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Solvent- and Catalyst-Free Synthesis of New Unsymmetrical Multidentate Thio-bis-aminophenol Ligands by Mannich Condensation

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Abstract: A one-pot, three-component, Mannich condensation of electron-rich aromatic compounds such as 5-methyl-2-hydroxyphenyl sulfide, 2-aminopyrimidine, and various aromatic aldehydes were used to prepare a series of new unsymmetrical multidentate aminophenol ligands. These compounds were synthesized in solvent-free conditions as a fast, simple, convenient, and uncatalyzed method. Details of the reaction conditions are discussed.

Keywords: Aminophenol, Mannich, multidentate, solvent-free, unsymmetrical

INTRODUCTION

Multicomponent reactions (MCRs) have attracted considerable attention because of their convergence, easy execution, mechanism, and multiple bond formation. Such a reaction may be employed for building structurally diverse molecules.[1] They also deliver fewer by-products then classical stepwise synthetic routes. This reduces time and saves raw materials.[2] The Mannich reaction (aminoalkylation) is an example of multicomponent condensation of a nonenolizable aldehyde, an amine (1° or 2°),

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and an enolizable carbonyl compound.[3] Direct aminoalkylation has great interest in synthetic organic chemistry and considerable importance for the synthesis of drugs, pesticides, and natural products.[4]

Many methods of aminoalkylation of electron-rich aromatic compounds have been studied to date. Katritzky and Risch reported an improved aminoalkylation of 2-naphthol and phenol derivatives with preformed iminium salts derived from aromatic aldehydes in a two-step sequence with 26–92% yields.[5] In recent years, aminoalkylation of electron-rich aromatic compounds in the presence of $LiClO_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $YbCl_3$, $TiCl_4$, and Me_3SiCl has been reported.[6–8] Also, a series of larger molecules such as diaminodinaphthols, diaminodiphenols, and diaminotetraphenols have been prepared from ethylenediamine, various amounts of paraformaldehyde, and 2,4-disubstituted phenols by controlling the stoichiometry and reaction conditions. By using 2,4-disubstituted phenols and varying those substituents, researchers modulate the electronic and steric properties of the alcohol moieties, affecting both how many phenol groups can bind to a transition metal and how strongly those phenols will bind.[9–13] Moreover, optically active aminophenol and aminonaphthol ligands have been used as ligands complexed to dialkyl zinc for enantioselective addition to aryl aldehydes. These ligands show highly efficient asymmetric induction to give the corresponding alcohols up to 99% ee yields.[14–16]

We now describe the synthesis of new multidentate thio-diaminodiphenol derivatives via a facial three-component and one-pot method for aminoalkylation of electron-rich aromatic compounds such as 5-methyl-2-hydroxyphenyl sulfide, using aromatic aldehydes and 2-aminopyrimidine in the absence of catalyst with short reaction time and solvent-free conditions. As such, utilization of environmentally friendly conditions (absence of organic solvent) provides the product not only in an easy workup procedure but also in accord with green sustainable chemistry principles.

RESULTS AND DISCUSSION

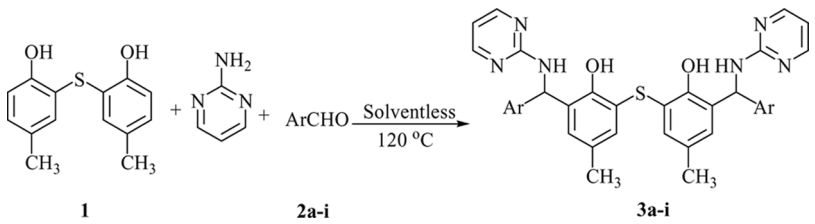
As part of a continuous effort to develop new N,O,S-ligand derivatives relevant to the Mannich reaction, we report a fast, simple, and convenient method for the synthesis of new thio-diaminodiphenol with heteroaryl amine and aromatic aldehydes in solvent-free conditions in moderate to good yields. The promising advantages, such as removal of organic solvent, lack of catalyst, easy workup, and short reaction time, are discussed. Our literature survey showed that thio-diaminodiphenol

has not previously been used for the synthesis of diaminodiphenol ligand derivatives.

