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Note

Synthesis and characterization of some novel isoxazoles and 1,5-benzothiazepines bearing *s*-triazine nucleus

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The title compounds **7a-d** and **8a-d** have been prepared starting from chalcones **6a-d** having *s*-triazine nucleus. These chalcones **6a-d** on cyclisation with hydroxylamine hydrochloride in presence of alkali and 2-aminothiophenol in presence of a few drops of glacial acetic acid give isoxazoles **7a-d** and 1,5-benzothiazepines **8a-d** respectively. All the products have been characterized by elemental analysis, IR, ^{1}H NMR and LCMS data.

Keywords: Isoxazoles, 1,5-benzothiazepines, glacial acetic acid, alkali, spectral data

The *s*-triazine nucleus containing chalcones and their derivatives have their own importance in heterocyclic chemistry due to their good biological activity. Chalcones have been studied extensively because of their wide range of biological activity. They are found to be effective as antiinflammatory[1], antibacterial[2], antiviral[3], cardiovascular[4] and anticancer[5] agents. The diverse properties of chalcones have prompted their synthesis in order to study their biological and pharmacological activity. Five membered heterocycles like isoxazoles have found wide application as pharmaceutical and agrochemical agents. The synthesis of isoxazole derivatives has attracted considerable attention from organic and medicinal chemists due to their considerable bioactivity. Various biological applications have been reported for isoxazoles such as antitumor[6], analgesic[7], antimicrobial[8] and chemotherapy[9]. 1,5-Benzothiazepines are gaining more attention due to their pharmacological significance. Compounds like Diltiazem[10] and Clentiazem are well explored as effective cardiovascular drugs and found to contain 1,5-benzothiazepine nucleus. Some of the benzothiazepines have been claimed to exhibit antispasmodic[11], neurolaptic[12] and antidepressant[13] activity.

