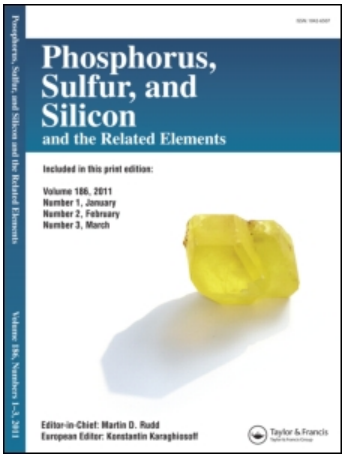

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: THE REACTIVITY OF ALKYLAZOLES TOWARDS ELECTROPHILIC REAGENTS

Salem E. Zayed[a]; Suzan Ibrahim Aziz[b]; Ayman Wahba Brian[b]; Rafat Milad Mohareb[b]; Eiman I. Abou Elmaged[b]; S. A. Metwally[c]; M. H. Elnagdil[d]
[a] Chemistry Department, Faculty of Science, Kena, Egypt [b] Chemistry Department, Faculty of Science, Cairo University, Giza, A. R., Egypt [c] Chemistry Department, Faculty of Science, Assiut University, Egypt [d] Chemistry Department, Faculty of Science, University of Kuwait, Safat, Kuwait

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: THE REACTIVITY OF ALKYLAZOLES TOWARDS ELECTROPHILIC REAGENTS

SALEM E. ZAYED,*‡ SUZAN IBRAHIM AZIZ,†
AYMAN WAHBA ERIAN,† RAFAT MILAD MOHAREB,†
EIMAN I. ABOU ELMAGED,† S. A. METWALLY§ and M. H. ELNAGDI¶

†*Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt;*
‡*Chemistry Department, Faculty of Science, Kena 83511 Egypt;* §*Chemistry Department, Faculty of Science, Assiut University, Egypt;* ¶*Chemistry Department, Faculty of Science, University of Kuwait, P.O. Box 5969, Safat, 13060 Kuwait*

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Several new condensed thiadiazoles and thiazoles and thiazoles are synthesized. The reactivity of alkylazoles towards electrophilic reagents is reported. New synthesis of thenylthiadiazoles, thiadiazolopyridines and pyridazines could be achieved.

Key words: Thiazoles and thiadiazoles, alkylheteroaromatics, and nucleophilic reagents and alkylazoles.

INTRODUCTION

Polyfunctionally substituted heteroaromatics are important as pharmaceuticals,[1,2] agrochemical[3–5] and as potential intermediates in dye industry.[6,7] In previous work from our laboratories we have developed efficient synthesis to different substituted alkylazoles and alkylazines we could show that these compounds are excellent precursors for synthesis of polyfunctionally substituted condensed azoles and condensed azines.[8,9]

RESULTS AND DISCUSSION

Work aimed at the exploration of the potential of thiadiazole (1) and thiazole (2) as precursors for polyfunctionally substituted heteroaromatics is reported here. Active methylene nitriles have been shown to condense with methyl and methylene ketones to yield aminothiophene derivatives.[10] This reaction has been extensively investigated and a variety of aminothiophenes could be prepared utilizing this procedure. Azolyl and azinyl acetonitriles have never been utilized as the active methylene component in these reactions. Refluxing (1) with acetone in ethanolic triethylamine results in the formation of the acetonylidene derivative 3a in 80% yield. Further heating of (3a) with sulfur in DMF solution resulted in the formation of the thiophenylthiadiazole derivative (4a). Compound 4a was formed directly

from the reaction of 1 with acetone and sulfur in refluxing DMF solution. Similar to its behaviour with acetone, 1 also reacted with acetophenone to yield (3b) in 60% yield. Refluxing the latter derivative in DMF in presence of sulfur and piperidine afforded (4b) (Chart 1).

Compound 1 reacted with malononitrile to afford a product that may be formulated as 5–7 (Chart 2). Monocyclic structures 5 and 6 were readily ruled out by the ^{1}H NMR of these products. Structure 7 was preferred based on ^{1}H NMR which showed, in addition to imine and amine protons, a C-H singlet at 7.5 ppm.