As the model reaction, we initially examined the one-pot, three-component Mannich reaction of 5-methyl-2-hydroxyphenyl sulfide (**1**),[17] 2-aminopyrimidine, and benzaldehyde in CH_3CN, EtOH, and MeOH in the presence of formic acid as catalyst at room temperature. We found that at least 24 h was needed for the reaction of 2-aminopyrimidine with benzaldehyde to afford the corresponding Schiff base. We then examined the same reaction under reflux conditions in the same solvents, in which the desired product was not observed and only the corresponding Schiff base was formed. When this reaction was performed in solvent-free conditions at 70–100°C in the absence of acid catalyst, the corresponding Schiff base was obtained. Our investigation demonstrated that the best result was obtained when temperature was fixed at 125°C, at which the reaction completed in 10 min. Therefore, we decided to examine the other reactions in solventless conditions at 125°C in the absence of acid catalyst.

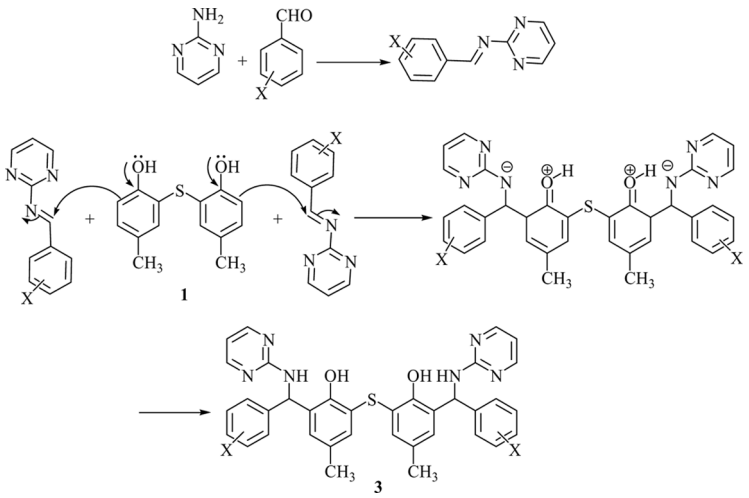
2-Aminopyrimidine was used in all Mannich condensations toward the synthesis of series of multidentate aminophenol ligands (**3a–i**). Thio-bis-aminophenols (**3a–i**) were prepared by combining 1 equivalent of thio-bis-phenol **1** with 2 equivalents aromatic aldehydes (**2a–i**) and 2 equivalents of 2-aminopyrimidine in solventless conditions during 10–30 min at 125°C (Scheme 1). Each compound was isolated by addition of ethanol to a cooled reaction mixture and filtration of the resulting precipitate in moderate to good yields.

To get insight into the reaction mechanism, we initially studied the reaction of compound **1** with aldehyde. No reaction progress was observed during several hours. Our studies confirmed that formation of Schiff bases play an important rule in the Mannich codensation toward the final products. When we isolated the Schiff bases and then allowed their reactions with bis-phenol **1**, we obtained the same products from a one-pot reaction of these compounds (Scheme 2).



1 2a-i 3a-i

Scheme 1. Synthesis of thio-bis-aminophenols (**3a–i**) by solvent-free Mannich reaction. Ar = a: ph, b: 4-Me-ph, c: 4-MeO-ph, d: 4-Br-ph, e: 3-Br-ph, f: 4-Cl-3-NO_2-ph, g: 4-NO_2-ph, h: 3-NO_2-ph, and i: 4-Cl-ph.



Scheme 2. Mechanism for the formation of compounds **3a–i**.

The thio-bis-phenol **1** was already synthesized and characterized by different means including x-ray spectroscopy.[17] The hydroxyl groups have been used to synthesize different multidentate macrocycles[18,19] and polymers[20] and studied for different applications in metal-ion complexation.[21] These previous synthetic studies indicated that the presence of a sulfur atom in the bis-phenol (**1**) not only plays an important role in the complexation behavior but also in the physical properties of polymers and dynamic behavior of macrocyclic compounds.

