Research Article

Magnetic Resonance in Chemistry

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Synthesis and characterization of benzothiazolyl-substituted anils

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New Schiff bases containing a hydroxynaphthyl ring and substituted benzothiazolyl groups have been synthesized. High-resolution NMR spectra confirmed that these anils exist as enol–keto tautomers in solution. The results from NMR data demonstrated that the proportion of enol tautomer exceeded 90% in these substituted anils. Some compounds exhibited thermochromism in solid state. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: synthesis; benzothiazoles; Schiff bases; thermochromism

Introduction

Schiff bases derived from hydroxynaphthaldehyde have attracted many researchers due to the wide application of these compounds as photochromic/thermochromic precursors.[1–6] Recently, Asiri *et al*. prepared Schiff bases derived from 2-hydroxynaphaldehyde or 2-hydroxybenzaldehyde and amino piperizine or pyridine compounds.[2] Based on the spectral characteristics, the authors concluded that compounds derived from the 2-hydroxylbenzaldehyde showed preference toward enol tautomers, whereas the 2-hydroxylnaphthaldehyde-substituted Schiff bases showed the presence of both keto and enol tautomers. Recently, Sashidara *et al*. showed formation of the keto-enamine tautomer with chromenedicarboxylaldehyde-related Schiff bases.[3] Using high-field NMR, they were able to determine the structure of these keto-enamines with accuracy. Benzothiazole and thiazole compounds may find biomedical applications. For example, ^{11}C-labeled (*N*-methyl-[^{11}*C*]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole has been used to image amyloid in patients with Alzheimer's disease.[7–18] We describe the synthesis and characterization of anils bearing both hydroxynaphthyl and substituted benzothiazolyl groups.

Results and Discussion

The synthesis of benzothiazolyl-substituted Schiff base was accomplished following Scheme 1.

In brief, appropriate amino-substituted benzothiazolyl compounds were condensed with 2-hydroxy naphthaldehyde in absolute ethanol to furnish the required anils. Hydroxy naphthaldehyde was chosen to facilitate further functionalization of these Schiff bases. These anils were obtained as crystalline solids with colors varying from bright yellow to orange at room temperature (Table 1).

The UV/VIS spectrum of these anils in both methanol and chloroform showed an intense absorption peak at approximately 405–420 nm (Table 2). Additional absorption peaks were also observed around 340 nm. The long wavelength absorption observed is due to the presence of naphthyl rings in the structure of these anils.

The FTIR spectra were similar for most of the anils with the presence of a broad band between 3500 and 3400 cm^{-1} due to either the OH of the enol or the NH groups associated with the keto tautomer (Table 2). Peaks at 1720 and 1625 cm^{-1} were observed, indicative of C═O or C═N stretching. The observed peaks in the IR spectra suggest the presence of both enol and keto tautomeric forms.

Generally, the keto–enol tautomers pass through equilibrium, and Scheme 2 illustrates the complex equilibrium between each of the species based on the present compound reported.

It can be seen from the scheme that the proton from the enol compound is transferred to the nitrogen atom forming a zwitterionic intermediate. This zwitterionic intermediate can rearrange to form a keto tautomer by shifting the double bond to the aromatic moiety. In an acidic environment, the keto tautomer gets protonated at the nitrogen atom forming a quaternary ammonium species. This quaternary ammonium species subsequently transfers the proton to the oxygen atom of the keto tautomer forming a protonated enolic species. Finally, this proton is released to form the original enolic compound. Depending on the structure and substituents present either in benzothiazole or naphthylene moiety; this equilibrium can be altered to form the more stable compound. Additionally, both temperature and solvent conditions can change the stability of one tautomer to another.

In essence, the keto–enol tautomerism is a complex phenomenon, which exists especially in certain Schiff bases. Furthermore, in our structural feature of the anil, we can anticipate a strong hydrogen bond between the proton and the oxygen or nitrogen atom, depending on whether it is enol or keto form, adding stability for the tautomers by forming a stable six-membered ring