The reaction of (1) with acetylacetone in the presence of sulfur afforded a product of molecular formula $C_{16}H_{14}N_4OS_2$. This was formulated as (10). Compound (10) is assumed to be formed via the condensation of 1 with acetylacetone to give the condensate intermediate (8). The latter in presence of sulfur affords the thioamide derivative (9) which cyclized under the reaction conditions to the final isolated product (10) (Chart 2).

Although some electron rich strained thiophenes have been recently found to undergo 4 + 2 cycloaddition with electron poor olefins[10,11] 4a, b did not react with electron poor olefins under a variety of conditions.

The methyl function in 3a showed reactivity toward electrophilic reagents. Coupling with benzenediazonium chloride afforded the pyridazine derivatives (13). Also 3a with benzylidenemalononitrile yielded (16) which is formed via the inter-

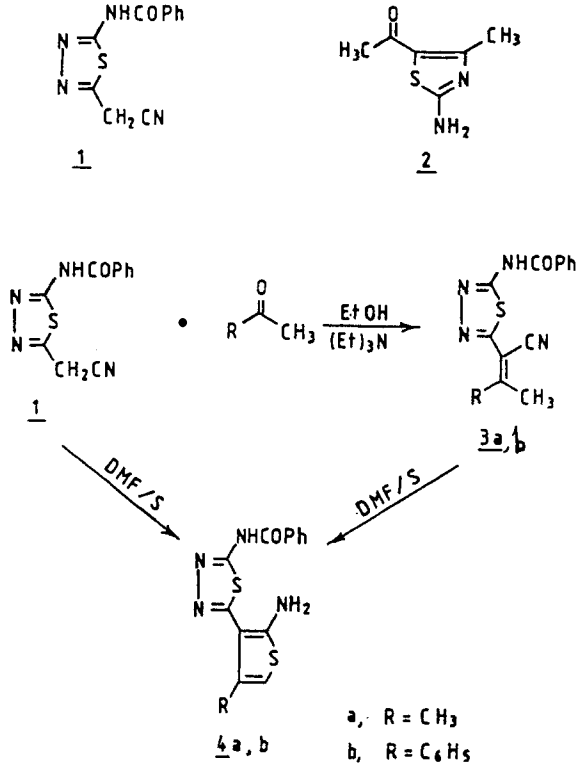

CHART 1

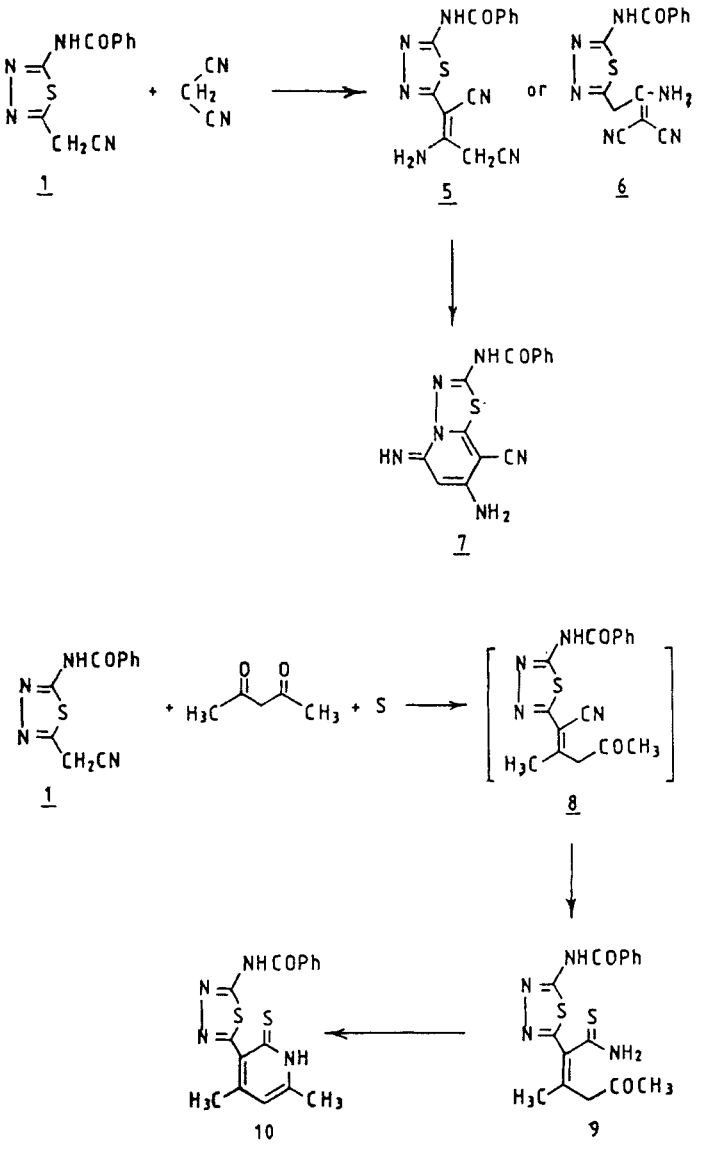

CHART 2

