Synthesis and some novel reactions of 8-chloro-2*H*-[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-3,4-dione and 6-chloro-2-hydrazino-1,3-benzothiazole

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3,8-Dichloro-4*H*-[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-4-one on reaction independently with sodium hydroxide solution and sodium azide undergo novel ring contraction reactions to give 7-chloro[1,2,4]triazolo[3,4-*b*][1,3]benzothiazole and 8-chloro tetrazolo[1′,5′:1,5][1,2,4]triazolo[3,4-*b*][1,3]benzothiazole respectively.

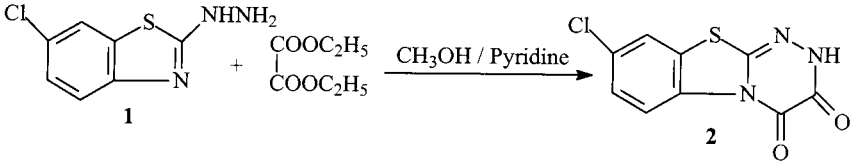
Keywords: 3,8-Dichloro-4*H*-[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-4-one, Favorskii ring contraction reaction, simple route for trisubstituted triazoles.

A large number of uses have been suggested for 1,2,4-triazines, reduced 1,2,4-triazines and condensed 1,2,4-triazines in literature. The preparations and uses of 4-amino-6-substituted-1,2,4-triazines as herbicides are well revealed in the patents.[1-4] From this series, 4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5-one has emerged as a well-known and widely used herbicide. Another group of biochemically active 1,2,4-triazine derivatives are the 5-nitro-2-furyl substituted-1,2,4-triazines. These compounds are useful as antibacterials and showed[5-7] tuberculostatic activities. Since benzothiazoles are also biologically quite active,[8-10] it was surmised that fused *as*-triazinobenzothiazoles would exhibit interesting properties. A survey of literature reveals that very little work has been carried out on the synthesis and chemistry of *as*-triazines fused with benzothiazole system. The present work is aimed at the preparation of some derivatives of this series for future evaluation.

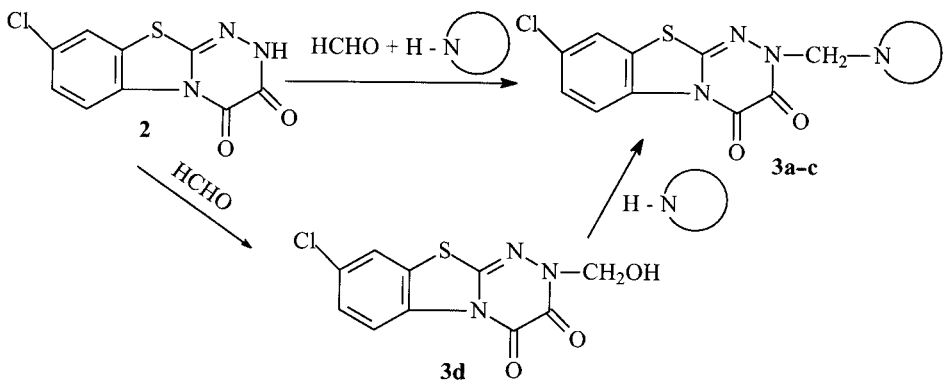
A number of reports have appeared recently on the synthesis and biological activities of simple and fused-*s*-triazoles.[11-13] The methods reported in the literature[14-17] for the preparation of 1,3,5-trisubstituted-*s*-triazoles are cumbersome. Hence, a simple route for the synthesis of such compounds is being reported here.

Result and discussion

In continuation of our studies on synthesis and reactions of 2*H*-[1,2,4]triazino[3,4-b][1,3]benzothiazole-3,4-dione,[18] we report herein synthesis and some novel reactions of a new heterocycle, 8-chloro-2*H*-[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-3,4-dione **2** which was prepared by refluxing 6-chloro-2-hydrazino-1,3-benzothiazole in methanol in the presence of pyridine with diethyl oxalate for **4h** (Scheme 1). Compound **2** contains replaceable active-NH. Hence, three Mannich bases **3a–c** were prepared by heating parent lactam compound **2** in dioxane independently with cyclic secondary amines (morpholine, piperidine, pyrollidine) and formaldehyde at 60 °C. These Mannich bases **3a–c** were also prepared from **2** by the stepwise reaction through the formation of 8-chloro-2-hydroxymethyl[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-3,4-dione **3d** (Scheme 2). Further, compound **2** when treated with phosphoryl chloride for 2 h yielded 3,8-dichloro-[1,2,4]triazino [3,4-*b*][1,3]benzothiazole-4-one, **4** (Scheme 3). Compound **4**