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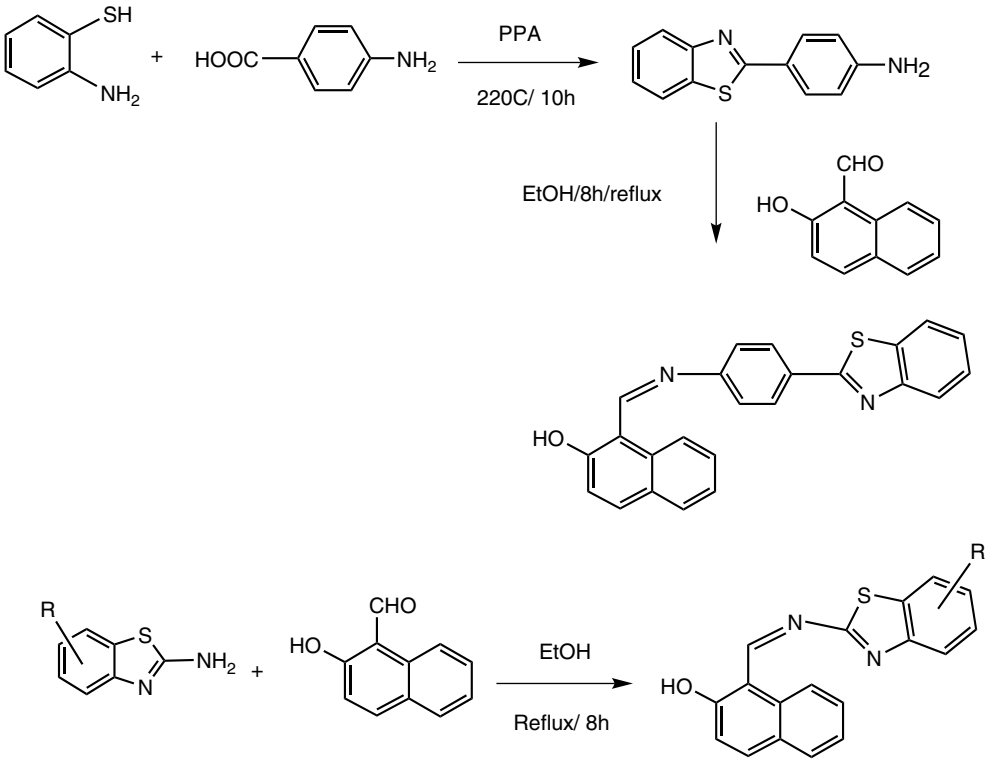
Magnetic Resonance in Chemistry



Scheme 1. Synthetic scheme for preparation of benzothiazolyl-substituted anils.

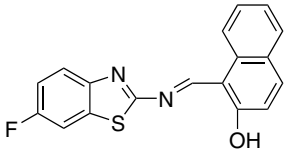
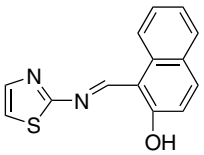
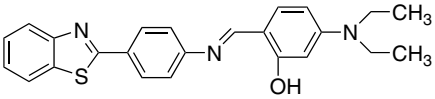
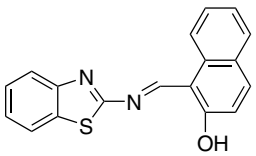
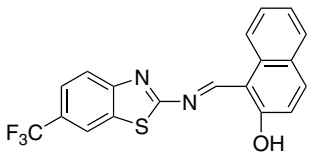
(III and IV), which, in principle, should enhance the stability of the tautomers. This is shown below in Scheme 3.

The stabilization of this structure with a six-membered ring causes a planar configuration for these compounds. Additionally, the hydrogen bond can easily be formed from structure I when compared with structure II, and the likely reason for such a trend lies in the fact that structure I retains the aromaticity on the naphthyl ring through the conjugation between the benzothiazolyl and naphthalene rings. On the other hand, the possibility of maintaining the aromaticity on the naphthyl ring is reduced considerably in structure II. Due to the presence of the planar structure, the electron delocalization can take place conveniently to the entire aromatic rings present in these anils. In this context, several reports have appeared describing the keto–enol tautomerism of naphthyl-substituted Schiff bases.[19–31] Based on the literature precedence of such an equilibrium system, we examined the NMR spectra of these anils to evaluate the nature of species present in solution, and the following paragraphs highlight the data obtained for all compounds.

The ^{1}H NMR spectra of the anils containing substituted benzothiazolyl rings in their structure were examined (Table 3). The ^{1}H NMR spectrum showed a broad signal at $\delta = 14.40$ ppm. This broad signal was assigned to the hydroxyl proton of the enol tautomer. The extreme high-frequency shift exhibited by this proton is ascribed due to the formation of a hydrogen bond to the nitrogen atom as discussed previously. In the previous reports,[1–3] the presence of hydrogen bonding in the enol tautomer has been deduced from the chemical shift of the OH protons with a broad singlet at approximately $\delta = 14$ ppm. Based on this literature, we suggest that our anils exist predominantly as enol tautomer. The signal at $\delta = 10.19$ ppm corresponds to the olefinic proton (=CH) next to the nitrogen atom. It is known that this proton appears typically in a range from $\delta = 7.9$ to 8.9 ppm in most of the reported compounds. An energy minimization calculation using within ChemBio3D Ultra using the MMFF94 force field with 5000 iterations with a convergence criteria of 0.01 RMS for the gradient resulted in a planar molecule. We propose that this planar conformation of our compounds accounts for high chemical shift value of this proton due to the ring-current effect from the naphthyl ring. Depending on the groups attached to the aromatic ring, the chemical shift of the neighboring proton showed considerable change. For example, the unsubstituted benzothiazolyl proton (H18) appeared at $\delta = 7.95$ ppm, whereas the monofluoro substitution shielded this proton ($\delta = 7.54$ ppm). Similarly, when a CF_3 group was introduced, this proton signal appeared at $\delta = 8.14$ ppm. Furthermore, this proton showed coupling to the fluorine atoms in the CF_3 group resulting in a complex multiplet. All other ^{1}H chemical shifts are consistent with those reported in the literature for other anils.[2]