mediates (14) and (15) (Chart 4). A similar mechanism has been suggested previously to account for formation of benzoazines from alkylazinyl carbonitriles.[8]

Attempts to prepare the condensate product (18) or (19) by direct reaction of (2) with aryladehyde (17) failed, the reaction giving instead of the Schiff's base (20a–c) (Chart 5). Attempted nitrosation of (2) in orthophosphoric acid resulted only the diazonium salt 21a which is coupled readily with several active hydrogen reagents. Thus, it coupled with β-naphthol (22) to give (23). Similarly, coupling with acetylacetone afforded the hydrazone (24) (Chart 4).

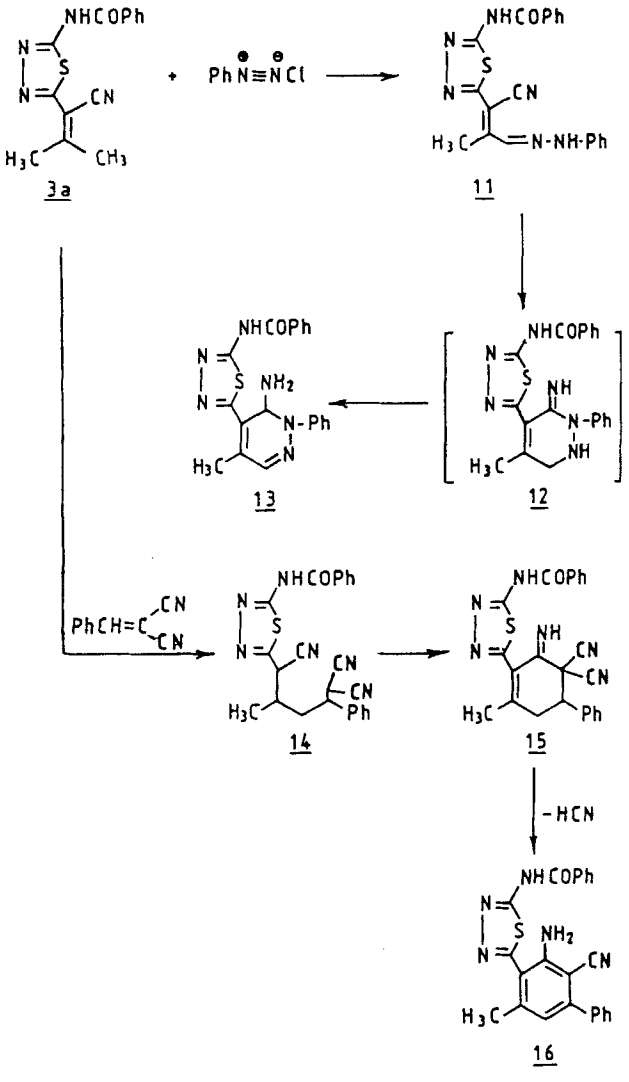

CHART 3

EXPERIMENTAL

All melting points are uncorrected, IR spectra were obtained on a Pye Unicam SP 1000 spectrophotometer using KBr discs. ^{1}H-NMR were recorded on a Varian EM 390-90 MHz, using TMS as the internal reference. The chemical shifts were expressed as 8 ppm. Analytical data were obtained from the microanalytical unit at Cairo University.