In the compound 5-methyl-2-hydroxyphenyl sulfide (**1**), hydroxyl and sulfide groups can direct electrophilic substitutions on the para position with respect to the sulfur and on the ortho position with respect to the hydroxyl group. Based on the coupling constant (*J*) observed in ^{1}H NMR spectra, we can conclude that hydroxyl group dominates in electronic direction for electrophilic substitution. The coupling constant was about 1.5 Hz for all final products (**3a–i**), as the structures show in Scheme 1 based on this evidence.

Identification of **3a–i** was carried out on the basis of spectroscopic data. The ^{1}H NMR spectra of these compounds show a sharp singlet for two methyl groups at about δ 2.1 ppm. Hydroxyl groups appear as broad signal at about δ 9.0 ppm. The mixed NH, methine, and pyrimidine H-5 protons were observed at about δ 6.5–6.7 ppm. As a result of the addition of D_2O into the sample solution of **3a**, the hydroxyl and amine proton signals disappeared in ^{1}H NMR spectrum. The pyrimidine H-4,6 moieties in all of the products were exhibited in the region of δ 8.3 ppm as

two doublets, indicating that two types of pyrimidine ring are in the products. Moreover, in compound **3a**, two types of NH signal appear as two well-resolved doublets at about δ 6.35 and 6.37. In addition, two types of CH signals showed at the positions 4,4′ on the phenolic rings as two well-resolved doublets. These spectroscopic data indicated that the obtained products have unsymmetric structures and that the hydrogen nuclei are diastrotopic. Also the number of carbons revealed in the ^{13}C NMR spectra of compounds **3a–i** was in agreement with unsymmetrical products. Details of ^{1}H NMR and ^{13}C NMR are presented in the experimental section. The OH and NH absorptions are observed at 3410–3250 cm^{-1} in IR spectra. Compounds **3a–i** exhibit the expected parent ions with low intensity in mass spectra. Table 1 illustrates reaction times and yields of the synthesized new aminophenol derivatives (**3a–i**).

In conclusion, this method could be considered as a convenient and environmentally friendly approach for the synthesis of new thio-bis-aminophenol ligands via one-pot, three Component Mannich condensation of 5-methyl-2-hydroxyphenyl sulfide (**1**), 2-aminopyrimidine, and aromatic aldehydes using solvent-free conditions. The present method has advantages such as no organic solvent, generality and simplicity of the procedure, less reaction time, elimination of acid catalyst, and moderate to good yields. To the best of our knowledge, this is the first report on the synthesis of compounds of type **3**, and these multidentate compounds may provide a valuable source of new potentially chelating agents for metal ions.

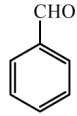
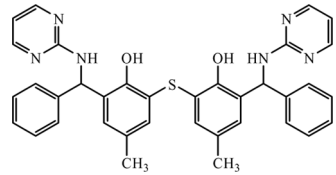
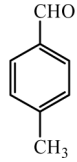
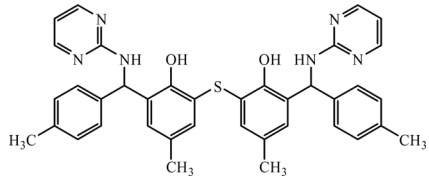
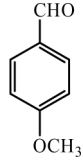
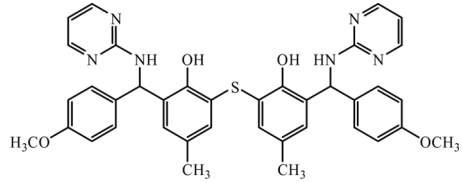
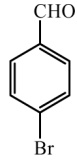
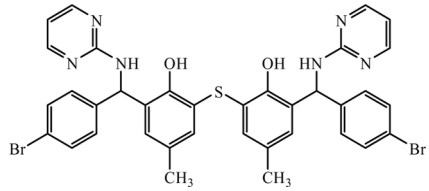
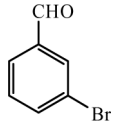
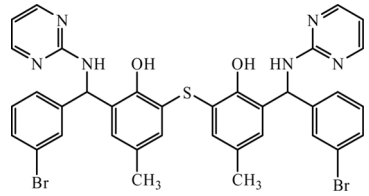
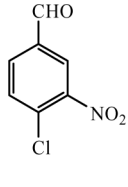
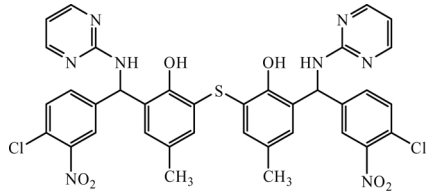
EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker DRX-500 Avance spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 mass selective detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