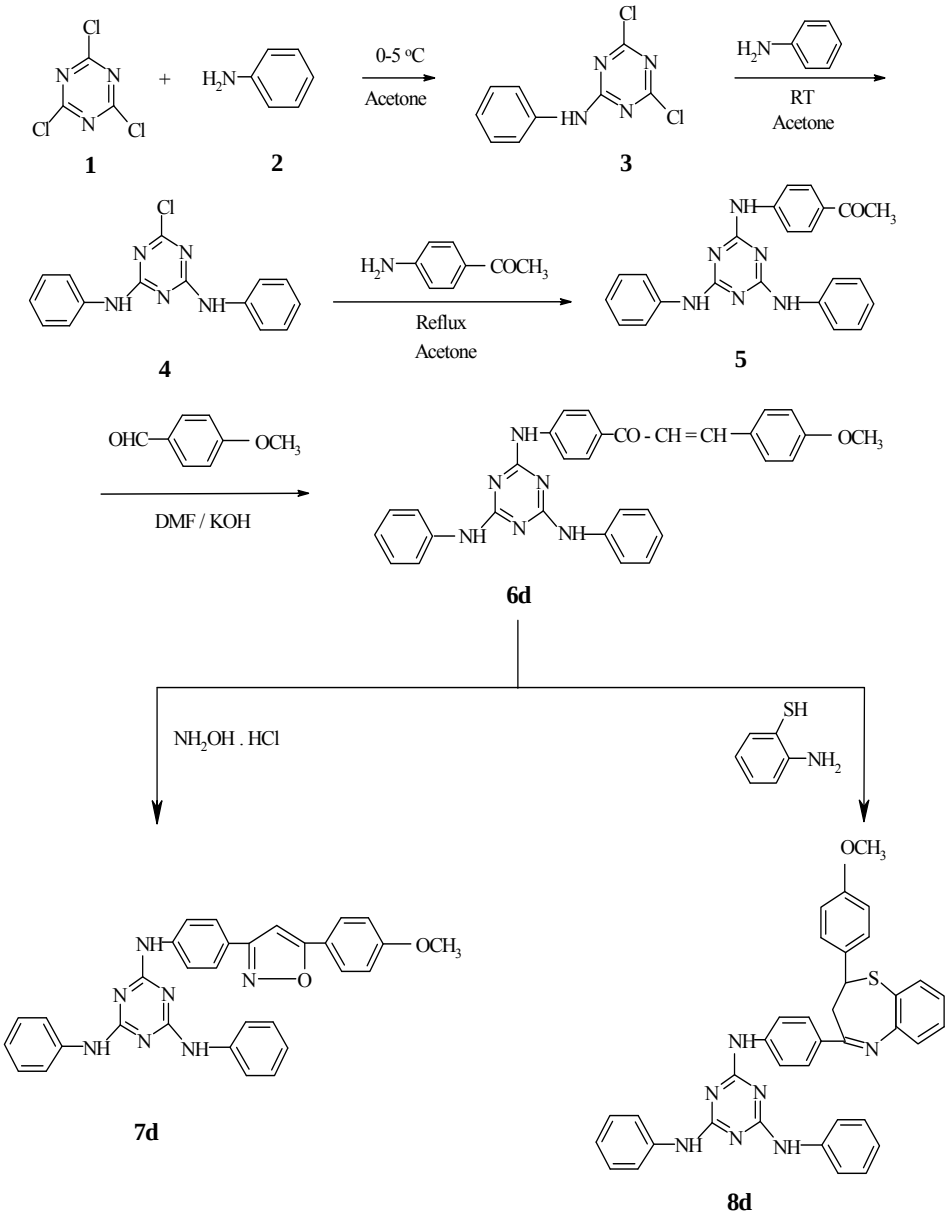
Results and Discussion

The required precursor 2,4-bis-(phenylamino)-6-[4′-{3″-(substituted phenyl)-2″-propenon-1″-yl}-phenylamino]-*s*-triazines **6a-d** were prepared from cyanuric chloride according to reported procedure[14,15]. The product **7d** was obtained by the treatment of **6d** with hydroxylamine hydrochloride in presence of alkali and well characterized from its spectral and analytical characterization data. Its IR spectra revealed the presence of -C=N group (isoxazole moiety) by exhibiting a strong absorption band at 1583 cm^{-1}. The ^{1}H NMR spectrum of **7d** in $CDCl_3$ showed two singlets at δ 3.88 and at 6.90 due to C_4‴-OCH_3 and C_4″-H of isoxazole ring protons. The complex multiplet at δ 7.00-7.90 is assigned for 21 aromatic protons. This was also supported by the mass spectrum of the compound which displayed the molecular ion peak at *m/z* 527. The C, H and N analysis of the compound **7d** was in good agreement with the proposed molecular formula $C_{31}H_{25}N_7O_2$.

Further, the reaction of **6d** with 2-aminothiophenol in presence of a few drops of glacial acetic acid was carried out with an interest that the reaction would proceed as shown in **Scheme I** and at the end, this attempt yielded **8a-d**. The IR spectrum of **8d** showed a strong absorption band at 1573 cm^{-1} due to -C=N group (benzothiazepine moiety). The ^{1}H NMR spectrum exhibited the following resonance, doublet of doublet at 3.10 for C_3″-H_a, doublet of doublet at 3.30 for C_3″-H_b, singlet at 3.89 for C_4‴-OCH_3 and doublet of doublet at 5.00 for C_2″-H_x proton. The aromatic cluster appeared at δ 6.90-8.10 with 25 aromatic protons. This was also supported by the electron ionization mass spectrum of the compound which displayed the molecular ion peak at *m/z* 621. The elemental analysis was also in good agreement with the molecular formula $C_{37}H_{31}N_7OS$.

Experimental Section

All the melting points were determined in an open capillary and are uncorrected. The reactions were monitored on TLC. The IR spectra were recorded in KBr pellets on a Perkin-Elmer 237 spectrometer. ^{1}H NMR spectra on a Bruker Avance DPX 400 MHz spectrometer with $CDCl_3$ as a solvent, using TMS as internal reference. Elemental analysis were carried out



Scheme I

on a Carlo Erba 1108 model analyzer. Mass spectra were recorded on a Hewlett Packard LCMS.

Preparation of 2-phenylamino-4,6-dichloro-*s*-triazine[16]**, 3**. Aniline (0.01 mole) was added slowly to cyanuric chloride (0.01 mole) in acetone (30 mL) with constant stirring over a period of 4 hr at 0 to 5°C. Then sodium carbonate (0.005 mole) dissolved in water (10 mL) was added dropwise to neutralize HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **3**; m.p. 196°C, yield 86%.

Preparation of 2,4-bis-(phenylamino)-6-chloro-*s*-triazine, 4. Aniline (0.01 mole) was added slowly to compound **3** (0.01 mole) in acetone (35 mL) with constant stirring over a period of 6 hr at RT. Then sodium carbonate (0.005 mole) dissolved in water (10 mL) was added dropwise to neutralize HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **4**; m.p. 179°C, yield 80%; IR (KBr): 772 (C-Cl), 1359 (C-N), 805 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 7.20 to 7.80 (m, 10 Ar-H and 2 NH).

Preparation of 2,4-bis-(phenylamino)-6-(4′-acetyl-phenylamino)-*s*-triazine, 5. 4-Aminoacetophenone (0.01 mole) and compound **4** (0.01 mole) were dissolved in acetone (40 mL). The reaction mixture was refluxed for 6 hr, cooled and poured into crushed ice. Then sodium carbonate (0.005 mole) dissolved in water (10 mL) was added to neutralize HCl evolved during the reaction. The solid separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **5**; m.p. 218°C, yield 75%; IR (KBr): 1662 (C=O), 1355 (C-N), 805 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 2.6 (s, 3H, $-COCH_3$), 7.0 to 7.95 (m, 14 Ar-H and 3 NH).