Scheme 1



- N = Morpholino (3a); Pipweidino (3b), Pyrrolidino (3c)

Scheme 2

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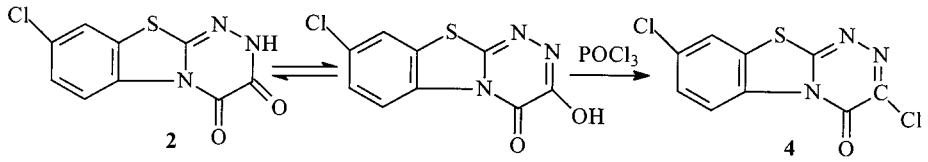


Scheme 3

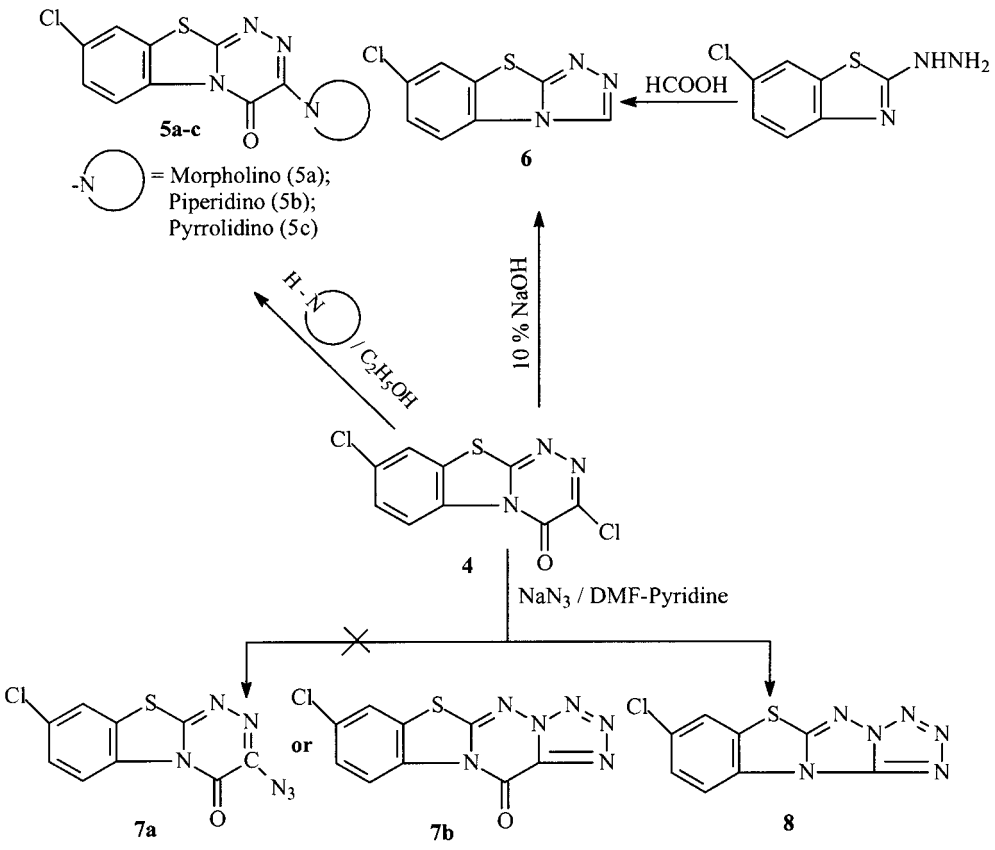
on treatment independently with cyclic secondary amines *viz*. morpholine, piperidine and pyrollidine afforded 3-morpholino **5a**, 3-piperidino **5b** and 3-pyrollidino-4*H*-[1,2,4]triazino[3,4-*b*][1,3]benzothiazole-4-one **5c** respectively (Scheme 4).