2-(5-N-benzoylamino-1,3,4-thiadiazol-2-yl)acetonitrile (1): A suspension of benzoylisothiocyanate (1.63 g, 0.01 mol) in dioxane was treated with cyanoacetic acid hydrazide (0.99 g, 0.01 mol). The reaction mixture was refluxed for 3 hours, then left to cool. The solid product, so formed, was collected by filtration. Recrystallization from dioxan afforded a pale yellow crystals, m.p. 220°C (83%). Analysis for $C_{11}H_8N_4OS$ (244.12). Calcd. C, 54.12, H, 3.3; N, 22.9; S, 13.1. Found C, 54.1 H, 3.2; N, 22.9; S, 13.1%. I.R 3300 cm^{-1} (NH), 2250 cm^{-1} (—CN), 1680 (C = 0) ^{1}H NMR, δ, 4.58 (s, 2H, CH_2), 7.32–7.46 (m, 5H, C_6H_5), 11.91 (s, 1H, NH).

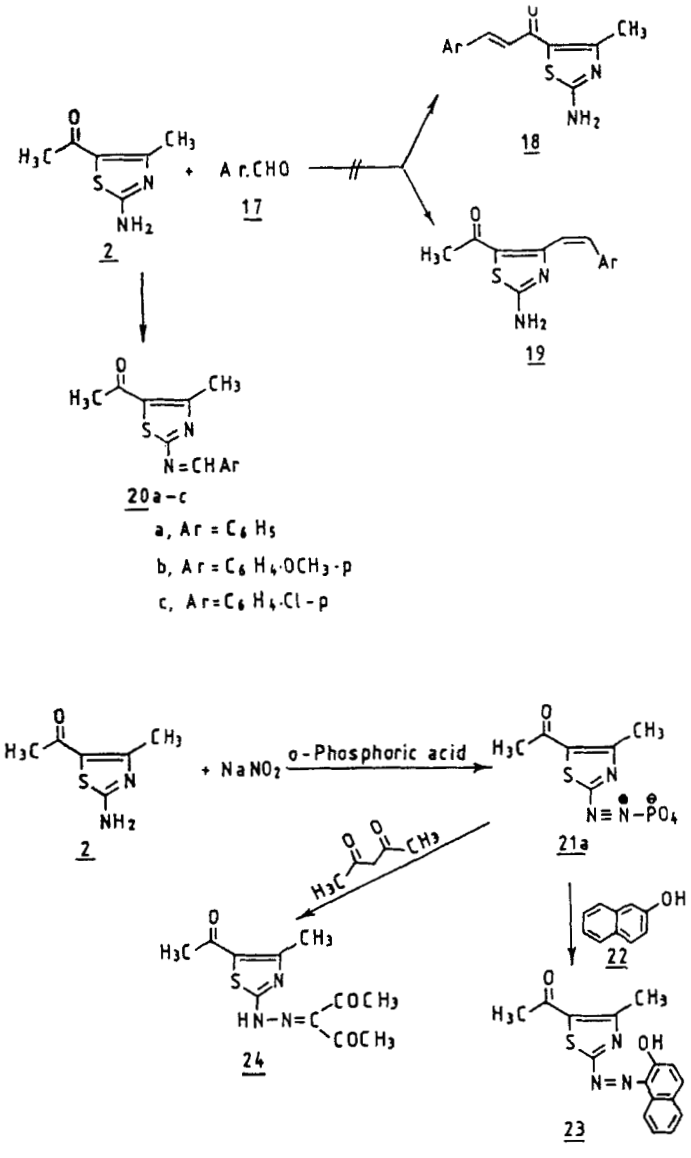

CHART 4

5-Acetyl-4-methlthiazole-2-amine (2): A suspension of thiourea (0.76 g, 0.01 mol) in ethanol was treated with α-chloro-acetyloacetene (1.16 g, 0.01 mol). The mixture was refluxed for 30 minutes then left to cool and the formed product was collected and recrystallized from ethanol (66%) m.p. 215°C. Analysis for $C_6H_8N_2OS$(156.13) Calcd. C, 46.15, H, 5.16; N, 17.94; S, 20.49%. Found C, 46.1, H, 5.1, N, 18.0; S, 20, 5% I.R 3350 cm^{-1}(NH_2), 2920 (CH_3), 1680 cm^{-1} (C = 0) ^1H NMR, δ. 2.21–2.29 (2s, 6H, $2CH_3$), 5.32 (s, 2H, NH2).