We also analyzed the ^{13}C NMR spectra for these benzothiazolyl-substituted anils and found the following trend (Table 3). The $(N)_2$-C-S carbon signal appeared at $\delta = 168–171$ ppm for all derivatives. This deshielding of the benzothiazolyl carbon is due to the presence of three bonded heteroatoms. The aromatic C–OH carbon signals appeared in the range of $\delta = 166–168$ ppm in all the compounds providing evidence that these compounds exist predominately as enol tautomers in solution; the C=O signal of the keto tautomer generally appears $\delta > 170$ ppm. It has also been found that the imine carbon (N=CH, C11) showed a chemical shift value of $\delta = 160–161$ ppm in all compounds. Finally, the (C1) carbon showed the largest shielding, $\delta = 109–110$ ppm. In essence, the ^{13}C chemical shifts obtained for these compounds strengthen our hypothesis that the enol–enamine structure was predominant for these benzothiazolyl-substituted anils. The other signals were consistent with the structure of the compounds.

Table 1. Physical properties of the anils[a]

Structure of compounds	Color of the product	Keto (%)	Enol (%)
 **1**	Orange crystals	1	99
 **2**	Brownish yellow crystals	6	94
 **3**	Golden shiny yellow crystals	3	97
 **4**	Orange yellow crystals	2	98
 **5**	Deep yellow crystals	6	94

[a] The percentages of keto/enol tautomers were calculated from the relative ^{1}H signal integration ratios between keto and enol tautomers. Aromatic protons were used for these calculations.

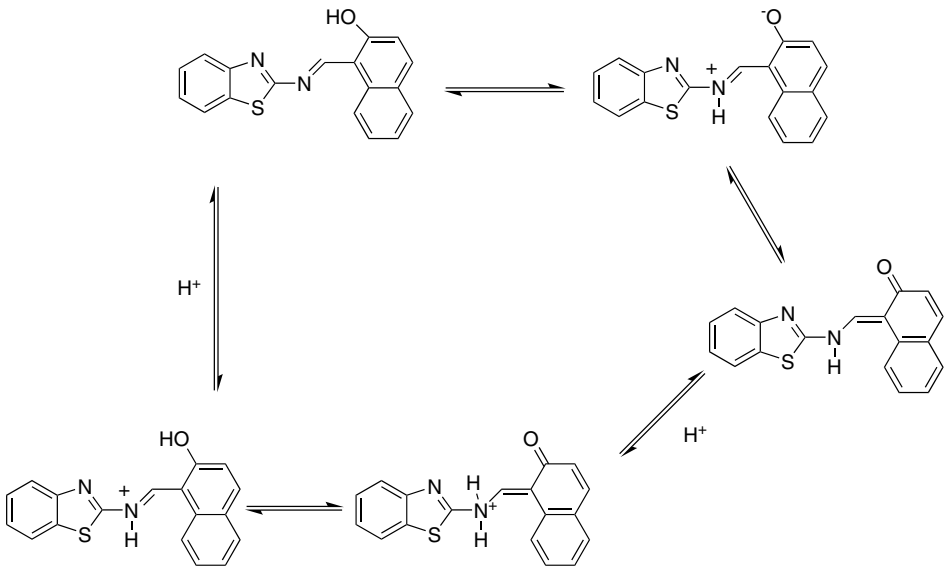
Table 1 shows the percentage of keto–enol compounds in solution, which was calculated from integrating the corresponding proton peaks. In some cases, the aromatic signals were used to estimate this relative values. Caution should be exercised here because the percentage of keto form of some compounds is very low, and, therefore, the percentages reported are only approximate values. We also used the method of Olivieri[22] and Alarcon *et al.*[32] to calculate approximate equilibrium constants for the tautomeric proton exchange and found that compound **1** showed a value of 0.70, whereas the others showed values in the range of 0.90–0.82. Interestingly, compound **5** showed a value of 0.62. We emphasize that our object was not to quantify the percentage of enol/keto form but rather to obtain a pure tautomer.

The effect from changing solvents was examined using one of the anils. The enol–keto equilibrium was monitored by observing chemical shift changes. Figure 1 presents the ^{1}H NMR spectra obtained in three different solvents at room temperature. In chloroform and benzene, we were able to observe the hydrogen-bonded OH peak at $\delta = \sim$14.5 ppm, whereas in dimethylsulfoxide-d_6 (DMSO-d_6) this peak was very broad. This may be due to exchange processes due to the presence of the residual water in DMSO-d_6. The spectrum was run with commercial deuterated DMSO-d_6 and no effort was made to remove the residual water from solvent expected due to the fast exchange of OH protons in polar solvent. The signal of the olefinic proton (=CH) was found to shift only slightly in all these solvents. However, we observed a marked shielding of the aromatic protons occurred in benzene compared with chloroform and DMSO-d_6. This may be rationalized by to the polarity difference between benzene and DMSO-d_6. It is also noteworthy that the benzene spectrum seems to be much cleaner when compared with the other two solvents. Notably, the peaks at $\delta = 10.8$ and 13.3 ppm are totally absent, suggesting that one of the tautomer is preferentially soluble in benzene when compared with the other two solvents. We propose that this could be used to our advantage to separate the keto–enol tautomers although detailed work is warranted.