Preparation of 2,4-bis-(phenylamino)-6-[4′-{3″-(4‴ - methoxyphenyl) - 2″-propenon-1″-yl}-phenyl-amino]-*s*-triazine, 6d. Compound **5** (0.01 mole) was dissolved in DMF (30 mL) and 4-methoxy-benzaldehyde (0.01 mole) was added to it. Then a solution of KOH (5 mL of a 40% aqueous solution) was added to the reaction mixture with constant stirring at RT. After 24 hr the reaction mixture was poured into crushed ice and neutralized with HCl. The solid product separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **6d**; m.p. 174°C, yield 66%; IR (KBr): 1647 (C=O), 1595 (-CH=CH-, str.), 1340 (C-N), 812 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.98 (s, 3H, $C_4‴$-OCH_3), 6.90 (d, lH, -CO-CH=), 7.15 to 7.80 (m, 18 Ar-H and 3 NH), 8.05 (d, 1H, Ar-CH=).

Similarly, the remaining compounds **6a-c** were prepared by this method.

General procedure for the preparation of of 2,4-bis-(phenylamino) - 6-[4′-{5″-(substitutedphenyl)-isoxazole - 3″ - yl}-phenylamino] - *s*-triazine, 7a-d. Compound **6a-d** (0.01 mole) was dissolved in alcohol (25 mL) and hydroxylamine hydrochloride (0.01 mole) was added to it. Then a solution of KOH (5 mL of a 40% aqueous solution) was added to the reaction mixture and refluxed for 6 hr. The reaction mixture was then cooled, poured into crushed ice and the solid product separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **7a-d**.

2,4-Bis-(phenylamino)-6-[4'-{5″-(4‴-chlorophe-nyl)-isoxazole-3″-yl}-phenylamino]-*s*-triazine, 7a: Yield 61%; m.p. 130°C; IR (KBr): 1580 (C=N, isoxazole moiety), 807 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 6.92 (s, 1H, $C_4″$-CH of isoxazole moiety), 7.00 to 8.15 (m, 18 Ar-H and 3 NH); MS: *m/z* 531.5. Anal. Calcd. for $C_{30}H_{22}N_7OCl$: C, 67.73; H, 4.14; N, 18.44. Found: C, 67.72; H, 4.12; N, 18.42%.

2,4-Bis-(phenylamino)-6-[4′-{5″-(4‴-nitrophenyl)-isoxazole-3″-yl}-phenylamino]-*s*-triazine, 7b: Yield 57%; m.p. 134°C; IR (KBr): 1579 (C=N, isoxazole moiety), 805 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 6.90 (s, 1H, $C_4″$-CH of isoxazole moiety), 7.00 to 7.90 (m, 18 Ar-H and 3 NH); MS: *m/z* 542. Anal. Calcd. for $C_{30}H_{22}N_8O_3$: C, 66.42; H, 4.06; N, 20.66. Found: C, 66.41; H, 4.08; N, 20.67%.

2,4-Bis-(phenylamino)-6-[4′-{5″-(3‴,4‴-dimeth-oxyphenyl)-isoxazole-3″-yl}-phenylamino]-*s*-triazi-ne, 7c: Yield 59%; m.p. 210°C; IR (KBr): 1581 (C=N, isoxazole moiety), 806 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.75 (s, 3H, $C_3‴$-OCH_3), 3.86 (s, 3H, $C_4‴$-OCH_3), 6.89 (s, 1H, $C_4″$-CH of isoxazole moiety), 7.00 to 7.90 (m, 17 Ar-H and 3 NH); MS: *m/z* 557. Anal. Calcd. for $C_{32}H_{27}N_7O_3$: C, 68.94; H, 4.85; N, 17.59. Found: C, 68.91; H, 4.83; N, 17.60%.

2,4-Bis-(phenylamino)-6-[4′-{5″-(4‴-methoxyphe-nyl)-isoxazole-3″-yl }-phenylamino]-*s*-triazine, 7d: Yield 61%; m.p. 108°C; IR (KBr): 1584 (C=N, isoxazole moiety), 808 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.88 (s, 3H, $C_4‴$-OCH_3), 6.91 (s, 1H, $C_4″$-CH of isoxazole moiety), 7.00 to 7.90 (m, 18 Ar-H and 3 NH); MS: *m/z* 527. Anal. Calcd. for $C_{31}H_{25}N_7O_2$: C, 70.59; H, 4.74; N, 18.60. Found: C, 70.62; H, 4.75; N, 18.61%.