Reaction of thiadiazole (1) *with ketones* (3a, b): A suspension of 1 (2.4 g, 0.01 mol) in ethanol (30 ml) and catalytic amount of triethylamine was treated with acetone, acetophenone (0.01 mol), the reaction mixture was refluxed for 3 hours, then left to cool. The resulting solution was poured onto

water and acidified with dilute hydrochloric acid. The solid products, so formed, were collected by filtration and crystallized from ethanol.

Compound 3a. Brown crystals (81%), m.p. 156°C. Analysis for $C_{14}H_{12}N_4OS$ (284.26) Calcd. C, 59.1, H, 4.2; N, 19.7, S, 11.2%. Found C, 59.1; H, 4.2; N, 19.7; S, 11.2%. I.R 3300 cm^{-1} (NH), 2920 cm^{-1} (CH_3), 2250 cm^{-1} (CN), 1680 cm^{-1} (C = 0). ^1H NMR, δ 2.7 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 7.4–8.1 (m, 5H, aromatic protons), 13.0 (s, br, 1H, NH).

Compound 3b. Brown crystals (62%), m.p. 160°C. Analysis for $C_{19}H_{14}N_4OS$ (346.33) Calcd. C, 65.8, H, 4.0; N, 16.1, S, 9.2%. Found C, 65.8; H, 4.1; N, 16.1; S, 9.3%. I.R 2245 cm^{-1} (CN), 1665 cm^{-1} (C = 0), ^1H NMR, δ 2.98 (s, 3H, CH_3), 6.8 (s, b 1H, NH, C = 0), 7.4–7.6 (m, 5H, C_6H_5) 7.85–8.2 (m, 5H, C_6H_5).

5-(4-Substituted-thein-3-yl-2-amine)-1,3,4-thiadiazole-2-N benzolyamine (4a, b): Solutions of 3a, b (0.01 mol) in DMF (20 ml) and a catalytic amount of piperdine were treated with sulfur (0.32 g, 0.01 mol). The reaction mixture was refluxed for 3 hours, then left to cool. The resulting solution was poured onto water and acidified with dilute hydrochloric acid. The solid products, so formed, were collected by filtration and crystallized from ethanol.

Compound 4a. Obtained in the form of brown crystals (62%) m.p. 165°C). Analysis for $C_{14}H_{12}OS_2$ (316.26). Calcd. C, 53.1; H, 3.8; N, 17.7; S, 20.2%. Found C, 53.2; H, 3.8; N, 17.7; S, 20.4%, IR. 3410–3320 cm^{-1} (NH_2 + NH), 2920 cm^{-1} (CH_3), 1680 cm^{-1} (C = 0). ^1H NMR δ 2.2 (s, 3H, CH_3), 6.98 (s, 1H, thiophen 5-H); 7.3–8.11 (m.5H.C_6H5), 5.3 (s, 2H, NH_2), 8.35 (s, 1H, NH).

Compound 4b. Separated in the form of brown needles (59%), m.p. 180°C). Analysis for $C_{19}H_{14}N_4OS_2$ (378.33), Calcd. C, 60.3; H, 3.7; N, 14.8; S, 16.9%. Found C, 59.9; H, 3.5; N, 14.9; S, 16.6% I.R. 3400-3310 cm^{-1} (NH_2 + NH), 1668 cm^{-1} (C = 0).

6-Amino-2-benzoylamino-4-imino-1,3,4-thiadiazolo [2,3-a] pyridine-7-carbonitrile (7): A suspension of 1 (2.4 g, 0.01 mol) in dioxane (30 ml) and a catalytic amount of piperidine was treated with malononitrile (0.66 g, 0.01). The reaction mixture was refluxed for 3 hours, then left to cool. The resulting solution was poured onto water and acidified with dilute hydrochloric acid. The solid product, so formed was collected by filtration and recrystallized from ethanol as a lemon yellow crystals (64%) m.p. 155°C. Analysis for $C_{14}H_{10}N_6OS$ (310.26) Calcd. C, 54.2; H, 3.2; N, 27.0; S, 10.3%. Found C, 54.1; H, 3.2; N, 26.8; S, 10.1%, IR. 3450-3310 cm^{-1} (NH_2, +NH), 2245 cm^{-1} (CN), 1655 cm^{-1} (C = 0), ^1H NMR. δ 7.0–8.2 (m, 6H, C_6H_5 + pyridine H-5), 8.3 (s, br, 2H, NH_2) 12.10 (s, 1H, NH).

