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Design and Synthesis of *Bis* Thiazol-2-ylidenes

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A series of novel *hitherto* unreported 4,4'-[N,N'-*bis*(3-phenyl-4-(4-substituted phenyl)-thiazol-2(3*H*)-ylidene)]methylenedianiline derivatives has been synthesized by the heterocyclization between the *bis*-1,3-disubstituted thiourea and substituted acetophenones in presence of iodine. Both conventional and non-conventional methods have been used for the synthesis of the targets. All the synthesized compounds were confirmed by spectral analysis.

Key Words: Bisthiourea, Bisthiazolidenes, Ultrasonication.

INTRODUCTION

Thiazole ring unit is a common feature of many bioactive molecules. Thiazole ring system possessing diversified types of pharmacological activities such as antifungal[1], antiinflammatory[2], antituberculosis[3], antitumor[4], *etc*. In the recent reviews, many examples of enhanced bioactivity of multivalent drug molecules have been cited[5]. Compounds bearing more than one thiazole ring unit also exhibit good biological activities, the bleomycin containing 2,4'-*bis* thiazole system acts as an anticancerous antibiotic and biological reports also existing on the 5,5'-*bis* thiazoles[6] and 2,2'-*bis* thiazoles[7]. Further, the 2-aminothiazole is a valuable pharmacophore unit present in many bioactive compounds including thrombotic[8] and bacterial DNA-gyrase[9] inhibitors that are potentially useful in cardiac and cancer treatment. Accordingly, thiazoline derivatives also possess biological activities such as antifungal[10], skin whitening properties[11] and have some interesting agricultural applications[12]. Recently, the synthesis of 2-amino-4-phenylthiazole through the condensation reaction between acetophenone and thiourea in the presence of iodine as the reagent was reported[13]. We now reported the synthesis of 4,4'-[N,N'-*bis*(3-phenyl-4-(4-substituted phenyl)-thiazol-2(3*H*)-ylidene)]-methylenedianiline derivatives through Hantzsch thiazole condensation of *bis*-1,3-disubstituted thiourea and acetophenones in presence of iodine followed by E_1 elimination. The synthesis of the title compound was carried out as presented in the **Scheme-I**.

EXPERIMENTAL

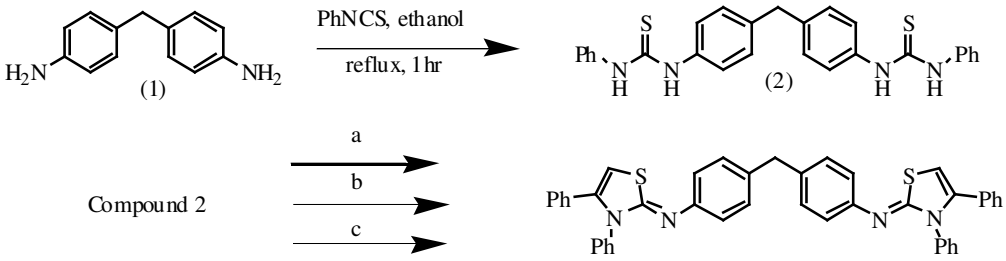
All chemicals were purchased from Sigma-Aldrich Chemical & Co. and used without purification. They included diphenylene diamine, phenyl isothiocyanate, acetophenone and substituted acetophenones. The solvents including petroleum ether (60-80 ºC), N,N-dimethyl formamide, dichloromethane, methanol, absolute ethanol and ethyl acetate were purchased from SD fine Chemicals Limited and used.

Melting points were determined in open capillary tubes. Thin layer chromatography was performed using silica gel on the glass plates. The spots were visualized under iodine chamber and under UV light. The spectra were recorded.

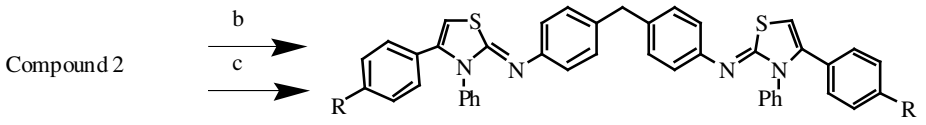
General procedure

Synthesis of 4,4'-[N,N'-*bis*(substituted thiourea)]-methylenedianiline (2): A mixture of diamine (**1**) (5 mmol) and phenyl isothiocyanate (10 mmol) dissolved in ethanol was refluxed for 1 h. The reaction was monitored by using TLC (pet. ether:ethyl acetate 4:1) and found to be completed in 1 h. The reaction mixture was cooled, solid product formed was filtered, dried and recrystallized from ethanol/N,N'-dimethyl formamide. Brown solid; yield 90 %; m.p. 95-97 ºC; IR (KBr, ν_{max}, cm^{-1}): 3316, 3030, 1591, 1505, 1490, 1108, 930, 768; ^1H NMR δ 7.25-7.60 (m, 10H, Ar-H), 6.90-7.10 (d, 8H, Ar-H), 3.45 (S, 2H, CH_2), 8.1-8.3 (s, 4H, -NH-); m/z 468.