α-Haloketones on treatment with sodium hydroxide solution undergo the well known Favorskii rearrangement to form carboxylates. To investigate whether such type of rearrangement is possible with the chloro compound **4** as well, compound **4** was boiled with 10% NaOH solution for 1 h. In this reaction, an entirely different product, 7-chloro[1,2,4]triazolo[3,4-*b*][1,3]benzothiazole **6** was obtained in 65% yield (Scheme 4). Its formation was confirmed by its elemental analysis, spectral data and undepressed mixed melting point with an authentic sample which was prepared by heating 6-chloro-2-hydrazino-1,3-benzothiazole with formic acid at 140 °C for 1.5 h. It clearly indicated that compound **4** on boiling with NaOH solution underwent decarboxylation with ring contraction to form a new fused heterocycle, 7-chloro[1,2,4]triazolo[3,4-*b*][1,3]benzothiazole **6**. A tentative mechanism can be adduced as shown in Scheme 5. It is a new convenient route for the preparation of substituted 1,2,4-triazolobenzothiazoles.

Another ring contraction reaction was also investigated by reacting the chloro compound **4** with sodium azide in a weak basic medium. Compound **4** when heated with sodium azide in DMF and pyridine for 4 h, the formation of compound, **7a** or **7b** was expected but the reaction resulted in the formation of pale yellow compound which has been assigned the structure, 8-chlorotetrazolo[1',5': 1,5][1,2,4] triazolo[3,4-*b*][1,3]benzothiazole **8** on the basis of elemental analysis and spectral data (Scheme 4). Its IR spectrum showed the absence of strong absorbtion band in the region 1650–1700 cm^{-1} due to carbonyl group and strong stretching absorption in the region 2120–2160 cm^{-1} due to $–N_3$, which should have been there if the compound had structure **7a** or **7b**.

In our earlier publication, we reported[19] a simple route, for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles. Following the same route we report herein synthesis of 1-(6-chloro-1,3-benzothiazol-2-yl)-3,5-dimethyl-1*H*-1,2,4-triazole **9a**, 1-(6-chloro-1,3-benzothiazol-2-yl)-3,5-dipheny-1*H*-1,2,4-triazole **9b** and 1-(6-chloro-1,3-benzothiazol-2-yl)-3,5-di(*p*-tolyl)-1*H*-1,2,4-triazole **9c**. 6-Chloro-2-hydrazine-1,3-benzothiazole was heated in the presence of anhydrous aluminium chloride independently with two mole of acetonitrile, benzonitrile and *p*-tolunitrile in an oil bath at 130–140 °C (for acetonitrile) and at 160–170 °C (for benzonitrile/*p*-tolunitrile) for **3h** to obtain **9a**, **9b**, and **9c** respectively (Scheme 6).

Thus, in conclusion the present research paper deals with new convenient routes for the synthesis of substituted [1,2,4]triazolobenzothiazoles, tetrazolotriazolobenzothiazoles and 3,5-disubstited-1*H*-1,2,4-triazoles.



Scheme 4

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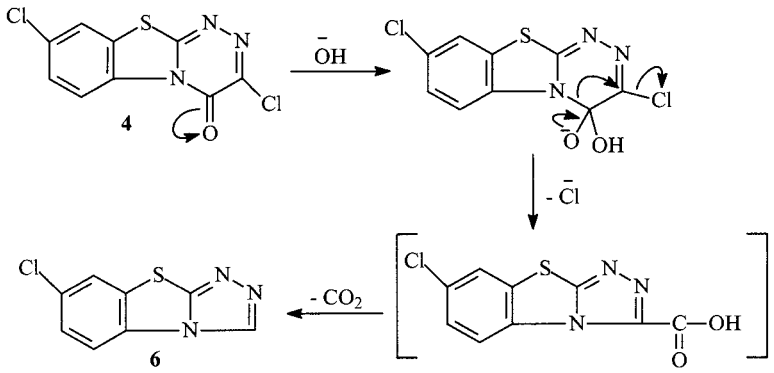
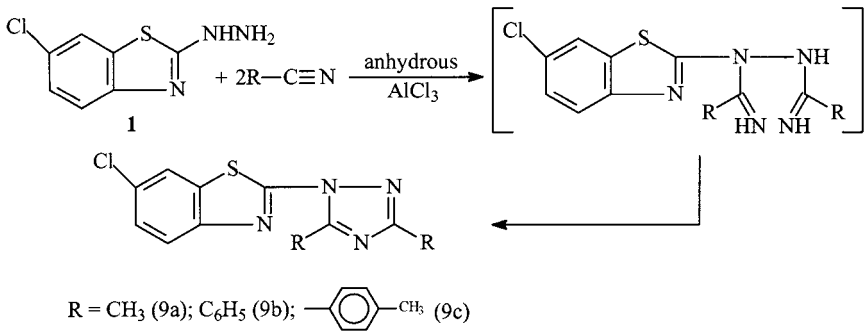