1,2-Dihydro-4,6-dimethyl-3-(2-benzoylamino-thiadiazole-5-yl) pyridine-2-thione (10): A suspension of 1 (2.4 g, 0.01 mol) in dioxane (30 ml) and a catalytic amount of piperidine was treated with acetylacetone (1 g, 0.01 mol), and sulphur (0.32 g, 0.01 mol). The reaction mixture was refluxed for 5 hours, then left to cool. The resulting solution was poured onto water and acidified with dilute hydrochloric acid. The solid product, so formed was collected by filtration. Recrystallization from ethanol gave brown crystals (65%) m.p. 176°C. Analysis for $C_{16}H_{14}N_4OS_2$ (342.3) Calcd. C, 56.1; H, 4.1; N, 16.3; S, 18.7%. Found C, 56.0; H, 4.1; N, 16.2; S, 18.5%, I.R. 3330 cm^{-1} (NH), 2920 cm^{-1} (CH_3), 1675 cm^{-1} (C = 0). ^1H NMR, δ 2.3 (s, 3H, CH_3), 2.7. (s 3H, CH_3), 7.2–8.2 (m, 6H, C_6H_5 + H_3-pyridine). 8.4 (s, br-2H, 2-NH), 11.8 (s, br 1H, N_1H – pyridine).

5-(2-Benzoylamino-1,3,4-thiadiazol-5-yl)-4-methyl-6-imino-1-phenylpyridazine (13): A cold solution of the diazonium salt (0.01 mol) (prepared by adding sodium nitrite solution (0.69 g, 0.01 mol) to a cold solution of aniline (0.93 g, 0.01 mol) containing the appropriate amount of hydrochloric acid (6 ml) with stirring) was added to a cold solution of 3a (2.8 g, 0.01 mol) in ethanol (30 ml) containing sodium hydroxide (2g). The solid product, so formed, was collected by filtration. Recrystallization from acetic acid obtained red crystals (52%), m.p. 210°C. Analysis for $C_{20}H_{18}N_6OS$ (390.39) Calcd. C, 61.5; H, 4.6; N, 21.5 S, 8.2%. Found, C, 61.6; H, 4.6; N, 21.6; S, 8.5%, I.R. 3400-3300 cm^{-1} (NH_2 + NH), 2920 cm^{-1} (CH_3), 1675 cm^{-1} (C = 0). ^1H NMR, δ 2.5 (s, 3H, CH_3); 4.2. (s, br, 2H, NH_2), 7.2–7.7 (m, 5H, C_6H_5), 7.72–8.3 (m, 5H, C_6H_5), 13.1 (s, br, 1H, NH).

5-(4-Methyl-6-phenylanthranilonitrile 3-yl)-1,3,4-thiadiazole-2-benzoylamine (16): A solution of 3a (2.8 g, 0.01 mol) in pyridine (20 ml) was treated with benzylidenemalononitrile (1.5 g, 0.01 mol). The reaction mixture was refluxed for 8 hours, then left to cool. The resulting solution was poured onto water and acidified with dilute hydrochloric acid to give a brown crystals on recrystallization from ethanol (56%), m.p. 190°C. Analysis for $C_{23}H_{17}N_5OS$ (411.4), Calcd. C, 67.14; H, 4.1; N, 17.0; S, 7.7%. Found C, 67.0; H, 4.0; H, 17.2; S, 7.9%, I.R. 3360 cm^{-1} (NH_2), 2920 cm^{-1} (CH_3) 2240 cm^{-1} (CN), 1668 cm^{-1} (C = 0). ^1H NMR, δ 2.5 (s, 3H, CH_3); 4.25 (s, br, 2H, NH_2), 7.32–7.9 (m, 6H, C_6H_5 + 1H, C_6H_1), 12.9 (s, 1 H, NH).