General Procedure for the Synthesis of Thio-bis-[5-methyl-3-(aryl(2-pyrimidinylamino)methyl]-2-phenol

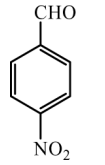
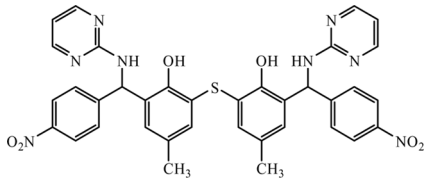
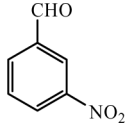
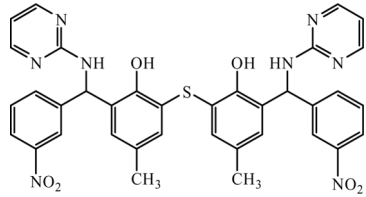
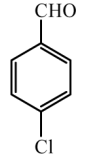
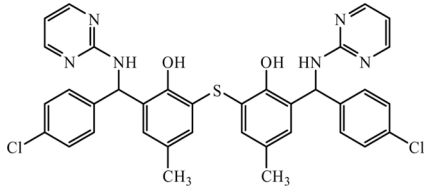
An aromatic aldehyde (4 mmol) was added to a mixture of compound **1** (2 mmol) and 2-aminopyrimidine (4 mmol). The reaction mixture was

Table 1. One-pot reactions of thio-bis-phenol 1,2-aminopyrimidine and aromatic aldehydes

Entry	Aldehyde	Product 3	Time (min)	Yield (%)	Mp (°C)
1			10	80	138–139
2			25	75	147–149
3			30	82	146–147
4			20	76	144–146
5			12	78	144–145
6			15	85	148–150

(*Continued*)

Table 1. Continued

Entry	Aldehyde	Product 3	Time (min)	Yield (%)	Mp (°C)
7			12	90	154–155
8			15	87	133–135
9			18	84	143–145

magnetically stirred on a preheated oil bath at 125°C for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to rt, and ethanol (10 mL) was added. The precipitate was filtered, washed with cold ethanol, dried, and purified by recrystallization from EtOH to give the thio-bis aminophenol **3** as color crystals.

Data

Thio-bis-[5-methyl-3-(phenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3a**)

Pale yellow crystal; IR (KBr): 3410, 3247, 3028, 2922, 1588, 1515, 1447, 1234, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (s, 6H, *CH*$_3$), 6.35 (d, 1H, $J = 3.2$ Hz, *NH*), 6.37 (d, 1H, $J = 3.2$ Hz, *NH*), 6.55 (d, 2H, $J = 3.2$ Hz, methine-H), 6.56–6.59 (m, 2H, pyrimidine H-5,5′), 6.91 (s, 1H, phenolic H-4), 6.92 (s, 1H, phenolic H-4′), 7.01 (s, 2H, phenolic H-6,6′), 7.29–7.38 (m, 10H, ph-H), 8.30 (d, 2H, $J = 4.8$ Hz, pyrimidine

H-4,6), 8.32 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.34 (broad, 2H, *OH*) ppm; ^{1}H NMR (500 MHz, $CDCl_3 + D_2O$): $\delta = 2.15$ (s, 6H, *CH*$_3$), 6.54 (s, 2H, methine-H), 6.55–6.58 (m, 2H, pyrimidine H-5,5′), 6.91 (s,1H, phenolic H-4), 6.92 (s,1H, phenolic H-4′), 7.01 (s, 2H, phenolic H-6,6′), 7.29–7.38 (m, 10H, ph-H), 8.29 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.31 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.98$, 54.28, 111.52, 111.53, 121.71, 127.20, 127.22, 127.54, 128.85, 129.76, 130.67, 130.68, 130.73, 130.74, 133.60, 141.53, 141.55, 152.54, 158.54, 161.78 ppm; MS: m/z (%) = 612 $[M]^+$, 611 $[M-1]^+$, 583, 527, 489, 377, 333, 262, 195, 183, 95. Anal. calcd. for $C_{36}H_{32}N_6O_2S$: C, 70.58; H, 5.22, N, 13.72. Found: C, 70.52; H, 5.28; N, 13.77.