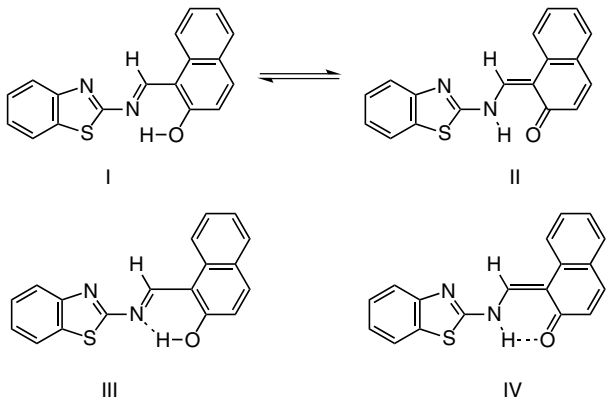
We examined the temperature influence on the ^{1}H chemical shift for compound **2** in benzene. On varying the temperature between 283 and 313 K, we observed that the hydrogen-bonded OH signal shifted by 0.18 ppm. At 283 K this peak appeared at $\delta = 14.53$ ppm,

Table 2. Physical data of benzothiazolyl-substituted anils

Compound	Physical data
1	UV (MeOH): 422, 348, 255 nm: IR (KBr); 3400-3200 (b, OH), 1747, 1600, 1567, 1480, 1450, 1312, 1255, 1193, 1144, 1120, 1033, 981, 848, 818, 741 cm^{-1}. M.p. 195-6 °C. R_f 0.75, chloroform/hexane mixture (80 : 20), single yellow spot: Mass spectra: low resolution (LRESIMS): calculated for $C_{18}H_{11}FN_2OS$: 322 (M^+), found (−ve mode): 321 (M-1); high resolution (HRESIMS): calculated for $C_{18}H_{11}FN_2OS$ Na: 345.0468, found (+ve mode): 345.0471.
2	UV (MeOH), 408, 349, 258 (sh), 228 nm: IR (KBr): 3563 (b, OH), 3285, 1830, 1623, 1556, 1488, 1428, 1401, 1363, 1326, 1255, 1228, 1194, 1146, 1093, 1034, 823, 757 cm^{-1}. M.p. 162-3 °C. R_f 0.55, chloroform/hexane mixture (80 : 20), single yellow spot. Mass spectra: low resolution (LRESIMS): Calculated for $C_{14}H_{10}N_2OS$: 253 (M^+), found (+ve mode): 255 (M+2), 277 ($M^+ + 1$+Na); high-resolution (HRESIMS): calculated for $C_{14}H_{10}N_2OS$ Na: 277.0406, found (+ve mode): 277.0403.
3	UV ($CHCl_3$): 411, 320, 279, 259, 244 nm: IR (KBr): 3300-3200 (b, OH), 1632, 1577, 1518, 1478, 1431, 1349, 1310, 1243, 1203, 1174, 1132, 1079, 1014, 967, 828, 792 cm^{-1}. M.p. 217-8 °C. (i) R_f, 0.11, chloroform/hexane mixture (80 : 20), single yellow spot. (ii) R_f 0.27 chloroform/hexane mixture (90 : 10), single yellow spot. Mass spectra: low resolution (LRESIMS): calculated for $C_{24}H_{22}N_3OS$: 401 (M^+), found (+ve mode): 402.1 (M+2); high-resolution (HRESIMS): calculated for $C_{24}H_{22}N_3OS$: 400.1489, found (−ve mode): 400.1488.
4	UV (MeOH): 423, 356 nm; UV ($CHCl_3$): 424, 347, 290, 239 nm: IR (KBr): 3550 (b, OH), 1747, 1625, 1622, 1560, 1477, 1441, 1390, 1322, 1257, 1224, 1156, 1090, 835, 759 cm^{-1}. M.p. 212-3 °C. R_f 0.66, chloroform/hexane mixture (80 : 20), single yellow spot. Mass spectra: low resolution (LRESIMS): calculated for $C_{18}H_{12}N_2OS$: 304 (M^+), found (−ve mode): 303.1 (M-1); high resolution (HRESIMS): calculated for $C_{18}H_{11}N_2OS$: 303.0598, found (−ve mode): 303.0599.
5	UV (MeOH); 425, 345, 262 nm; IR (KBr): 3430 (b), 2923, 1651, 1622, 1601, 1563, 1488, 1455, 1413, 1320, 1285, 1167, 1107, 1050, 1022, 822 cm^{-1}. M.p. 180-1 °C. R_f 0.88, chloroform/hexane mixture (80 : 20), single yellow spot. Mass spectra: low resolution (LRESIMS): calculated for $C_{19}H_{10}F_3N_2OS$: 372 (M+), found (−ve mode): 371.1 (M-1); High resolution (HRESIMS): calculated for $C_{19}H_{10}F_3N_2OS$: 371.0471, found (−ve mode): 371.0471.