Scheme 5



Scheme 6

Experimental

All melting points were determined in capillary tube and uncorrected. IR spectra were recorded in potassium bromide pellets on a Bomen, MB 104 FT infrared spectrophotometer. The ^{1}H NMR were obtained on a FT Gemino 60 (60MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a FT VG-7070H mass spectrophotometer using the EI technique at 70ev. Microanalysis was performed on a Heraeus CHN–O Rapid analyzer. All the reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel-G plate using iodine vapour for detection.

8-Chloro-2H-[1,2,4]triazino[3,4-b][1,3]benzothiazole-3,4-dione (**2**): A mixture of 8-chloro-2-hydrazino-1,3-benzothiazole (1.99g, 0.01 m mole), methanol (20 ml), pyridine (0.5 ml) and diethyl oxalate (6 ml) was refluxed on a water bath for 4 h. The insoluble product obtained was filtered, washed with water and then with ethanol. It was crystallised from dioxane to collect 1.5g 60% of **2**, m.p. 292 °C. EI-MS (*m/z* - RA%): 255 (M+2, 30), 253 (M^+, 90), 225 (10), 169 (100), 142 (30); IR (cm^{-1} KBr): 3190, 1720, 1680, 1610, 1590, 1500, 1330; ^{1}H NMR (DMSO, ppm): (7.3–8.1 (m,3H, Ar-H), 12.1 (s,1H, NH, exchange with D_2O). Found: C, 42.48; H, 1.39; N, 16.40; $C_9H_4N_3O_2$ SCl requires: C, 42.68; H, 1.58; N, 16.60.

8-Chloro-2-(morpholino/pyridino/pyrollidino)methyl[1,2,4]triazino [3,4-b][1,3]benzothiazole-3,4-diones (**3a–c**): A mixture of 2 (2.53g, 0.01 m mole) dioxane (25 ml), formaldehyde (38/41, w/v; 2 ml) and appropriate cyclic secondary amine (0.01mmole) was refluxed on a water bath at 60 °C for 2 h and the mixture was kept over night. The products **3a–c** thus obtained were crystallised from DMF-ethanol solvent.

3a: 2.8g (80%) m.p. 295 °C; IR (cm^{-1}, KBr): 3010, 1710, 1680, 1610, 1580, 1490, 1320; ^{1}H NMR (DMSO–d_6),: (3.1(t, 4H, two–N–CH_2), 3.5 (s, 2H, –N–CH_2–N), 4.3 (t, 4H, two–OCH_2), 7.2–7.9 (m, 3H, Ar–H). Found: C, 47.52; H, 3.41; N, 15.69. $C_{14}H_{13}N_4O_3SCl$ requires C, 47.72; H, 3.71; N, 15.90.

3b: 2.7g (75%) m.p. 270 °C; IR (cm^{-1}, KBr): 3000, 1700, 1670, 1600, 1570, 1480, 1310; ^{1}H NMR (DMSO–d_6): (1.3 (quintet, 2H,CH_2), 1.8 (quintet,4H two CH_2), 3.1 (t, 4H, two–NCH_2), 3.6 (s, 2H, –N–CH_2–N). 7.3–7.7 (m, 3H, Ar–H). Found: C, 51.12; H, 4.08; N, 15.84. $C_{15}H_{15}H_4O_2SCl$ requires C, 51.42; H, 4.28; N, 16.00.

3c: 2.8g (80%) m.p. 220 °C; IR (cm^{-1}, KBr): 3015, 1715, 1685, 1595, 1570, 1500, 1330; ^{1}H NMR (DMSO–d_6): (1.5 (quintet, 4H, two CH_2), 3.0 (t, 4H, –two N–CH_2), 3.5 (s, 2H, –N–CH_2–N). 7.4–7.9 (m, 3H, Ar–H). Found: C, 49.75; H, 3.62; N, 16.45. $C_{14}H_{13}N_4O_2SCl$ requires C, 50.00; H, 3.86; N, 16.66.