Synthesis of 4,4'-[N,N'-*bis*(3,4-diphenyl-thiazol-2(3*H*)-ylidene)]methylenedianiline (3i): *in situ* method: To a stirred solution of acetophenone (10 mmol) in aqueous methanol (1:1) (10 mL), potassium bromide-potassium bromate (2:1) (1 g, 5 mmol available bromine) was added, followed by drop-wise addition of dil. HCl (1 N, 10 mL). The reaction mixture was allowed to stir for further 90 min. To the mixture, a solution of bisthiourea (**2**) (5 mmol) dissolved in DMF, added a catalytic amount of iodine and allowed to reflux for overnight. To the



(a) Phenacylbromide (5mmol acetophenone, KBr & $KBrO_3$ (2:1, 1g, 5mmol available Br_2), 1N HCl), I_2, DMF, reflux, overnight; (b) acetophenone, I_2, ethanol, reflux, 2hrs; (c) acetophenone, I_2, ethanol, ultrasonication, 30 mins



(b) 4-substituted acetophenones(R = $-NH_2$, -Cl, $-OCH_3$, $-CH_3$), I_2, ethanol, reflux, 2hrs;
(c) 4-substituted acetophenones(R = $-NH_2$, -Cl, $-OCH_3$, $-CH_3$), I_2, ethanol, ultrasonication, 30 mins

Scheme-I

mixture added 10 mL of 1 N NaOH to neutralize and the DMF was concentrated under reduced pressure, extracted with ethyl acetate, washed with water and dried over sodium sulphate, concentrated to get the crude product. The reaction was monitored by using TLC(Pet. ether:ethyl acetate 4:1) and found to be completed within 3 h. The product was purified by column chromatography. Yellowish orange solid; Yield 61 %; m.p. 104-109 ºC; IR (KBr, ν_{max}, cm^{-1}): 3050, 2951, 1822, 1434, 1306, 1180, 748, 691; ^1H NMR δ 7.68-7.99 (m, 20H, Ar-H), 7.55-7.67(d, 8H, Ar-H), 4.9 (s, 2H, CH_2), 5.92(s, 2H, -CH-S in thiazolidene ring); m/z 672(m + 2).

Reflux method: To the ethanol solution of 2 mmol of acetophenone, added 3 equivalent of *bis* thiourea compound (**2**) and 2.2 equivalent of iodine, stir and allowed to reflux for 2 h. The reaction was monitored by TLC and found to be completed within 2 h. It was made alkaline by adding 5 % NaOH, extracted with dichloromethane (DCM). The organic solvent was evaporated under reduced pressure. The brown colour crude product was re-crystallized from ethanol. Brown solid; yield 82 %; m.p. 104-109 ºC.

Ultrasonication method: To the ethanol solution of 2 mmol acetophenone, added 3.0 equivalent of bisthiourea (**2**) and 2.2 equivalent of iodine were ultra-sonicated in cleaning ultrasonic bath at 45 ºC for 0.5 h. The reaction was monitored by TLC and found to be completed within 22 min. The solvent was evaporated under reduced pressure. The brown colour crude product was re-crystallized from ethanol. Brown solid; yield 88 %; m.p. 105-109 ºC.

Synthesis of 4,4'-(N,N'-*bis*(3-phenyl-4-(4-substituted phenyl)-thiazol-2(3*H*)-ylidene))-methylenedianiline derivatives (3ii-v): To study the comparison between the conventional method and non-conventional method, the heterocyclization were carried out by both reflux and ultrasonication method. The time taken for the completion of the reaction and yields obtained by conventional and non-conventional methods are given in Table-1. The crude products obtained were purified by column chromatography and studied their spectral analysis.

4,4'-(N,N'-*Bis*(3-phenyl-4-(4-amino-phenyl)-thiazol-2(3*H*)-ylidene))methylenedianiline (3ii): Brown solid; m.p. 107-109 ºC; IR (KBr, ν_{max}, cm^{-1}): 3052, 2959, 1905, 1434, 1308, 1176, 749, 692; ^1H NMR δ 7.56-7.67 (m, 10H, Ar-H), 7.68-7.70 (m, 8H, Ar-H), 7.20-7.36(m, 8H, Ar-H), 5.26(s, 2H, CH_2), 6.52 (s, 2H, -CH-S in thiazolidene ring), 8.68 (s, 4H, $-NH_2$); m/z 668.

4,4'-(N,N'-*Bis*(3-phenyl-4-(4-chloro-phenyl)-thiazol-2(3*H*)-ylidene))methylenedianiline (3iii): Pale yellow solid; m.p. 74-77 ºC; IR (KBr, ν_{max}, cm^{-1}) 3050, 2964, 1964, 1906, 1305, 1171, 748, 695; ^1H NMR δ 7.56-7.68 (m, 10H, Ar-H), 7.68-7.70 (m, 8H, Ar-H), 7.17-7.37(m, 8H, Ar-H), 5.28(s, 2H, CH_2), 6.57(s, 2H, -CH-S in thiazolidene ring); m/z 736.