Thio-bis-[5-methyl-3-(4-methylphenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3b**)

Pale yellow crystal; IR (KBr): 3410, 3275, 3022, 2920, 1588, 1513, 1448, 1234, 801 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (s, 6H, *CH*$_3$), 2.36 (s, 6H, *CH*$_3$), 6.53–6.55 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.92 (s, 1H, phenolic H-4), 6.93 (s, 1H, phenolic H-4′), 7.00 (s, 2H, phenolic H-6,6′), 7.15–7.30 (m, 8H, tolyl-H), 8.25 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.27 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.35 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.99$, 21.74, 54.01, 111.35, 111.37, 121.70, 121.72, 127.18, 127.19, 129.55, 129.96, 130.53, 130.57, 130.65, 130.67, 133.43, 133.46, 137.13, 138.56, 138.58, 152.52, 152.56, 158.51, 161.78 ppm; MS: m/z (%) = 640 $[M]^+$, 554, 454, 350, 244, 212, 197, 152, 120, 105, 91. Anal. calcd. for $C_{38}H_{36}N_6O_2S$: C, 71.25; H, 5.62; N, 13.12. Found: C, 71.30; H, 5.55; N, 13.10.

Thio-bis-[5-methyl-3-(4-methoxyphenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3c**)

Pale yellow crystal; IR (KBr): 3410, 3278, 3002, 2931, 1587, 1512, 1454, 1248, 1177, 801 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.16$ (s, 6H, *CH*$_3$), 3.82 (s, 6H, O*CH*$_3$), 6.43–6.57 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.84–7.30 (m, 12H, phenolic H-4,4′,6,6′, OMe-ph-H), 8.25 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.28 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.34 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.00$, 53.76, 55.67, 111.40, 111.42, 114.22, 114.29, 121.70, 121.72, 128.39, 128.41, 129.98, 130.52, 130.54, 130.65, 130.67, 133.50, 133.61, 133.63, 152.50, 152.53, 158.51, 159.04, 161.74 ppm; MS: m/z (%) = 672 $[M]^+$, 615, 602, 574, 500, 486, 366, 260, 213, 152, 135, 95. Anal. calcd. for $C_{38}H_{36}N_6O_4S$: C, 67.85; H, 5.35; N, 12.50. Found: C, 67.90; H, 5.26; N, 12.59.

Thio-bis-[5-methyl-3-(4-bromophenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3d**)

Pale yellow crystal; IR (KBr): 3410, 3251, 3025, 2921, 1587, 1568, 1514, 1488, 1448, 1235, 1180, 1010, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.16$ (s, 6H, *CH_3*), 6.45–6.50 (m, 4H, *NH*, methine-H,), 6.57 (t, 1H, $J = 4.8$ Hz, pyrimidine H-5), 6.59 (t, 1H, $J = 4.8$ Hz, pyrimidine H-5′), 6.87 (d, 1H, $J = 1.3$ Hz, phenolic H-4), 6.88 (d, 1H, $J = 1.3$ Hz, phenolic H-4′), 7.03 (d, 2H, 1.3, phenolic H-6,6′), 7.24 (d, 2H, $J = 2.9$ Hz, 4-Br-ph-H), 7.26 (d, 2H, $J = 2.9$ Hz, 4-Br-ph-H), 7.45 (d, 2H, $J = 1.9$ Hz, 4-Br-ph-H′), 7.46 (d, 2H, $J = 1.9$ Hz, 4-Br-ph-H′), 8.27 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.29 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.26 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.96$, 53.98, 111.72, 111.74, 121.46, 121.77, 121.79, 129.00, 129.02, 129.29, 130.71, 130.76, 130.94, 131.89, 133.92, 133.98, 140.70, 152.52, 158.55, 161.67 ppm; MS: m/z (%) = 772 $[M]^+$, 770 $[M]^+$, 768 $[M]^+$, 750, 584, 414, 276, 183, 120, 95. Anal. calcd. for $C_{36}H_{30}Br_2N_6O_2S$: C, 56.10; H, 3.89; N, 10.90. Found: C, 56.01; H, 3.95; N, 10.95.