Scheme 2. Scheme showing the keto–enol tautomeric equilibrium of anils.



Scheme 3. Illustration of the keto–enol tautomerism with hydrogen bonds.

Table 3. ^{1}H and ^{13}C chemical shifts of benzothiaozlyl-substituted anils

	Compound						Compound				
^{1}H	**1**	**2**	**4**	**5**	**3**	^{13}C	**1**	**2**	**4**	**5**	**3**
1	–	–	–	–	–	**1**	109	109.7	109.9	109.6	109.2
2-OH	14.4	14.5	13.72	14.4	14.45	**2**	166.4	164.9	165.1	167.3	164.4
3	7.19	7.2	7.21	7.18	–	**3**	120.1	119.8	121.9	120.1	98.8
4	7.92	7.9	8.12	7.96	–	**4**	138.1	136.9	138.2	138.8	152.3
5	7.79	7.78	7.91	7.8	6.29	**5**	129.5	129.4	129.2	129.6	104.4
6	7.43	7.4	7.42	7.44	7.2	**6**	124.5	124.1	124.3	124.6	134.4
7	7.62	7.58	7.66	7.62	8.47	**7**	128.7	128.4	129	128.9	160.9
8	8.28	8.27	8.31	8.3	–	**8**	119.7	119.7	119.6	119.8	–
9	–	–	–	–	–	**9**	133.1	133.1	132.5	133.2	151.4
10	–	–	–	–	–	**10**	128	127.9	127.7	127.9	121.5
11	10.11	10.11	9.99	10.19	8.13	**11**	161.4	159.8	163.2	161.8	123.1
12	–	–	–	–	–	**12**	–				135.1
13	–	–	–	–	8.13	**13**	168.3	171.1	169.2	171.1	123.1
14	–	–	–	–	7.35	**14**	–				121.5
15	–	7.71	–	–	–	**15**	159.6	141.4	133.8	139.1	167.6
16	–	7.24	–	–	–	**16**	148.2	118.1	151.3	153.7	–
17	–	–	–	–	8.08	**17**	–	–			128.7
18	7.54	–	7.95	8.14	7.51	**18**	108.1	–	108.1	109.6	126.3
19	–	–	7.39	–	7.39	**19**	160.2	–	126.7	161.9	125.1
20	7.23	–	7.54	7.72	7.92	**20**	115.2	–	125.1	119.1	121.6
21	7.92	–	8.08	8.05	–	**21**	123.7	–	122.4	123.6	130.7
others					25: 3.44 26: 1.24	**others**				22: 126.9	22: 154.2 25: 44.8 26: 12.7

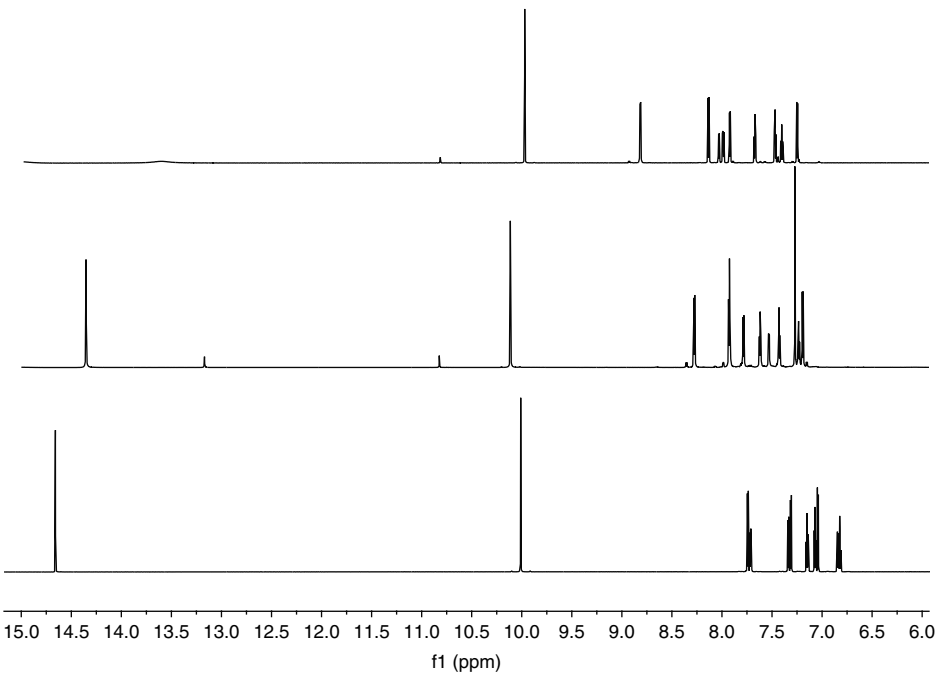


Figure 1. ^{1}H NMR spectra of compound **1** in different solvents at room temperature (solvent used: lower panel, benzene; middle panel, chloroform; top panel, DMSO-d_6).

