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Site-selective formation of *N*-arylmethylimidazoles and *C*-arylimines in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with aromatic aldehydes

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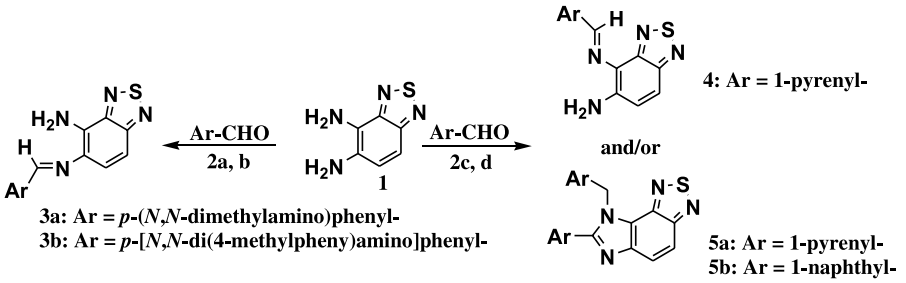
Abstract—Regioselective formation of *N*-arylmethylimidazoles and *C*-arylimines was found in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with selected aromatic aldehydes. The regiochemistry of the reaction products was confirmed by single crystal X-ray analysis. Gibbs free energy calculation using DFT method at the B3LYP/6-31G(d) level supports the regio-selectivity observed. The 4-imine obtained in the reaction of 4,5-diamino-2,1,3-benzothiadiazole with pyrene-1-carboxaldehyde showed an unusually low magnetic field shift of the imine proton that was reproduced by molecular calculations.

1. Introduction

Since introduction of hetero atoms perturbs the photo- and electro-chemical properties of aromatic π-systems, various types of heteroaromatic compounds have been studied as carrier (hole and electron) transporting and light emitting materials for electroluminescent (EL) devices.[1] In this context, condensed heterocyclic ring systems with thiadiazole, imidazole, and oxadiazole substructures have been extensively studied.[2] During the course of our investigation for heteroaromatic EL materials, it was found that *N*-arylmethylimidazoles and *C*-arylimines were formed in the reactions of 4,5-diamino-2,1,3-benzothiadiazole (**1**) with arylaldehydes **2** in a regioselective manner, depending upon the nature of **2**. Imine **4** resulting from the reaction of pyrene-1-carboxaldehyde (**2c**) and **1** showed an unusual ^{1}H NMR chemical shift of the imine proton at 11 ppm. This unusual chemical shift is explained by use of a molecular orbital calculation, which is also applied to explain the regioselective formation of arylmethylenimidazole **5**.

2. Results and discussion

The reactions of 4,5-dibromo-2,1,3-benzothiadiazole (**1**) with arylaldehydes **2** are represented in Scheme 1. The



Scheme 1.

Keywords: Thiadiazole; Regioselective formation; Chemical shift; B3LYP/6-31G(d).
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reactions with *p*-(*N*,*N*-dimethylamino)benzaldehyde (**2a**) and *p*-[*N*,*N*-di(4-methylphenyl) amino]benzaldehyde (**2b**) in toluene under reflux conditions gave the corresponding 5-imino derivatives **3a** and **3b** in 30 and 40% yields, respectively. Corresponding isomeric 4-imines were not found in the reaction mixtures. On the other hand, the reaction of **1** with pyrene-1-carboxaldehyde (**2c**) afforded 4-imino compound **4** and 8-arylmethylenimidazole **5a** in 9 and 15% yields, respectively. Similar reaction of **1** with naphthalene-1-carboxaldehyde (**2d**) gave imidazole **5b** as the only product in 20% yield. The formation of 8-arylmethylen-7-arylbenz[*d*]imidazoles is well documented in the reaction of *o*-phenylenediamine with aromatic aldehydes.[3]

The product structures are deduced from spectral data and confirmed by single crystal X-ray analysis of **3a**, **4**, and **5b**. The ORTEP drawings are shown in Figures 1–3.

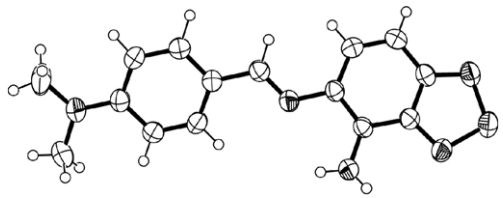


Figure 1. ORTEP drawing of **3a**.

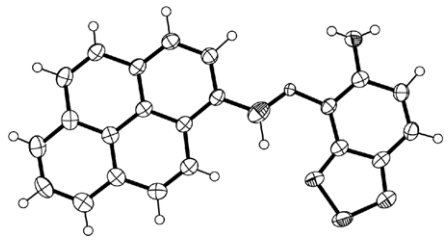


Figure 2. ORTEP drawing of **4**.