General procedure for the preparation of 2,4-bis-(phenylamino)-6-[4′-{2″-(substituted phenyl)-2″,3″-dihydro-1″,5″-benzothiazepine-4″-yl}-pheny-lamino]-*s*-triazine, 8a-d. Compound **6a-d** (0.01 mole) was dissolved in alcohol (25 mL) and 2-aminothiophenol (0.01 mole) was added to it. Then a few drops of glacial acetic acid was added to the reaction mixture and refluxed for 10 hr. The reaction mixture was then cooled, poured into crushed ice and the solid product separated out was filtered, washed with water, dried and purified by recrystallization from alcohol to give **8a-d**.

2,4-Bis-(phenyl amino)-6-[4′-{2″-(4‴-chlorophe-nyl)-2″, 3″ - dihydro-1″, 5″-benzothiazepine-4″-yl}-phenyl amino]-*s*-triazine, 8a: Yield 59%; m.p. 80°C; IR (KBr): 1570 (C=N, benzothiazepine moiety), 734 (C-S-C, benzothiazepine moiety), 806 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.11 (dd, 2H, $C_3″$-H_a of benzothiazepine moiety), 3.34 (dd, 2H, $C_3″$-H_b of benzothiazepine moiety), 5.10 (dd, 1H, $C_2″$-H_x of benzothiazepine moiety), 6.90 to 8.10 (m, 22 Ar-H and 3 NH); MS: *m/z* 625.5. Anal. Calcd. for

$C_{36}H_{28}N_7SCl$: C, 69.06; H, 4.48; N, 15.67. Found: C, 69.05; H, 4.46; N, 15.65%.

2,4-Bis-(phenyl amino)-6-[4′-{2″-(4‴-nitrophenyl)-2″,3″-dihydro-1″,5″-benzothiazepine-4″-yl}-phenyl amino]-*s*-triazine, 8b: Yield 56%; m.p. 90°C; IR (KBr): 1569 (C=N, benzothiazepine moiety), 732 (C-S-C, benzothiazepine moiety), 807 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.00 (dd, 2H, C_3''-H_a of benzothiazepine moiety), 3.25 (dd, 2H, C_3''-H_b of benzothiazepine moiety), 5.10 (dd, 1H, C_2''-H_x of benzothiazepine moiety), 6.90 to 8.10 (m, 22 Ar-H and 3 NH); MS: *m/z* 636. Anal. Calcd. for $C_{36}H_{28}N_8SO_2$: C, 67.92; H, 4.40; N, 17.61. Found: C, 67.89; H, 4.39; N, 17.64%.

2,4-Bis-(phenyl amino)-6-[4′-{2″-(3‴,4‴-dimethoxyphenyl)-2″,3″-dihydro-1″,5″-benzothiazepine-4″-yl}-phenyl amino]-*s*-triazine, 8c: Yield 60%; m.p. 99°C; IR (KBr): 1583 (C=N, benzothiazepine moiety), 730 (C-S-C, benzothiazepine moiety), 804 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.15 (dd, 2H, C_3''-H_a of benzothiazepine moiety), 3.36 (dd, 2H, C_3''-H_b of benzothiazepine moiety), 3.73 (s, 3H, C_3'''-OCH_3), 3.84 (s, 3H, C_4'''-OCH_3), 5.15 (dd, 1H, C_2''-H_x of benzothiazepine moiety), 6.90 to 8.10 (m, 21 Ar-H and 3 NH); MS: *m/z* 651. Anal. Calcd. for $C_{38}H_{33}N_7SO_2$: C, 70.05; H, 5.07; N, 15.05. Found: C, 70.08; H, 5.06; N, 15.07%.

2,4-Bis-(phenyl amino)-6-[4′-{2″-(4‴-methoxyphenyl)-2″,3″-dihydro-1′,5″-benzothiazepine-4″-yl}-phenyl amino]-*s*-triazine, 8d: Yield 63%; m.p. 75°C; IR (KBr): 1573 (C=N, benzothiazepine moiety), 731 (C-S-C, benzothiazepine moiety), 806 cm^{-1} (C-N, *s*-triazine); ^1H NMR ($CDCl_3$): δ 3.05 (dd, 2H, C_3''-H_a of benzothiazepine moiety), 3.33 (dd, 2H, C_3''-H_b of benzothiazepine moiety), 3.89 (s, 3H, C_4'''-OCH_3), 5.00 (dd, 1H, C_2''-H_x of benzothiazepine moiety), 6.90 to 8.10 (m, 22 Ar-H and 3 NH); MS: *m/z* 621. Anal. Calcd. for $C_{37}H_{31}N_7OS$: C, 71.49; H, 4.99; N, 15.78. Found: C, 71.46; H, 5.01; N, 15.81%.

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