whereas at 313 K this peak appeared at $\delta = 14.34$ ppm. The deshielding caused by lowering the temperature is consistent with a strengthening of the hydrogen bond. However, the CH peak for the olefinic proton shows only a minor shift of 0.03 ppm, in keeping with the lower sensitivity of olefinic protons chemical shifts to temperature changes than the chemical shifts of hydrogen-bonded protons. For compound **1** in chloroform, the hydrogen-bonded NH protons intensity at $\delta = 14.4$ ppm decreased with increasing temperature with a concomitant increase in the peak intensity of the signal at $\delta = 13.1$ ppm (Fig. 2). We also observed that there was slight shift of the aromatic proton signals in this solvent as the temperature was altered. In summary, the hydrogen

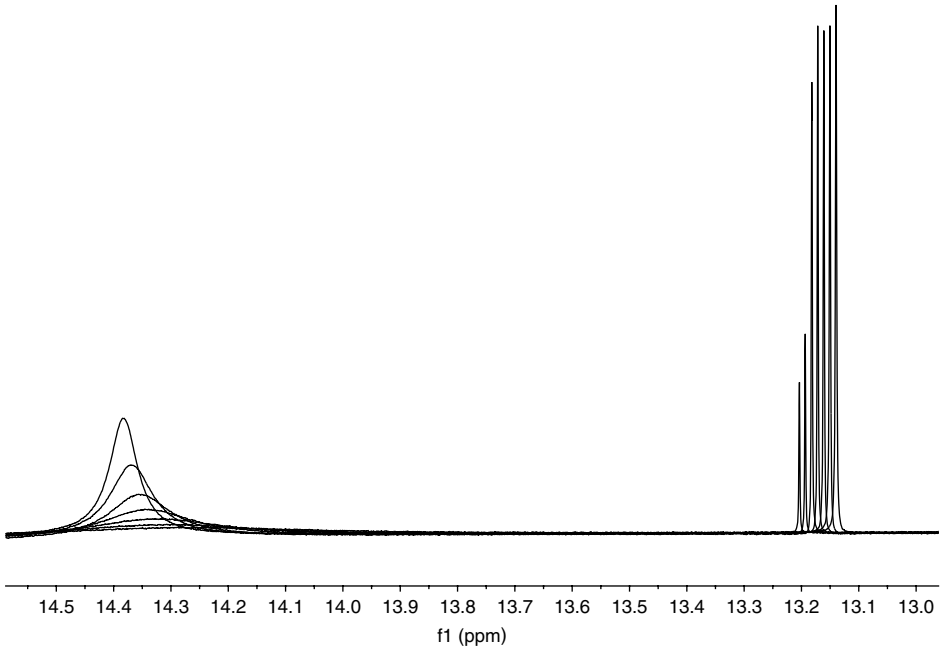
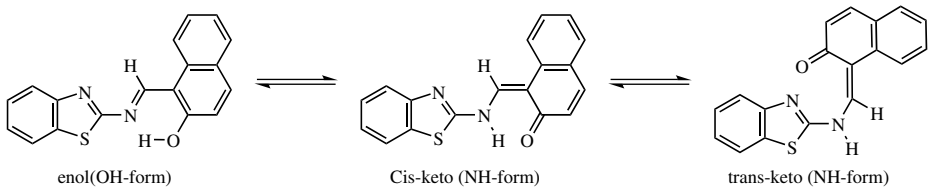


Figure 2. ^{1}H NMR spectra of compound **1** in chloroform at various temperatures.



Scheme 4. Proton transfer equilibrium of the anils.

bonding characteristics was less pronounced due to the breaking of this bond at high temperatures.

Thermochromism

Many Schiff bases exhibit thermochromism. Carles *et al*.[19] showed that salicylidene Schiff bases exhibit thermochromism in the solid state. Oagawa *et al*.[20] also studied the properties of crystalline forms of certain anils exhibiting thermochromism using X-ray crystallography. According to Cohen *et al*.[12] there are two crystal forms, which exhibit either photochromism or thermochromism. In general, a yellow compound was found to show photochromic property, whereas the red compounds exhibited the thermochromic property. Furthermore, Cohen *et al*.[33,34] also proposed an intramolecular proton transfer mechanism. Accordingly, Scheme 4 shows the mechanism for the proton transfer.

In the above scheme, the enol form is hydrogen-bonded to the nitrogen, which is in equilibrium with the *cis*-keto-NH form, whereas it has been converted into the keto form while retaining the configuration as *cis*. On the other hand, there is also another possible tautomer that can be formed depending on the conditions. This tautomer exist as a *trans*-keto form where the hydrogen atom resides on the nitrogen without forming a hydrogen bond with the C═O group. There are four possible pathways through which a compound can exhibit thermochromism which includes (i) proton transfer, (ii) electron delocalization depending on planarity of the molecule, (iii) a change of crystal packing due to temperature and (iv) due to rotation of the bonds. Also deepening of the color due to temperature may be indicative of a higher population of the keto tautomer. The existence of keto forms in the solid state was demonstrated by Inabe *et al*.[21] for *N*,*N*-bis(2-hydroxy-1-naphthylmethylene)-1,4-phenylenediamine. They rationalized the existence of these two forms due to delocalization of the electrons, which imparts stabilization for these two structures. Based on literature precedence, we examined the thermochromic property of these newly synthesized anils. Figure 3 shows the thermochromic property exhibited by these anils. Compound **1** changed slightly from orange red to light orange at lower temperatures. Compounds **2** and **3** did not show much change in their color on lowering the temperature. However, compound **4** showed considerable change in color at −40 °C. The compound converted into a yellow product in solid state on lowering the temperature. The color change imparted by these anils may also be attributed due to the structural variation associated with the anils. Compound **2** has only a thiazolyl moiety, whereas compounds **1** and **4** have the benzothiazolyl moiety in their structure. Although compound **3** contains the benzothiazolyl ring in the structure it has an extended chain and perhaps does not show any thermochromic effect under our experimental conditions.