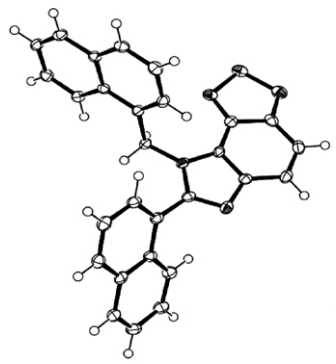
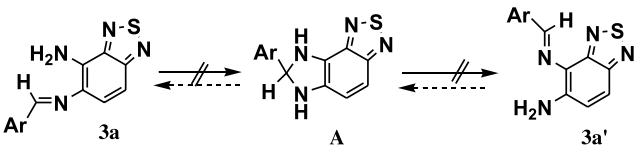


Figure 3. ORTEP drawing of **5b**.

In the reaction of **1** with aromatic aldehydes **2**, the regioselective formation of imines was observed with selected aromatic aldehydes **2**. Isomerization of 5-imino derivative **3a** to the corresponding regioisomer via the cyclic imidazoline intermediate **A** (Scheme 2) was not observed. The starting imine **3a** was recovered quantitatively after toluene reflux for 24 h, while under the same conditions, 4-imino compound **4** was inert.



Scheme 2.

Gibbs free energy calculation using DFT method at the B3LYP/6-31G(d) level[4–6] supports the selective formation of 5-imine **3a** and 4-imine **4** over the corresponding isomers, respectively, although the difference is not large. The molecular calculation estimates that **3a** is 0.81 kcal/mol more stable than **3a**′ and *C*-pyrenyl-4-imino derivative **4** is 0.45 kcal/mol more stable than the 5-imino isomer **4**′.[7]

Imidazole **5** seems less congested than the regioisomeric 6-arylmethyl derivative **5**′, in which the steric repulsion between the arylmethyl group and the proton on the *peri*-position is expected. The molecular calculation supports the selective formation of the imidazole **5**; 8-arylmethyl compound **5a** is 1.98 kcal/mol more stable than the corresponding **5**′.[4–6] As one of possible routes to **5**, a cyclization of the imino compound such as **4** to produce the imidazoline intermediate like **A**, followed by the reaction of the imidazoline with the additional aldehyde could be considered. Electron-donating groups of **3a** and **3b** would reduce the electrophilicity of the imino carbon, which prevents the following cyclization. In the *C*-pyrenylimine **4** with the large substituent compared to naphthyl group, the cyclization from **4** would not proceed perfectly due to the steric factor, which resulted in a mixture of **4** and **5a**.

The most characteristic difference between imines **3** and **4** in the ^{1}H NMR spectra is the imine proton of **4** appearing at an extraordinarily low magnetic field (11.28 ppm). On the other hand, the imine protons of **3a** and **3b** were observed in the usual position at 8.55 and 8.56 ppm, respectively. The single crystal X-ray analysis of **4** shows the close proximity of the imine proton with the nitrogen atom of benzo-2,1,3-thiadiazole ring (0.209 nm) induces the formation of a six-membered ring, that in turn deshields by the nitrogen atom of the 2,1,3-thiadiazole ring with the imine proton.

To compare with the theoretical value of ^{1}H NMR signals, the molecular geometries of **3** and **4** were fully optimized at B3LYP/6-31G(d) level. The calculation of ^{1}H NMR chemical shift was carried out using the Gauge-Independent

Table 1. Chemical shift (ppm) of imine protons of **3** and **4**

Compound	Observed[a]	Calculated[b]	Compound	Observed[a]	Calculated[b]
3a	8.55	8.60	**4**	11.28	11.86
3a′	—	10.48	**4′**	—	9.94
3b	8.56	—	—		

[a] Measured in $CDCl_3$.
[b] Calculated values using HF/6-31G(d).

Atomic Orbitals (GIAO) method[4,8] at Hartree–Fock (HF)/6-31G(d) level, to well reproduce the low field shift of the imine proton of **4**, as summarized in Table 1.