5-Acetyl-4-methylthiazol-2-N-arylideneamine (20a–c): A solution of 2 (1.56 g, 0.01 mol) in DMF (20 ml) and a catalytic amount of piperidine was treated with appropriate aldehydes (0.01 mol). The reaction mixture was refluxed for 8 hours, then left to cool. The resulting solutions were poured onto water and acidified with dilute hydrochloric acid. The solid products so formed, were collected by filtration and recrystallized from ethanol to give yellow products. 20a was obtained in 62% yield m.p. 220°C. Analysis for $C_{13}H_{12}N_2OS$ (244.24). Calcd. C, 63.9; H, 4.9; N, 11.4; S, 13.1%, Found C, 63.9; H, 4.5; N, 11.4; S, 13.0%, I.R. 3360 cm^{-1} (NH_2), 2920 cm^{-1} (CH_3); 2225 cm^{-1} (CN), 1677 cm^{-1} (C = 0). 1H NMR δ. 2.5 (2s, 6H, $2CH_3$); 4.25 (s, br, 2H, NH_2), 7.3–7.7 (m, 6H-C_6H_5 + 1H-styryl).

20b was obtained in 58% yield, m.p. 270°C. Analysis for $C_{14}H_{14}N_2O_2S$ (274.25). Calcd. C, 61.3; H, 5.1; N, 10.2; S, 11.6%, Found C, 61.2; H, 5.0; N, 10.1; S, 11.5%. I.R. 2920 cm^{-1} (CH_3), 1680 cm^{-1} (C = 0) ^1H NMR δ 2.22 (s, 3H—CH_3), 3.3 (s, 3H.0-CH_3), 6.9–7.5 (m ~ 6H, 1H styryl + C_6H_5).

20c was obtained in 61% yield, m.p. 275°C. Analysis for $C_{13}H_{11}N_2$ ClOS (278.73), Calcd. C, 56.0; H, 3.9; N, 10.0; S, 11.5%, Found C, 56.1; H, 4.0; N, 10.1; S, 1.6%, I.R. 1680 cm^{-1} (C = 0), 2920 cm^{-1} (CH_3). ^1H NMR δ 2.2–2.3 (s, 3H, CH_3), 6.93 (s, 1H, CH=N), 7.3–7.9 (m, 4H, C_6H_4).

Coupling of aminothiazoles (23 *and* 24): A cold solution of the diazonium salt (0, mol) (prepared by adding, with stirring, sodium nitrite solution (0.69 g, 0.01 mol) to a cold solution of 2 (1.56 g, 0.01 mol) containing the appropriate amount of o-phosphoric acid) was added to a cold solution of β-naphthol, acetylacetone (0.01 mol) in ethanol (30 ml) containing sodium hydroxide (*2g*). The solid products, so formed, were collected by filtration.

Compound 23 was recrystallized from dioxan in the form of reddish yellow crystals (52%) m.p. 185°C. Analysis for $C_{16}H_{13}N_3O_2S$ (311.27), Calcd. C, 61.7; H, 4.2; N, 13.4; S, 10.2%, Found C, 61.6; H, 4.2, N, 13.3; S, 10.0%, I.R. 3500 cm^{-1} (OH), 2920 cm^{-1} (CH_3), 1680 cm^{-1} (C = 0), 1590 cm^{-1} (C=N).

Compound 24 was recrystallized from benzene in the form of dark green crystals (42%) m.p. 152°C. Analysis for $C_{11}H_{13}N_3O_3S$ (267.21) Calcd. C, 49.4; H, 4.9; N, 15.7; S, 11.9%, Found C, 49.3, H, 5.0; N, 15.6; S, 12.0%. I.R. 3300 cm^{-1} (NH), 2920 cm^{-1} (CH_3), 1690 cm^{-1} (C = 0), 1595 cm^{-1} (C = N), ^1H NMR, δ 2.22 (2s, 6H, 2—CH_3, CO), 2.45–2.48 (2s, 6H, 2—CH_3), 8.21 (s, 1H, NH).

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