In summary, we have synthesized anils containing substituted benzothiazolyl groups. ^{1}H and ^{13}C NMR spectroscopy suggest the preponderance of the enol forms. Solvent change affected the chemical shifts of hydrogen-bonded OH groups. Variable-

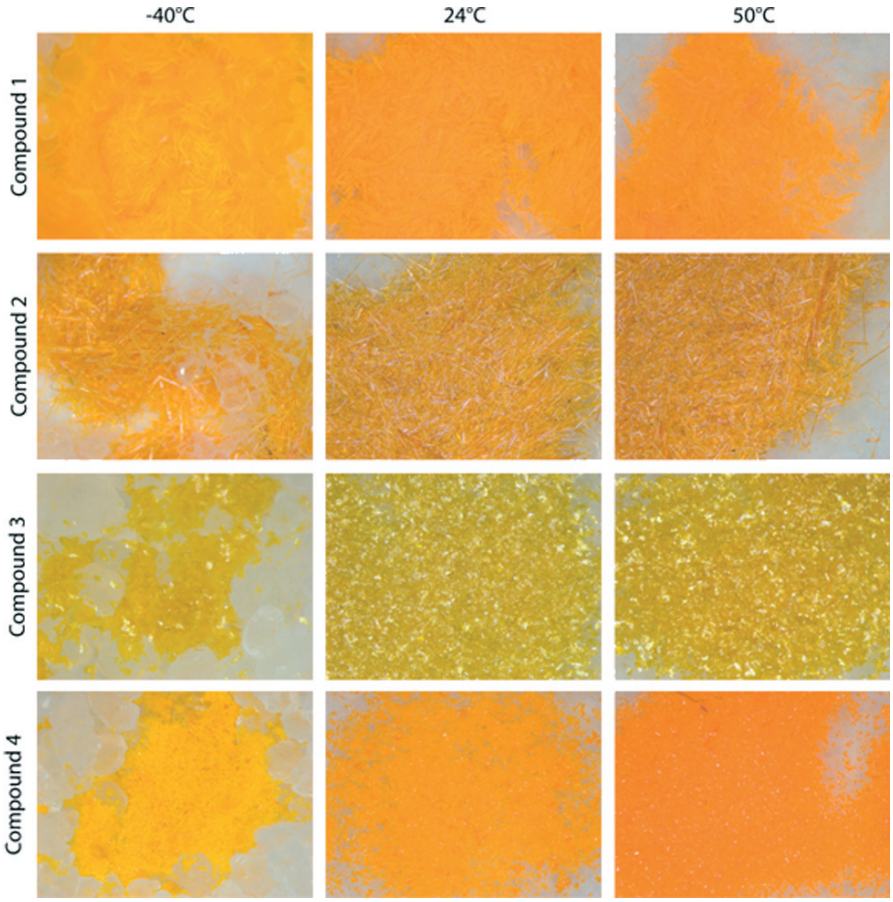


Figure 3. Thermochromism of anils at various temperatures.

temperature ^{1}H NMR gave evidence for the weakening of the hydrogen-bonded OH peak at higher temperatures. Some benzothiazolyl-substituted anils also showed thermochromism.

Experimental

All chemicals were obtained from Sigma-Aldrich and used without further purification. The deuterated solvents were obtained from Cambridge Isotopic Laboratories and used without further purification. The NMR spectra were acquired in both chloroform and dimethyl sulfoxide-d_6 on a Bruker 900 MHz spectrometer fitted with a cryoprobe, and the chemical shifts are reported relative to chloroform peak at $\delta = 7.27$ ppm or DMSO-d_6 at $\delta = 2.54$ ppm, respectively, for ^{1}H NMR and $\delta = 77$ ppm for ^{13}C NMR and $\delta = 39.5$ ppm in the case of chloroform and DMSO-d_6, respectively. For each sample, the probe was matched and tuned and the proton 90° pulse measure (~9 μs). UV/Vis spectra were obtained with a Lambda UV spectrometer using either methanol or chloroform as solvent. Infrared spectra were taken as KBr disc on a Lambda FTIR spectrometer. Melting points were measured on a Fisher-Jones electrothermal melt apparatus, benzoic acid used as a calibration standard at 122-3 °C. During melting point determination, we observed that the compounds changed into dark red color and eventually formed a dark red liquid on melting. The R_f values were measured by spotting the compound on a silica gel (60 mesh) plate (aluminum based) supplied by Merck, Germany. The plates were developed using hexane/chloroform (20 : 80) solvent mixture. Low-resolution electrospray ionization mass spectrometry (LRESIMS) measurements were carried out on a Bruker Esquire HCT (high capacity 3D ion trap) instrument with a Bruker ESI source. Some of the spectra were done in positive ion mode (+ve) and others in negative ion mode (−ve) depending on the mode that produced the best result. High-resolution electrospray ionization (HRESIMS) accurate mass measurements were carried out on a Bruker MicrOTOF-Q (quadrupole-Time of Flight) instrument with a Bruker ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as reference calibrant.

