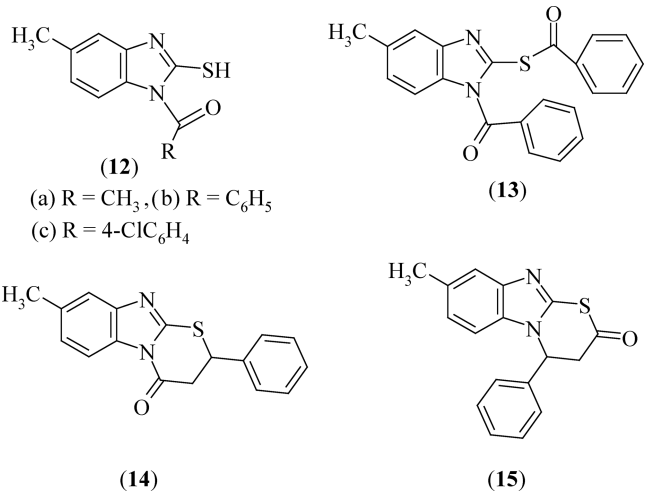
SCHEME 3

3-chloropropanoyl chloride under the same optimized PTC conditions underwent simultaneous S- and N-cycloalkylation or cycloacylation to give the condensed tricyclic products, 8-methyl-3,4-dihydro-2*H*-[1,3]thiazino[3,2-a]benzimidazole (**8**) 9-methyl-2,3,4,5-tetra hydro[1,3]-thiazino[3,2-a]benzimidazole (**9**), 7-methyl[1,3]thiazolo[3,2-a]benzimi-dazol-3(2*H*)-one (**10**), and/or 8-methyl-2,3-dihydro-4*H*-[1,3]thi- azino [3,2-a]bezimidazol-4-one (**11**) (Scheme 3).

On the other hand, acylation of 2-mercaptobenzimidazole (**1**) by acetyl chloride, benzoyl chloride, 4-chlorobenzoyl chloride, and/or cinnamoyl chloride under the same optimized PTC reaction conditions led to N-monoacylation (**12a–c**) predominantly in addition to the N- and S-dibenzoylated product (**13**) with benzoyl chloride. With cinnamoyl chloride, both N- and S-monoacylation followed an internal Michael addition to give two different tricyclic adducts, (**14**, **15**), which were separated by column chromatography using silica gel and ether:petroleum ether (1:3) as an eluent (Scheme 4).

EXPERIMENTAL

Melting points that are reported were uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum RXIFT-IR spectrophotometer (cm^{-1}). NMR spectra were recorded on Bruker Avance DPX400 spectrometer, using TMS as the internal standard (chemical shifts in δ values in ppm). Elemental analyses were preformed using a Perkin-Elmer 2400, Series II microanalyzer. The key starting material, 2-mercaptobenzimidazole (**1**), is an Aldrich product and was used without further purification.



SCHEME 4

General Procedure

To a solution of 2-mercaptobenzimidazole (1.65 g, 0.01 mol, **1**) in acetonitrile (50 mL) was added anhydrous K_2CO_3 (2.7 g, 0.02 mol) and TBAB (0.9 g, 0.003 mol); the monohalogen organic reagent (0.03 mol) or a dihalgen organic reagent (0.01 mol), such as 1,3-dibromopropane, 1,4-dibromobutane, chloroacetyl chloride, and/or 3-chloropropanoyl chloride; or an acid chloride (0.02 mol), such as acetyl chloride, benzoyl chloride, 4-chlorobenzoyl chloride, and/or cinnamoyl chloride. The mixture was stirred vigorously at 25°C and monitored by TLC over the reaction period. After completion of the reaction, the mixture was filtered to separate the solid K_2CO_3, and the organic solvent was evaporated; then the residue was triturated with petroleum ether (60–80°) to remove the excess unreacted halogen reagent. The residue was then crystallized from a suitable solvent to give products **2–15**. The K_2CO_3 residue was dissolved in water (50 mL) and acidified by hydrochloric acid (15%) to confirm if an acidic byproduct existed. In all cases, there was no by-product isolated from the K_2CO_3 residue.

