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SYNTHESIS OF NOVEL PYRAZOLO[5,1-*b*][1,3]BENZOTHIAZOLES: A NEW PERICYCLIC PATHWAY

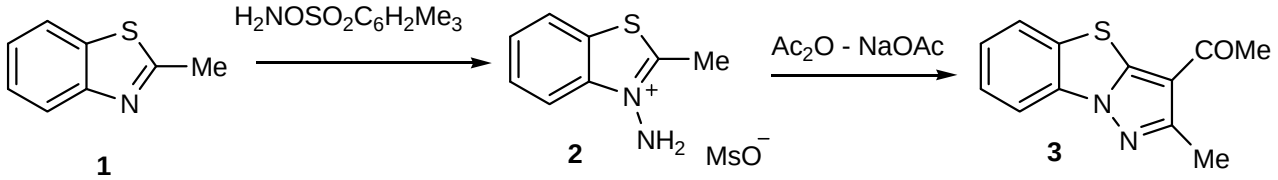
Betül Tekiner-Gulbas,[b] László Filák,[a] Gyöngyvér Ágnes Vaskó,[a] Orsolya Egyed,[a] Ismail Yalçin,[b] Esin Aki-Sener,[b] Zsuzsanna Riedl,[a] and György Hajós[a*]

[a]Chemical Research Center, Hungarian Academy of Sciences, H-1025 Budapest, Pusztaszeri út 59, Hungary. [b]Ankara University, Faculty of Pharmacy, TR-06100 Tandogan, Ankara, Turkey. E-mail: ghajos@chemres.hu

Abstract – 2-Benzylbenzothiazoles were easily *N*-aminated by tosyl hydroxylamine, and the obtained *N*-amino salts were reacted with ethyl orthoformate to give new derivatives of the pyrazolo[5,1-*b*][1,3]benzothiazole ring system. Mechanistic considerations suggest that the ring closure reaction proceeds *via* deprotonation of the *N*-amino salt followed by electrocyclization to provide the tricyclic ring system. The procedure opens an easy access to variously substituted derivatives of the target ring system.

INTRODUCTION

Benzothiazoles and related compounds have recently been proved to be of high interest from the view point of pharmaceutical applications[1-4] and, hence, novel functionalization and extension of our activity[5,6] in this area seemed important. A particularly straightforward way of structural modification of azoles can be the *N*-amination of the ring-nitrogen atom, by which a new functional group (*i.e.* an NH_2 moiety) is introduced into the heterocycle allowing new derivatizations and/or ring closures.



Scheme 1

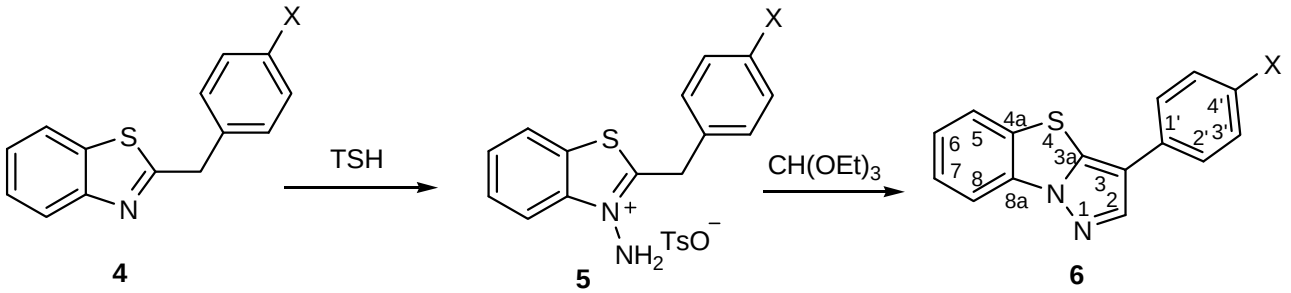
The literature survey in this respect indicated that very limited work on *N*-amination of benzothiazoles has been published. Three decades ago Koga *et al*.[7] reported that reaction of 2-methylbenzothiazole (**1**) with mesityl hydroxylamine gave rise to the *N*-amino mesitylanesulfonate salt (**2**) which compound was treated with acetic anhydride to result in formation of 2-methyl-3-acetylpyrazolo[5,1-*b*]benzothiazole (**3**) in low yield. Other derivatives of this ring system have also been synthesized by different methods.[8] More recently, another *N*-amination reaction of benzothiazoles has also been reported.[9]

RESULTS AND DISCUSSION

We are now reporting a new generally extendable ring closure reaction to pyrazolobenzothiazoles starting from *N*-amino-2-benzylbenzothiazoles (**5a-f**) which can easily be prepared by reaction of the appropriate 2-benzylbenzothiazoles (**4**) with *O*-tosylhydroxylamine[10] (TSH) in high yields.