3. Conclusion

Regioselective formation of imines **3** and **4** and imidazole **5** was found in the reaction of 4,5-diamino-2,1,3-benzothiadiazole (**1**) and arylaldehydes **2** and molecular calculation of Gibbs free energy supports the product selectivity. Interestingly, considerable low magnetic field shift was observed for the imine proton of **4** in the ^{1}H NMR spectrum. The single-crystal X-ray analysis gave evidence of a deshielding mechanism by the nitrogen atom of the thiadiazole ring with the imine proton.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400. IR spectra were measured as KBr pellets using a JASCO FT/IR-420. High-resolution mass spectra (HRMS) were measured using JEOL JMS-70. Melting points were determined by differential scanning calorimeter (DSC) of a Perkin–Elmer Pyris 1. Column chromatography was conducted using silica gel 60 (70–230 mesh, Merck). In general, all organic reagents were used as received. Toluene was dried over activated molecular sieves 4A.

4.2. General procedure for the reaction of 4,5-diamino-2,1,3-benzothiadiazole (1) with aryl aldehydes 2

In a 300 ml three-necked flask equipped with Dean-Stark trap, a solution of **2** (6.02 mmol) in toluene (10 ml) was added to a solution of **1** (1.00 g, 6.02 mmol) in toluene (140 ml). The mixture was heated under reflux for 6 h and the solvent was evaporated in vacuo. The residue was column-chromatographed using a 5:1 mixture of toluene and ethyl acetate for **3a** and **3b**, a 19:1 mixture of toluene and ethyl acetate for **4**, **5a**, and **5b**.

4.2.1. 4-Amino-5-[*p*-(*N*,*N*-dimethylamino)benzylidene]-2,1,3-benzothiadiazole 3a. Red crystal (ethyl acetate/hexane); mp 145 °C; IR (KBr) cm^{-1} 3478, 3369, 1600, 1525, 1358, 1163, 818; ^{1}H NMR ($CDCl_3$) δ: 3.08 (s, 6H), 5.18 (brs, 2H), 6.76 (d, 2H, J=8.8 Hz), 7.34 (d, 1H, J=9.2 Hz), 7.59 (d, 1H, J=9.2 Hz), 7.83 (d, 2H, J=8.8 Hz), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 109.09, 120.17, 122.55, 125.64, 128.86, 129.43, 129.56, 130.07, 133.39, 133.88, 144.23, 148.16, 150.98, 154.37, 155.43; HRMS (EI) *m*/*z* calcd for $C_{15}H_{15}N_5S$ 297.1048. Found 297.1053; Anal. calcd for $C_{15}H_{15}N_5S$: C, 60.58; H, 5.08; N, 23.55. Found: C, 60.45; H, 5.06; N, 23.32.

4.2.2. 4-Amino-5-[*p*-[*N*,*N*-di(4-methylphenyl)amino]-benzylidene]-2,1,3-benzothiadiazole 3b. Red crystal (ethyl acetate/*n*-hexane), mp 153 °C; IR cm^{-1} 3455, 3353, 3031, 1596, 1502, 1322, 1275, 823; ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 6H), 5.21 (brs, 2H), 7.02–7.14 (m, 10H), 7.33 (d, 1H, J=9.2 Hz), 7.58 (d, 1H, J=9.2 Hz), 7.75 (d, 2H, J=8.8 Hz), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 109.09, 120.17, 122.55, 125.64, 128.86, 129.43, 129.56, 130.07, 133.39, 133.88, 144.23, 148.16, 150.98, 154.37, 155.43; HRMS (EI) *m*/*z* calcd for $C_{27}H_{23}N_5S$ 449.1671. Found 449.1674; Anal. calcd for $C_{27}H_{23}N_5S$: C, 72.13; H, 5.16; N, 15.58. Found: C, 71.88; H, 5.18; N, 15.32.

4.2.3. 5-Amino-4-[(pyren-1-yl)methylidene]-2,1,3-benzothiadiazole 4. Deep orange crystal (chloroform/acetone); mp 200 °C; IR (KBr) cm^{-1} 3427, 3330, 3038, 1608, 1515, 1302, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.23 (brs, 2H), 7.28 (d, 1H, J=9.2 Hz), 7.75 (d, 1H, J=9.2 Hz), 8.03–8.28 (m, 7H), 8.94–9.00 (m, 2H), 11.28 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 117.19, 120.87, 121.73, 123.83, 124.50, 124.97, 125.05, 125.55, 125.84, 125.89, 126.31, 127.35, 128.14, 128.56, 129.33, 130.05, 130.32, 130.74, 132.00, 147.65, 150.18, 150.75, 152.77; HRMS (EI) *m*/*z* calcd for $C_{23}H_{14}N_4S$ 378.0939. Found 378.0943; Anal. calcd for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; Found: C, 72.59; H, 3.84; N, 14.57.