Thio-bis-[5-methyl-3-(3-bromophenyl(2-pyrimidinyl amino)methyl)-2-phenol **(3e)**

Pale yellow crystal; IR (KBr): 3411, 3251, 3020, 2920, 1586, 1569, 1512, 1448, 1234, 1185, 783 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (s, 6H, *CH_3*), 6.53–6.67 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.86 (s, 1H, phenolic H-4), 6.88 (s, 1H, phenolic H-4′), 7.03 (s, 2H, phenolic H-6,6′), 7.17–7.56 (m, 8H, 3-Br-ph-H), 8.24 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.27 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.22 (broad, 2H, *OH*) ppm;^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.00$, 53.93, 111.71, 111.73, 121.77, 121.79, 123.07, 126.04, 126.08, 129.22, 130.28, 130.30, 130.35, 130.65, 130.68, 130.72, 130.98, 131.00, 133.93, 133.99, 144.07, 144.09, 152.46, 152.51, 158.54, 161.67 ppm; MS: m/z (%) = 772 $[M]^+$, 770 $[M]^+$, 768 $[M]^+$, 584, 414, 308, 278, 227, 197, 152, 120, 95. Anal. calcd. for $C_{36}H_{30}Br_2N_6O_2S$: C, 56.10; H, 3.89; N, 10.90. Found: C, 56.07; H, 3.93; N, 10.85.

Thio-bis-[5-methyl-3-(4-chloro-3-nitro phenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3f**)

Yellow crystal; IR (KBr): 3412, 3250, 3033, 2924, 1586, 1537, 1448, 1349, 1235, 1048, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.18$ (s, 6H, *CH_3*), 6.54–6.68 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.88 (d,

1H, $J = 1.5$ Hz, phenolic H-4), 6.90 (d, 1H, $J = 1.5$ Hz, phenolic H-4′), 7.06 (d, 2H, $J = 1.5$ Hz, phenolic H-6,6′), 7.45 (m, 6H, 4-Cl-3-NO_2-ph-H), 8.26 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.28 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 8.92 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.90$, 54.03, 112.21, 112.23, 121.92, 124.19, 124.21, 125.91, 128.23, 130.92, 130.95, 131.51, 131.53, 132.10, 132.16, 132.20, 134.62, 134.65, 142.73, 148.18, 152.35, 152.38, 158.60, 161.51 ppm; MS: m/z (%) = 771 $[M]^+$, 578, 552, 523, 368, 313, 236, 185, 95. Anal. calcd. for $C_{36}H_{28}Cl_2N_8O_6S$: C, 56.03; H, 3.63; N, 14.53. Found: C, 56.10; H, 3.68; N, 14.47.

Thio-bis-[5-methyl-3-(4-nitrophenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3g**)

Yellow crystal; IR (KBr): 3412, 3254, 3038, 2924, 1586, 1519, 1505, 1463, 1448, 1407, 1346, 1238, 1181, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.17$ (s, 6H, *CH*$_3$), 6.57–6.64 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.87 (d, 1H, $J = 1.5$ Hz, phenolic H-4), 6.89 (d, 1H, $J = 1.5$ Hz, phenolic H-4′), 7.04 (d, 2H, $J = 1.5$ Hz, phenolic H-6) 7.06 (d, 2H, $J = 1.5$ Hz, phenolic H-6′), 7.53 (d, 2H, $J = 2.1$ Hz, 4-NO_2-ph-H), 7.55 (d, 2H, $J = 2.1$ Hz, 4-NO_2-ph-H), 8.16 (d, 2H, $J = 1.5$ Hz, 4-NO_2-ph-H′), 8.18 (d, 2H, $J = 1.5$ Hz, 4-NO_2-ph-H′), 8.28 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.30 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.09 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.93$, 54.58, 112.07, 112.10, 121.86, 121.91, 124.01, 128.06, 128.08, 128.67, 130.95, 131.04, 131.35, 134.29, 134.42, 147.42, 147.44, 149.28, 152.36, 152.40, 158.60, 161.58 ppm; MS: m/z (%) = 702 $[M]^+$, 578, 552, 524, 433, 368, 313, 285, 228, 201, 181, 151, 129, 95. Anal. calcd. for $C_{36}H_{30}N_8O_6S$: C, 61.54; H, 4.27; N, 15.95. Found: C, 61.50; H, 4.30; N, 16.00.