4,4'-(N,N'-*Bis*(3-phenyl-4-(4-methyl-phenyl)-thiazol-2(3*H*)-ylidene))methylenedianiline (3iv): Pale yellow solid; m.p. 79 ºC; IR (KBr, ν_{max}, cm^{-1}) 3057, 2951, 1915, 1435, 1306, 1226, 748, 690; ^1H NMR δ 7.56-7.70 (m, 10H, Ar-H), 7.86-7.95 (m, 8H, Ar-H), 7.0-7.36(m, 8H, Ar-H), 3.70(S, 2H, CH_2), 4.04 (s, 2H, -CH-S in thiazolidene ring), 2.51 (s, 3H,-CH_3); m/z 696.

4,4'-(N,N'-*Bis*(3-phenyl-4-(4-methoxy-phenyl)-thiazol-2(3*H*)-ylidene))methylenedianiline (3v): Light brown solid;

TABLE-1
REACTION TIME (min) AND YIELD (%) OF THE REACTION BY CONVENTIONAL AND NON-CONVENTIONAL METHODS

Compounds		3i	3ii	3iii	3iv	3v
By reflux method	Yield (%)	82	77	70	67	80
	Time (min)	80	90	120	135	90
By ultrasonication method	Yield (%)	88	81	82	80	84
	Time (min)	22	22-28	26-30	26-30	22-25

m.p. 107-111 ºC; IR (KBr, ν_{max}, cm^{-1}) 3051, 2955, 1965, 1905, 1307, 1246, 751, 711; ^1H NMR δ 7.56-7.70 (m, 10H, Ar-H), 7.85-8.01 (m, 8H, Ar-H), 6.99-7.42(m, 8H, Ar-H), 4.52(s, 2H, CH_2), 5.76(s, 2H, -CH-S in thiazolidene ring), 3.30 (s, 3H, -O-CH_3); m/z 728.

RESULTS AND DISCUSSION

Reaction of compound bearing amino group with phenyl isothiocyanate in presence of ethanol gives the corresponding disubstituted thiourea[14]. Similarly, 4,4'-diaminodiphenylmethane (**1**) on treatment with twice the molar weight of phenyl isothiocyanate gives the corresponding disubstituted *bis* thiourea compound (**2**). The disubstituted *bis* thiourea product formed was collected by evaporating the solvent under reduced pressure. The formation of *bis* thiourea was confirmed by IR spectrum which showed the characterization bands at 3316 cm^{-1} represents the N-H stretching, the band at 1591 cm^{-1} represents aromatic C=C and the band at 1490 cm^{-1} represents aromatic C=S. Then, the proton NMR peaks and intense molecular ion peak at 468 in mass spectrum are also in agreement with the structure of the *bis* thiourea compound (**2**). Further, the bisthiourea (**2**) on treating with phenacylbromide (prepared by treating 5 mmol of acetophenone with mixture of potassium bromide and potassium bromate (2:1, 1 g, 5 mmol available bromine) in the presence 1 N hydrochloric acid) in presence of catalytic amount of iodine undergoes Hantzsch thiazole condensation followed by E_1 elimination gives corresponding bisthiazolidene product (**3i**)[15]. The formation of the bisthiazolidene product was confirmed from mass spectrum which showed the m/z values 671. Then, the proton NMR values was also in agreement with the 4,4'-(N,N'-*bis*(3,4-diphenyl-thiazol-2-ylidene))methylenedianiline product (**3i**). To carry out the reaction in shorter time and in convenient method, the ethanol solution of bisthiourea (**2**) was treated with acetophenone in presence of iodine as the reagent and allowed to reflux the reaction mixture for 2 h. We found that the time for completion of the reaction was reduced and yield comparatively higher than in the above method. Further, we carried out the heterocyclization by non-conventional method using ultrasonication, the reaction was found to be completed within 22 min. We finally concluded that the reaction was easily carried out in ultrasonication method with good yield and shortest time period. Both the conventional and non-conventional methods were followed to carry out the heterocyclization of bisthiourea (**2**) with various substituted acetophenones, the corresponding bisthiazolidenes were obtained. The mass spectra and the proton NMR values were in agreement with the expected products (**3ii-3v**). The yields and the reaction times were compared and found the better results in non-conventional method.

Conclusion

We designed and synthesized the hitherto unreported 4,4'-[N,N'-*bis*(3-phenyl-4-(4-substituted phenyl)-thiazol-2(3*H*)-ylidene)]methylenedianiline derivatives in good yields by non-conventional method using ultrasonication and moderate yield by conventional method. This methodology has been confirmed by the synthesis of various bisthiazolidene derivatives.

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