4.2.4. 7-[4-(*N*,*N*-Dimethylamino)phenyl]-8-[(peren-1-yl)methyl]imidazo[4,5-*e*]-2,1,3-benzothiadiazole 5a. Yellow crystal (chloroform/acetone); mp 262 °C. IR (KBr) cm^{-1} 3039, 1604, 1523, 1430, 1288, 837. ^{1}H NMR ($CDCl_3$) δ: 6.64 (s, 2H), 7.21 (d, 1H, J=8.2 Hz), 7.60–7.82 (m, 7H), 7.85–8.10 (m, 10H), 8.16 (d, 1H, J=8.0 Hz), 8.25 (d, 1H, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 48.1, 116.3, 121.5, 123.8, 124.0, 124.3, 124.6, 125.7, 127.0, 127.4, 128.6, 128.7, 130.4, 130.5, 131.1, 132.5, 142.6, 144.6, 153.1, 154.7; HRMS (FAB) *m*/*z* calcd for $C_{40}H_{22}N_4S$ 590.1555. Found 590.1565; Anal. calcd for $C_{23}H_{14}N_4S$: C, 81.33; H, 3.75; N, 9.48. Found: C, 81.32; H, 3.86; N, 9.30.

4.2.5. 7-[4-(*N*,*N*-Dimethylamino)phenyl]-8-[(naphth-1-yl)methyl]imidazo[4,5-*e*]-2,1,3-benzothiadiazole 5b. Yellow crystal (chloroform/acetone); mp 220 °C. IR (KBr) cm^{-1} 3062, 1607, 1515, 1287, 1072, 804. ^{1}H NMR ($CDCl_3$) δ: 6.32 (s, 2H), 6.54 (d, 1H, J=7.4 Hz), 7.10 (dd, 1H, J=7.4, 7.4 Hz), 7.31 (dd, 1H, J=8.2, 8.2 Hz), 7.40–7.53 (m, 5H), 7.64 (d, 1H, J=8.2 Hz), 7.77–7.94 (m, 6H), 8.18 (d, 1H, J=9.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 48.1, 116.3, 122.3, 123.0, 125.1, 125.2, 126.0, 126.5, 126.9, 128.1, 128.5, 128.9, 130.2, 130.6, 132.2, 132.3, 133.6, 133.7, 142.5, 144.5, 152.5, 154.5; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{19}N_4S$

$[M+H]^+$: 443.1328. Found 443.1330; Anal. calcd for $C_{28}H_{18}N_4S$: C, 75.99; H, 4.10; N, 12.66. Found: C, 76.13; H, 3.77; N, 12.22.

4.3. X-ray crystallography

All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation.

4.3.1. Crystal data: for $C_{15}H_{15}N_5S$ 3a. Monoclinic space group $P21/n$, a=12.9379 (6) Å, b=8.1971 (4) Å, c=14.8002 (7) Å, β=114.075 (2)°, V=1433.1 (1) Å^3, Z=4, crystal size 0.35×0.30×0.15 mm^3, T=300 K; Of the 3513 reflections that were collected, 3276 were unique; equivalent reflections were merged (maximum 2θ=55.0°, R_{int}=0.000). Refinement gave R_1=0.043 [$I>3\sigma(I)$] and wR_2 [$I>3\sigma(I)$]=0.121.

4.3.2. Crystal data: for $C_{23}H_{14}N_4S$ 4. Triclinic space group P-1, a=8.040 (3) Å, b=15.349 (8) Å, c=15.42 (1) Å, α=107.80 (4)°, β=104.23 (4)°, γ=95.50 (7)°, V=1725.9 (2) Å^3, Z=4, crystal size 0.50×0.20×0.02 mm^3, T=123 K; Of the 16,268 reflections that were collected, 7617 were unique (maximum 2θ=55.0° R_{int}=0.093); equivalent reflections were merged. Refinement gave R_1=0.073 [$I>3\sigma(I)$] and wR_2 [$I>3\sigma(I)$]=0.200.

4.3.3. Crystal data: for $C_{28}H_{18}N_4S$ 5b. Triclinic space group P-1, a=9.210 (7) Å, b=11.505 (7) Å, c=11.614 (7) Å, α=111.55 (2)°, β=93.37 (2)°, γ=112.31 (3)°, V=1030 (1) Å^3, Z=2, crystal size 0.30×0.12×0.10 mm^3, T=123 K; Of the 38,986 reflections that were collected, 4687 were unique; equivalent reflections were merged (maximum 2θ=55.0°, R_{int}=0.070). Refinement gave R_1=0.043 [$I>2\sigma(I)$] and wR_2 [all reflections]=0.112.

Crystal data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC deposition numbers **3b** (227522), **4** (227523) and **5b** (227524). The supplementary crystallographic data for this paper can be obtained free of charge from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

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