Thio-bis-[5-methyl-3-(3-nitrophenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3h**)

Pale yellow crystal; IR (KBr): 3409, 3252, 3034, 2925, 1587, 1529, 1449, 1412, 1349, 1235, 1130, 801 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.16$ (s, 6H, *CH*$_3$), 6.59–6.67 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.87 (d, 1H, $J = 1.5$ Hz, phenolic H-4), 6.89 (d, 1H, $J = 1.5$ Hz, phenolic H-4′), 7.06 (d, 2H, $J = 1.5$ Hz, phenolic H-6), 7.47–8.14 (m, 8H, 3-NO_2-ph-H), 8.28 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.30 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.05 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.92$, 54.23, 112.05, 112.09,

121.88, 121.91, 122.02, 122.04, 122.62, 128.67, 129.71, 130.84, 130.92, 131.31, 131.34, 133.63, 133.65, 134.38, 134.47, 144.15, 144.17, 148.78, 152.41, 152.48, 158.59, 161.62 ppm; MS: m/z (%) = 702 $[M]^+$, 552, 538, 523, 379, 368, 313, 246, 228, 151, 129, 95. Anal. calcd. for $C_{36}H_{30}N_8O_6S$: C, 61.54; H, 4.27; N, 15.95. Found: C, 61.57; H, 4.32; N, 15.90.

Thio-bis-[5-methyl-3-(4-chlorophenyl(2-pyrimidinyl amino)methyl)-2-phenol (**3i**)

Pale yellow crystal; IR (KBr): 3412, 3257, 3028, 2922, 1587, 1513, 1449, 1235, 1091, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.15$ (s, 6H, *CH*$_3$), 6.51–6.67 (m, 6H, *NH*, methine-H, pyrimidine H-5,5′), 6.87 (s,1H, phenolic H-4), 6.88 (s,1H, phenolic H-4′), 7.02 (s, 2H, phenolic H-6,6′), 7.30 (m, 8H, 4-Cl-ph-H), 8.23 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4,6), 8.26 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4′,6′), 9.27 (broad, 2H, *OH*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.96$, 53.90, 111.65, 111.67, 121.77, 121.78, 128.68, 128.70, 128.93, 129.40, 129.42, 130.66, 130.70, 130.90, 133.32, 133.34, 133.87, 133.89, 140.17, 140.18, 152.51, 158.52, 161.68 ppm; MS: m/z (%) = 681 $[M]^+$, 494, 370, 264, 232, 139, 120, 95. Anal. calcd. for $C_{36}H_{30}Cl_2N_6O_2S$: C, 63.44; H, 4.40; N, 12.33. Found: C, 63.38; H, 4.36; N, 12.39.

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REFERENCES

1. (a) Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; (b) Thmson, L. A.; Ellman, J. A. Synthesis and application of small molecule libraries. *Chem. Rev.* **1996**, *96*, 555–600.
2. (a) Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. Facile synthesis of 1,7-dicarbonyl compounds via three-component Michael addition reactions. *Tetrahedron Lett.* **2004**, *45*, 2649–2651, (b) Wang, L. M.; Xia, J.; Qin, F.; Qian, C.; Sun, J. $Yb(OTf)_3$-catalyzed one-pot synthesis of quinazolin-4 (3*H*)-ones from anthranilic acid, amines, and ortho esters (or formic acid) in solvent-free conditions. *Synthesis* **2003**, 1241–1247.
3. Arend, M.; Westermann, B.; Risch, N. Modern variants of the Mannich reaction. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1077.