General procedure for synthesis of anil derivatives: In a 100 ml round bottom flask, the appropriate benzothiazole compound (0.05 mol), the respective aldehyde (0.05 mol) and 50 ml of absolute ethanol were placed. The contents were stirred and the resulting solution was refluxed over an oil bath for 8 h. The precipitated anils were filtered under vacuum, washed with a copious amount of ethanol and dried in vacuum. The compounds were further purified by crystallization using chloroform solvent. ^{1}H NMR and ^{13}C NMR peaks were assigned using COSY, TOCSY, HSQC and HMBC experiments. Sample acquisition parameters are as follows for the various experiment, ^{1}H NMR (SW = 20 ppm; O1 = 8 ppm; D1 = 1 s and 32 scans acquired), ^{13}C NMR (SW = 230 ppm; O1 = 105 ppm; D1 = 1 s and 128 scans acquired), COSY/TOCSY (NS = 8 and TD = 256 or 512, mixing time = 70 ms), HSQC (F1 SW2 = 180 ppm, O2 = 80 ppm, ^{1}J coupling = 145 Hz, D1 = 1 s and TD = 256, 16 scans acquired) and HMBC (F1 SW2 = 220 ppm, O2 = 110 ppm, long-range coupling = 8 Hz, D1 = 1 s and TD

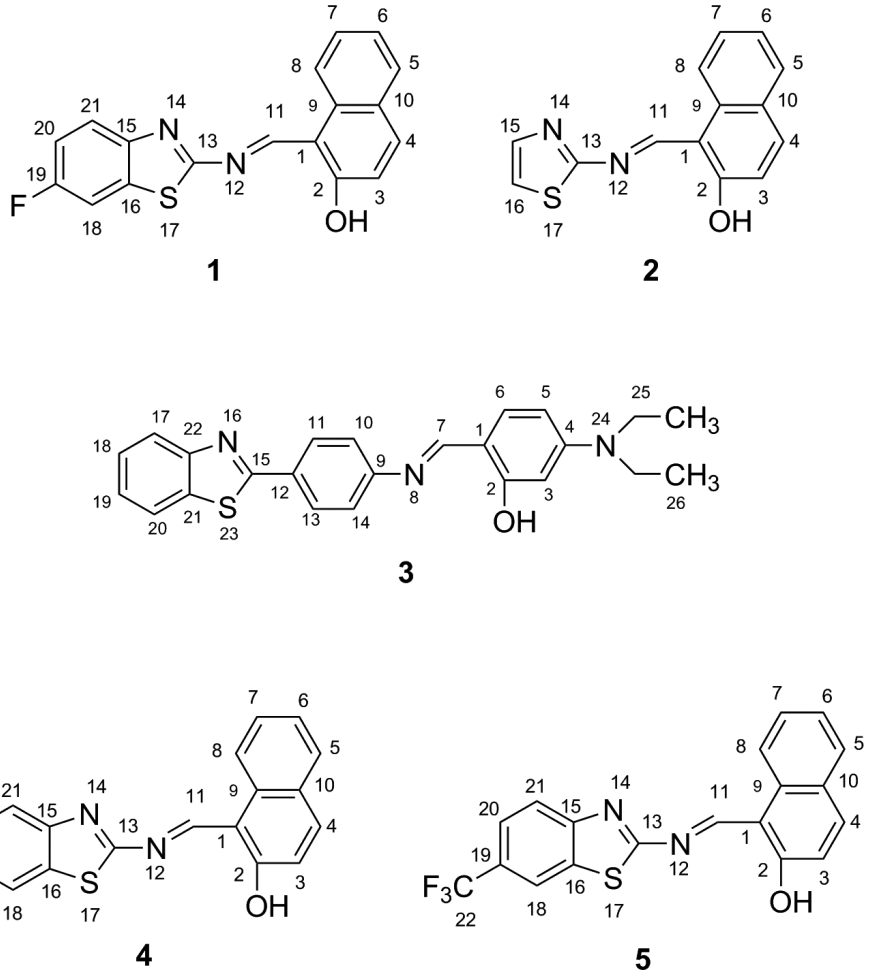


Figure 4. Structures of synthesized compounds along with the atom numbering.

= 256, 64 scans acquired). Figure 4 shows the structures of the benzothiazolyl-substituted anils prepared in the present study.

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