Although the above cited references provide evidence for *N*-amination of the benzothiazole ring, amination of ring-sulfur atoms can not be excluded as such transformations with other sulfur heterocycles have also been reported.[11] In order to find experimental support for the supposed *N*-amination, ^{15}N chemical shifts were determined by ^{15}N -^{1}H HMQC measurements, based on direct N-H coupling (NH_2) or on multiple bond couplings (N3). The observed shifts (-194.0 ppm for ring N and -314.0 ppm for amine-N) are in good agreement with data observed for some related *N*-amino salts (*i.e.* *N*-aminoisoquinolinium compounds,[12] -211.2 ppm for ring N and -306.0 ppm for amine-N).

We have found that variously substituted *N*-amino salts (**5**) when reacted with triethyl orthoformate under reflux conditions can be transformed to novel pyrazolo[5,1-*b*][1,3]benzothiazoles by one simple manipulation step in medium to good yields.



4 **5** **6**

X	H	Me	Br	Cl	F	NO_2
	a	**b**	**c**	**d**	**e**	**f**

Scheme 2

As to the mechanism of this cyclization the following sequence of reaction steps leading to formation of the tricyclic pyrazoles can be proposed (Figure 1)

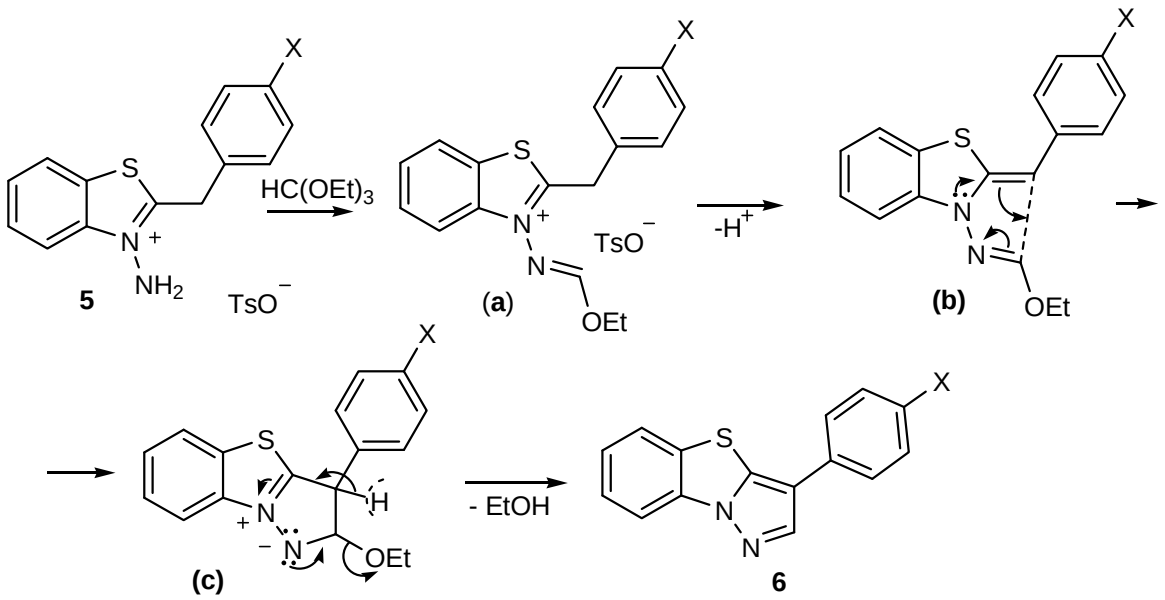
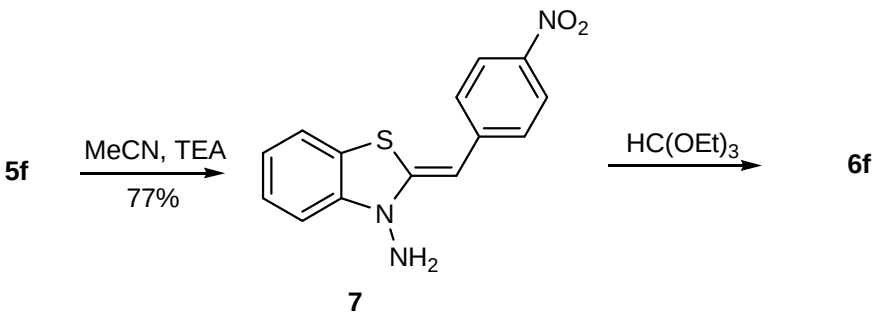


Figure 1. Suggested reaction mechanism for ring closure of **5** to give the tricyclic **6**

The first step is obviously a condensation reaction between the starting *N*-amino salt (**5**) and the triethyl orthoformate reagent to give an iminoether-containing intermediate (**a**) followed by a deprotonation to afford the neutral species (**b**). In this intermediate an electrocyclization can take place (arrows) with participance of a C=N and C=C double bond as well as by the lone pair of the ring-nitrogen atom. This valence bond isomerization leads to the zwitterionic third intermediate (**c**) which can easily undergo ethanol elimination to give the stable heteroaromatic final product (**6**). In one case (*i.e.* with **5f**) the deprotonated conjugate base (**7**) was also isolated and it was reacted with the ortho ester to yield the fused pyrazole (**6f**).