3-[(5-Methyl-1H-benzimidazol-2-yl)thio]pentane-2,4-dione (2)

Yellow crystals from ethanol; $C_{13}H_{14}N_2O_2S$ (262.33), calcd.: C, 59.52; H, 5.38; N, 10.68; found: C, 59.44; H, 5.32; N, 10.75; yield 65%; m.p. 236–238°C; IR (KBr), 1465, 1616, 1703, 2962, 3115, 3332; ^{1}H NMR, δ ($CDCl_3$+DMSO-d_6), 2.36 (s, 6H, 2×COC$\underline{H}_3$), 2.55 (s, 3H, C$\underline{H}_3$), 3.23 (s, 1H, C$\underline{H}$), 6.93–7.38 (3H, Ar-$\underline{H}$), 12.32 (b, 1H, NH).

Ethyl [(5-methyl)-1H-benzimidazol-2-yl)thio]acetate (3)

White crystals from ethanol; $C_{12}H_{14}N_2O_2S$ (250.32), calcd.: C, 57.58; H, 5.64; N, 11.19; found: C, 57.42; H, 5.61; N, 11.31; yield 73%; m.p. 189–191°C; IR (KBr), 1624, 1738, 2925, 2981, 3465; ^{1}H NMR, δ ($CDCl_3$), 1.29 (t, 3H, C<u>H</u>$_3$), 2.45 (s, 3H, C<u>H</u>$_3$), 4.25 (q, 2H, OC<u>H</u>$_2$), 5.09 (s, 2H, SC<u>H</u>$_2$), 6.89–7.12 (3H, Ar-<u>H</u>), 11.02 (b, 1H, NH).

6-{[(5-Methyl-1H-benzimidazol-2-yl)thio]methyl}pyrimidin-4(3H)-one (4)

Yellow crystals from petroleum ether 60–80°C; $C_{13}H_{12}N_4OS$ (272.33), calcd.: C, 57.34; H, 4.44; N, 20.57; found: C, 57.23; H, 4.37; N, 20.64; yield 48%; m.p. 174–175°C; IR (KBr), 1675, 2921, 2975, 3316, 3383; ^{1}H NMR, δ ($CDCl_3$+DMSO-d_6), 2.44 (s, 3H, C<u>H</u>$_3$), 4.22 (s, 2H, SC<u>H</u>$_2$), 5.54 (b, 1H, NH), 6.97–8.22 (5H, Ar-<u>H</u>), 12.55 (b, 1H, NH).

1-Benzyl-2-(benzylthio)-5-methyl-1H-benzimidazole (5)

Yellow crystals from benzene; $C_{22}H_{20}N_2S$ (344.47), calcd.: C,76.71; H, 5.85; N, 8.13; found: C, 76.56; H, 5.78; N, 8.26; yield 81%; m.p. 108–110°C; IR (KBr), 1599, 2831, 2925, 3033; ^{1}H NMR, δ ($CDCl_3$), 2.41, 2.44 (s, 3H, C<u>H</u>$_3$), 4.58 (s, 2H, SC<u>H</u>$_2$), 5.19 (s, 2H, NC<u>H</u>$_2$), 6.96–7.62 (13H, Ar-<u>H</u>).

2-(Isopropylthio)-5-methyl-1H-benzimidazole (6a)

White crystals from petroleum ether 60–80°C; $C_{11}H_{14}N_2S$ (206.31), calcd.: C, 64.04; H, 6.84; N, 13.58; found: C, 63.85; H, 6.81; N, 13.67; yield 42%; m.p. 118–120°C; IR (KBr), 1615, 2954, 3042, 3394; ^{1}H NMR, δ ($CDCl_3$), 1.44 (d, 6H, 2×CH_3), 2.46 (s, 3H, C<u>H</u>$_3$), 3.99 (m, 1H, SC<u>H</u>), 7.02–7.43 (3H, Ar-<u>H</u>), 9.56 (b, 1H, NH).

1-(4-Methoxyphenyl)-2-[(5-methyl-1H-benzimidazol-2-yl)thio]ethanone (6b)

Pale yellow crystals from ethanol; $C_{17}H_{16}N_2O_2S$ (312.39), calcd.: C, 65.36; H, 5.16; N, 8.97; found: C, 65.27; H, 5.11; N, 9.06; yield 48%; m.p. 218–220°C; IR (KBr), 1601, 2940, 3126, 3345; ^{1}H NMR, δ ($CDCl_3$), 2.38 (s, 3H, C<u>H</u>$_3$), 3.90 (s, 3H, OC<u>H</u>$_3$), 5.69 (s, 2H, SC<u>H</u>$_2$), 6.77–8.05 (7H, Ar-<u>H</u>), 9.95 (b, 1H, NH).