*Alternative route for the preparation of **3a–c**. 8-Chloro-2-hydroxymethyl[1,2,4]triazino[3,4-b][1,3]benzothiazole-3,4-dione* **3d**: A mixture of 2 (2.53 g, 0.01 mmole) dioxane (25 ml) and formaldehyde (38/41w/v, 2 ml) was refluxed on a water bath at 60 °C for 1 h and the mixture was kept over night. The product thus obtained was crystallised from benzene to give **3d**. 2.22 g (80%), m.p. > 300 °C; IR (cm^{-1}, KBr): 3300, 3010,1720, 1680, 1600, 1570, 1490, 1050; ^{1}H NMR ($CDCl_3$), 3.5 (s, 2H, N–CH_2–O), 4.2 (s, 1H, –OH), 7.3–7.8 (m, 3H, Ar–H). Found: C, 42.10; H, 1.93; N, 14.64. $C_{10}H_6N_3O_3SCl$ requires C, 42.40; H, 2.13; N, 14.84.

A mixture of **3d** (2.84 g, 0.01 m mole) dioxane (25 ml) and appropriate secondary amine (0.01 m mole) was heated on a water bath at 60 °C for 2 h. The mixture was cooled and the products thus obtained were crystallised from proper solvents. Their melting points were undepressed on admixture with the samples **3a–c** prepared by the above method.

3,8-Dichloro-4H-[1,2,4]triazino[3,4-b][1,3]benzothiazole-4-one (**4**): A mixture of 2 (2.53 g, 0.01 m mole) and phosphorous oxychloride (40 ml) was refluxed for 2 h. After cooling the contents were poured into ice and kept overnight. The separated solid was filtered washed with water and crystallised from dimethyl formamide to give **4**. 1.35 g (50%), m.p. 320 °C; EI–MS (*m/z*: RA%): 273 (M+2, 13), 271(M^+, 39), 243 (40), 208(20), 169(100), IR(cm^{-1}, KBr): 3010, 1680, 1600, 1580, 771: ^{1}H NMR (DMSO-d_6): (7.4–7.9 (m, 3H, Ar–H). Found: C, 39.65; H, 1.01; N, 15.21. $C_9H_3N_3OSCl_2$ requires C, 39.85; H, 1.10; N, 15.49.

8-Chloro-3-(morpholino/pyridino/pyrilidino)-4H-[1,2,4]triazino [3,4-b][1,3]benzothiazole-4-one (**5a–c**): A mixture of **4** (2.71 g, 0.01 m mole), ethanol (25 ml) and 2 ml of appropriate cyclic secondary amine (morpholine/piperidine/pyrollidine) was refluxed on a water bath for 2 h and the mixture was kept over night. The solid product thus obtained was filtered and crystallised from proper solvent to give **5a–c**.

5a: 2.10 g (65%), m.p. 240 °C; IR(cm^{-1}, KBr): 3010, 1680, 1600, 1580, 771; ^{1}H NMR (DMSO-d_6): (3.3 (t, 4H, two N–CH_2), 4.1 (t, 4H, two OCH_2), 7.4–7.9 (m, 3H, ArH) Found: C,48.14; H, 3.21; N,17.10. $C_{13}H_{11}N_4O_2SCl$ requires C, 48.44; H, 3.41; N, 17.39.

5b: 2.40 g (75%), m. p. >300 °C; IR(cm^{-1}, KBr): 3000, 1670, 1600, 1570, 1490; ^{1}H NMR (DMSO-d_6): (1.4 (quintet, 2H, CH_2), 1.9 (quintet, 4H, two CH_2), 3.3 (t, 4H, two–NCH_2–), 7.2–7.6 (m, 3H,

Ar–H). Found: C, 52.30; H, 3.92; N, 17.31 $C_{14}H_{13}N_4OSCl$ requires C, 52.50; H, 4.06; N, 17.50.

5c: 2.23 g (70%), m.p. >300 °C; IR(cm^{-1}, KBr): 3005, 1685, 1600, 1575, 1490; ^1H NMR (DMSO-d_6): (1.6 (quintet, 4H, two CH_2), 3.2 (t, 4H, two N–CH_2), 7.3–7.7 (m, 3H, Ar–H) Found: C, 50.78; H, 3.39; N, 18.10. $C_{13}H_{11}N_4OSCl$ requires C, 50.98; H, 3.59; N, 18.30.