4. (a) Paqett, L. O. (Ed.). *Encyclopedia of Reagents for Organic Synthesis*; Wiley: London, 1995; vol. 4, p. 2582; (b) Tramontini, M.; Angionili, L. Further advances in the chemistry of Mannich bases. *Tetrahedron* **1990**, *46*, 1791–1837.
5. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Belyakov, S. A.; Ghiviriga, I.; Steel, P. J. Amino(hetero)arylmethylation of phenols with *N*-[α-amino(hetero)arylmethyl]benzotriazoles. *J. Org. Chem.* **1999**, *64*, 6071–6075.
6. Mojtahedi, M. M.; Sharifi, A.; Mohsenzadeh, F.; Saidi, M. R. Microwave-assisted aminomethylation of electron-rich compounds under solvent-free condition. *Synth. Commun.* **2000**, *30*, 69–72.
7. Saidi, M. R.; Azizi, N.; Naimi-jamal, M. R. Lithium perchlorate–assisted one-pot three-component aminoalkylation of electron-rich aromatic compounds. *Tetrahedron Lett.* **2001**, *42*, 8111–8113.
8. Huang, T.; Li, C. J. Synthesis of amino acids via a three-component reaction of phenols, glyoxylates, and amines. *Tetrahedron Lett.* **2000**, *41*, 6715–6719.
9. Subramanian, P.; Spence, J. T.; Ortega, R.; Enemark, J. H. Molybdenum(VI)–dioxo complexes with sterically bulky ligands. *Inorg. Chem.* **1984**, *23*, 2564–2572.
10. Amudha, P.; Thirumavalavan, M.; Kandaswamy, M. Synthesis, spectral, electrochemical, and magnetic properties of new phenoxo-bridged dicopper (II) complexes derived from unsymmetrical binucleating ligands. *Polyhedron* **1999***, 18, 1363–1369.*
11. Tshuva, E. Y.; Gendeziuk, N.; Kol, M. Single-step synthesis of salans and substituted salans by Mannich condensation. *Tetrahedron Lett.* **2001**, *42*, 6405–6407.
12. Higham, C. S.; Dowling, D. P.; Shaw, J. L.; Cetin, A.; Ziegler, C. J.; Farrell, J. R. Multidentate aminophenol ligands prepared with Mannich condensations. *Tetrahedron Lett.* **2006**, *47*, 4419–4423.
13. D'Hardemare, A. du M.; Jarjayes, O.; Mortini, F. Solvent- and catalyst-free selective Mannich reaction on catechols and *para*-substituted phenols: A convenient route to catechol- and phenol-iminodiacetic acid ligands. *Synth. Commun.* **2004**, *34*, 3975–3988.
14. Palmieri, G. A practical o-hydroxybenzylamines promoted enantioselective addition of dialkylzincs to aldehydes with asymmetric amplification. *Tetrahedron: Asymmetry* **2000**, *11*, 3361–3373.
15. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. Use of readily available chiral compounds related to the Betti base in the enantioselective addition of diethylzinc to aryl aldehydes. *Tetrahedron* **1999**, *55*, 14685–14692.
16. Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. Synthsis of chiral ligands derived from the Betti base and their use in the enantioselective addition of diethylzinc to aromatic aldehydes. *Tetrahedron Lett.* **2002**, *43*, 8367–8369.
17. Shockravi, A.; Alizadeh, R.; Aghabozorg, H.; Moghimi, A.; Rostami, E.; Bavili, S. Synthesis and crystal structure determination of 2,2′-sulfinyl-bis

(4-methyl phenol) and 2,2′-thio-bis(4-methyl phenol). *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 2519–2527.
18. Shockravi, A.; Bavili, S.; Rostami, E.; Yousefi, A.; Dehjurian, A.; Tohidi, R. Synthesis of new dibenzosulfid and dibenzosulfoxide macrocyclic compounds. *J. Incl. Phenom. Macrocycl. Chem.* **2004**, *49*, 163–166.
19. Shockravi, A.; Bavili, S. Synthesis of new dibenzosulfid macrocyclic diamide. *J. Incl. Phenom. Macrocycl. Chem.* **2005**, *52*, 223–227.
20. Shockravi, A.; Mehdipour-Ataei, S.; Abouzari-Lotf, E.; Yousefi, A. *Eur. Polym. J.* **2006**, *42*, 133–134.
21. Shockravi, A.; Shamsipur, M.; Fattahi, H.; Taghdiri, M.; Heidarian, D.; Alizadeh, K.; Rostami, E.; Abbaszadeh, M.; Yousefi, A. *J. Incl. Phenom. Macrocycl. Chem.* **2008**, *61*, 153–160.