1-Isopropyl-2-(isopropylthio)-5-methyl-1H-benzimidazole (7a)

White crystals from petroleum ether 60–80°C; $C_{14}H_{20}N_2S$ (248.39), calcd.: C, 67.70; H, 8.12; N, 11.28; found: C, 67.58; H, 8.08; N, 11.33; yield 33%; m.p. 238-9°C; IR (KBr), 1587, 2947, 3138; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 1.04 (m, 6H, 2×CH_3), 1.43 (m, 3H, CH_3), (m, 3H, CH_3) 2.56

(s, 3H, C<u>H</u>$_3$), 3.20 (m, 1H, NC<u>H</u>), 3.79 (m, 1H, SC<u>H</u>), 6.83–7.04 (3H, Ar-<u>H</u>).

1-(4-Methoxyphenyl)-2-({1-[2-(4-methoxyphenyl)-2-oxoethyl]-1H-benzimidazol-2-yl}thio)ethanone (7b)

Yellow crystals from ethanol; $C_{26}H_{24}N_2O_4S$ (460.55), calcd.: C, 67.81; H, 5.25; N, 6.08; found: C, 67.70; H, 5.21; N, 6.17; yield 32%; m.p. 156–158°C; IR (KBr), 1601, 1675, 2927, 3109; ^{1}H NMR, δ ($CDCl_3$), 2.44 (s, 3H, C<u>H</u>$_3$), 3.89 (s, 3H, OC<u>H</u>$_3$), 3.94 (s, 3H, OC<u>H</u>$_3$), 4.97 (s, 2H, SC<u>H</u>$_2$), 5.59 (s, 2H, NC<u>H</u>$_2$), 6.92–8.05 (11H, Ar-<u>H</u>).

8-Methyl-3,4-dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole (8)

Pale yellow crystals from ethanol; $C_{11}H_{12}N_2S$ (204.29), calcd.: C, 64.67; H, 5.92; N, 13.71; found: C, 64.58; H, 5.89; N, 13.77; yield 77%; m.p. 150–152°C; IR (KBr), 1608, 2927, 3106; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.45 (m, 2H, C<u>H</u>$_2$), 2.47 (s, 3H, C<u>H</u>$_3$), 3.24 (t, 2H, SC<u>H</u>$_2$), 4.15 (t, 2H, NC<u>H</u>$_2$), 6.99–7.65 (3H, Ar-<u>H</u>).

9-Methyl-2,3,4,5-tetrahydro[1,3]-thiazino[3,2-a]benzimidazole (9)

White crystals from petroleum ether 60–80°C; $C_{12}H_{14}N_2S$ (218.32), calcd.: C, 66.02; H, 6.46; N, 12.83; found: C, 65.89; H, 6.42; N, 12.87; yield 63%; m.p. 130–132°C; IR (KBr), 1613, 2927, 3111; ^{1}H NMR, δ ($CDCl_3$), 1.88 (m, 2H, C<u>H</u>$_2$), 2.22 (m, 2H, C<u>H</u>$_2$), 2.47 (s, 3H, C<u>H</u>$_3$), 2.87 (t, 2H, SC<u>H</u>$_2$), 4.30 (t, 2H, NC<u>H</u>$_2$), 7.06–7.60 (3H, Ar-<u>H</u>).

7-Methyl[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-one (10)

Pale yellow crystals from ethanol; $C_{10}H_8N_2OS$ (204.25); calcd.: C, 58.80; H, 3.95; N, 13.72; found: C, 58.72; H, 3.90; N, 13.84; yield 64%; m.p. 217–218°C; IR (KBr), 1607, 1704, 2816, 2923, 3086; ^{1}H NMR, δ ($CDCl_3$), 2.43 (s, 3H, C<u>H</u>$_3$), 4.55 (s, 2H, SC<u>H</u>$_2$), 7.16–7.83 (3H, Ar-<u>H</u>).