7-Chloro[1,2,4]triazolo[3,4-b][1,3]benzothiazole from **4** (**6**): Compound **4** (1 g) was refluxed with NaOH solution (10%, 20 ml) for 1 h. On cooling, a crystalline compound was separated. It was filtered and dissolved in HCl solution. It was filtered again and the filtrate neutralised with NaOH solution. A solid compound thus separated was filtered and crystallised from ethanol to get **6**. 1.2 g (60%), m.p. 280 °C; EI-MS (*m/z*, RA%) 210 ($M+2$, 25), 208 (M^+,75), IR (cm^{-1}, KBr): 3010, 1600, 1570, 1500; ^1H NMR ($CDCl_3$): (7.4–7.9 (m, 3H, Ar–H), 8.5 (s, 1H, CH) Found: C, 46.05; H, 1.28; N, 20.02. $C_8H_3N_3SCl$ requires C, 46.15; H, 1.44; N, 20.19.

7-Chloro[1,2,4]triazolo[3,4-b][1,3]benzothiazole from 6-chloro-2-hydrazino-1,3-benzothiazole (**6**): A mixture of 6-chloro-2-hydrazino-1,3-benzothiazole **1** (1 g) and formic acid (10 ml) was refluxed over an oil bath at 140 °C for 1.5 h. The contents of the flask were cooled and poured on crushed ice with stirring. The white product was filtered, washed with water and recrystallised from ethanol to get **6**. 1.3 g (65%) m.p. 280 °C; mixed point with the compound prepared from **4** was undepressed.

8-Chlorotetrazolo[1',5';1,5][1,2,4]triazolo[3,4-b][1,3]benzothiazole (**8**): A mixture of **4** (2.71 g, 0.01 m mole), DMF (25 ml), Pyridine (1 ml) and sodium azide (0.5 g) was refluxed for 3 h. After cooling, the solid that separated was extracted with ether. The ether was evaporated and the solid product obtained was crystallised from minimum quantitiy of DMF to give **8**. 1.5 g (60%), m.p. 305 °C; EI-MS (*m/z*. RA%), 252 (M+2, 10), 250 (M^+, 30), IR (cm^{-1}, KBr); 2990, 1620, 1600, 1590, 1500, 1380; ^1H NMR ($CDCl_3$): (7.3–7.6 (m, 3H, Ar–H). Found: C, 38.25; H, 1.1; N, 33.42. $C_8H_3N_6SCl$ requires C, 38.4; H, 1.2; N, 33.6.

1-(6-Chloro-2-benzothiazolyl)-3,5-dimethyl/3,5-diphenyl/3,5-di(p-tolyl)-1H-1,2,4-triazole (**9a/9b/9c**): A mixture of 8-chloro-2-hydrazino-1,3-benzothiazole (1.99 g, 0.01 m mole), powered anlydrous aluminium chloride (6 g) and the appropriate alkyl / aryl nitrile (0.045 mmole) was heated in an oil bath at 130–140 °C (for acetonitrile) and at 160–170 °C (for benzonitrile/*p*-tolunitrile) for 3 h, then kept at room temperature for 0.5 h and decomposed with ice cold HCl. It was kept overnight and alkyl/aryl nitrile removed by steam distillation. The solid compound was filtered and crystallised from ethanol to give **9a/9b/9c**.

9a: 1.84 g (70%), m. p. 340 °C, IR(cm^{-1}, KBr): 3010,2900, 1600, 1570, 1535, 1260; ^1H NMR (DMSO-d_6): (1.5 (s, 6H, two CH_3), 7.3–7.7 (m, 3H, Ar–H) Found: C, 49.80; H, 3.10, N, 21.01. $C_{11}H_9N_4SCl$ requires C, 50.00; H, 3.40; N; 21.21.

9b: 2.47 g (65%), m. p. 242 °C, IR(cm^{-1}, KBr): 2995, 1600, 1580, 1500, 1270; ^1H NMR (DMSO-d_6): (7.2–7.9 (m, 13H, Ar–H). Found: C, 64.64; H, 3.15,: N, 14.13. $C_{21}H_{13}N_4SCl$ requires C, 64.95; H, 3.35; N, 14.43.

9c: 2.91 g (70%), m. p. 286 °C, IR(cm^{-1}, KBr): 3010, 2990, 1600, 1550, 1500, 1460, 1285; ^1H NMR (DMSO-d_6): (1.9 (s, 6H, Ar–CH_3), (7.3–8.0 (m, 11H, Ar–H) Found: C, 66.14; H, 3.88; N, 13.25. $C_{23}H_{17}N_4SCl$ requires C, 66.34; H, 4.08; N, 13.46.

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