8-Methyl-2,3-dihydro-4H-[1,3]thiazino[3,2-a]bezimidazol-4-one (11)

White crystals from ethanol; $C_{11}H_{10}N_2OS$ (218.28); calcd.: C, 60.53; H, 4.62; N, 12.83; found: C, 60.45; H, 4.59; N, 12.96; yield 58%; m.p. 108–110°C; IR (KBr), 1594, 1718, 2944, 3110; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.44 (s, 3H, C<u>H</u>$_3$), 3.21 (t, 2H, SC<u>H</u>$_2$), 3.46 (t, 2H, C<u>H</u>$_2$), 7.07–7.99 (3H, Ar-<u>H</u>).

1-Acetyl-5-methyl-1H-benzimidazole-2-thiol (12a)

White crystals from ethanol; $C_{10}H_{10}N_2OS$ (206.27), calcd.: C, 58.23; H, 4.89; N, 13.58; found: C, 58.13; H, 4.84; N, 15.62; yield 64%; m.p.

180–181°C; IR (KBr), 1556, 1594, 1645, 2565, 2960, 3135; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.43 (s, 3H, C<u>H</u>$_3$), 2.58 (s, 3H, C<u>H</u>$_3$), 6.90–7.05 (3H, Ar-<u>H</u>), 12.06 (s, 1H, S<u>H</u>).

1-Benzoyl-5-methyl-1H-benzimidazole-2-thiol (12b)

White crystals from ethanol; $C_{15}H_{12}N_2OS$ (268.33), calcd.: C, 67.14; H, 4.51; N, 10.44; found: C, 67.08; H, 4.50; N, 10.51; yield 32%; m.p. 200–202°C; IR (KBr), 1621, 1707, 2565, 2947, 3137; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.38 (s, 3H, C<u>H</u>$_3$), 6.90–8.04 (8H, Ar-<u>H</u>), 12.83 (s, 1H, S<u>H</u>).

1-(4-Chlorobenzoyl)-5-methyl-1H-benzimidazole-2-thiol (12c)

White crystals from benzene/ethanol; $C_{15}H_{11}ClN_2OS$ (302.78), calcd.: C, 59.50; H, 3.66; N, 9.25; found: C, 59.42; H, 3.64; N, 9.33; yield 67%; m.p. 237–238°C; IR (KBr), 1592, 1710, 2568, 2929, 3062; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.37 (s, 3H, C<u>H</u>$_3$), 6.89–7.96 (7H, Ar-<u>H</u>), 12.33 (s, 1H, S<u>H</u>).

S-(1-Benzoyl-5-methyl-1H-benzimidazol-2-yl)benzene-carbothioate (13)

Yellow crystals from ethanol; $C_{22}H_{16}N_2O_2S$ (372.44), calcd.: C, 70.95; H, 4.33; N, 7.52; found: C, 70.88; H, 4.30; N, 7.65; yield 51%; m.p. 197–199°C; IR (KBr), 1600, 1711, 2925, 3068; ^{1}H NMR, δ ($CDCl_3$+ DMSO-d_6), 2.39 (s, 3H, C<u>H</u>$_3$), 7.07–7.91 (13H, Ar-<u>H</u>).

8-Methyl-2-phenyl-2,3-dihydro-4H-[1,3]thiazino[3,2-a] benzimidazol-4-one (14)

White crystals from ethanol; $C_{17}H_{14}N_2OS$ (294.37), calcd.: C, 69.36; H, 4.79; N, 9.52; found: C, 69.27; H, 4.72; N, 9.61; yield 48%; m.p. 187–189°C; IR (KBr), 1599, 1721, 2934, 3030; ^{1}H NMR, δ ($CDCl_3$), 2.50 (s, 3H, C<u>H</u>$_3$), 3.51 (m, 2H, C<u>H</u>$_2$), 4.93 (dxd, 1H, C<u>H</u>), 7.17–8.09 (8H, Ar-<u>H</u>).

8-Methyl-4-phenyl-3,4-dihydro-2H-[1,3]thiazino[3,2-a] benzimidazol-2-one (15)

White crystals from ethanol; $C_{17}H_{14}N_2OS$ (294.37), calcd.: C, 69.36; H, 4.79; N, 9.52; found: C, 69.22; H, 4.78; N, 9.59; yield 33%; m.p. 130–131°C; IR (KBr), 1612, 1704, 2925, 3047; ^{1}H NMR, δ ($CDCl_3$), 2.48 (s, 3H, C<u>H</u>$_3$), 2.52 (dxd, 2H, C<u>H</u>$_2$), 6.53 (dxd, 1H, C<u>H</u>), 7.17–7.94 (8H, Ar-<u>H</u>).

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