Scheme 3

CONCLUSION

These results convincingly show that a new and effective cyclization pathway to fused benzothiazoles has been found by which a series of novel derivatives – with particular interest to introduction of reactive

groups – can be prepared. From theoretical view point, the pericyclic nature of the ring closure step is of theoretical importance. Extension of this ring closure methodology for novel related cases as well as biological test of the new derivatives is in progress.

EXPERIMENTAL

Melting points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR experiments were performed on Varian INOVA-200 or Varian INOVA-400 spectrometers, ^{1}H and ^{13}C chemical shifts are expressed in ppm (δ). The elemental analysis has been carried out with an Elementar Vario EL III apparatus. The starting benzylbenzothiazoles (**4**) were synthesized according to lilterature procedures.[13]

General Procedure for *N*-amination of 2-benzylbenzothiazoles.

To a solution of 2-benzylbenzothiazoles (**4a-f**, 1 mmol) in CH_2Cl_2 (5 mL), a solution of TSH reagent (1.5 mmol) in CH_2Cl_2 (10 mL) was added at 0 ^{o}C. The reaction mixture was stirred at rt for 2 h. The deposited white crystals were filtered off and recrystallized from MeCN-Et_2O mixture.

3-Amino-2-benzyl-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (5a)

Starting from **4a** (0.225 g), white crystals (0.390 g, 95%), mp 157-158 ºC; IR (KBr): 3217, 3116, 2926, 1497, 1437, 1221, 1180, 1034, 1012, 764, 685 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 8.3 (dd, J = 8.7, 1.1 Hz, 1H, H7), 8.0 (dd, J = 8.1, 1 Hz, 1H, H4), 7.8 (m 1H, H5), 7.7 m, 1H, H6), 7.4 (m, 5H, H-phenyl), 7.3 (br. s, 2H, H-NH_2), 7.6 (m, 2H, H2 + H6 (anion)), 7. 0 (m, 2H, H3 + H5 (anion)), 4.9 (s, 2H, CH_2), 2.3 (s, 3H, CH_3 (anion)); ^{13}C NMR (DMSO-d_6) δ: 178.7, 142.4, 141.2, 138.3, 132.1, 129.2 (2C), 128.5 (2C), 128.4, 127.9, 127.5 (2C), 126.2, 124.7 (2C), 122.6, 116.3, 35.5, 20.3; Anal. Calcd for $C_{21}H_{20}N_2O_3S_2$ (412.53): C, 61.14; H, 4.89; N, 6.79; S, 15.55. Found: C, 60.97; H, 4.84; N, 6.70; S, 15.60.

3-Amino-2-(4-methylbenzyl)-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (5b)

Starting from **4b** (0.240 g), white crystals (0.410 g, 96%); mp 151-153 ºC; IR (KBr): 3218, 3120, 2925, 1516, 1434, 1222, 1174, 1031, 1011, 765, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 8.3 (d, J = 8 Hz, 1H, H7), 8.2 (d, J = 8 Hz, 1H, H4), 7.8 (m, 1H, H5), 7.7 (m, 1H, H6), 7.5 (m, 2H, H2 + H6 (anion)), 7.4 (br. s, 2H, H-NH_2), 7.3 (m, 4H, H-tolyl), 7.0 (m, 2H, H3 + H5 (anion)), 4.8 (s, 2H, CH_2), 2.4 (s, 3H, H-CH_3-tolyl), 2.3 (s, 3H, CH_3 (anion)); ^{13}C NMR (DMSO-d_6) δ: 178.7, 145.6, 141.4, 137.8, 137.5, 130.6, 129.7 (4C), 129.2, 128.3, 127.8 (2C), 127.1, 125.4 (2C), 124.5, 116.5, 35.0, 20.7, 19.8; Anal. Calcd for $C_{22}H_{22}N_2O_3S_2$ (426.55): C, 61.95; H, 5.20; N, 6.57; S, 15.03. Found: C, 61.73; H, 5.10; N, 6.70; S, 15.32.

3-Amino-2-(4-bromobenzyl)-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (5c)

Starting from **4c** (0.3 g), white crystals (0.340 g, 69%); mp 165 ºC; IR (KBr): 3260, 3137, 2915, 1489,

1462, 1220, 1193, 1124, 1012, 772, 682cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 8.3 (d, J = 8.7 Hz, 1H, H7), 8.1 (d, J = 8.1, 1H, H4), 7.8 (m, 1H, H5), 7.7 (m, 1H, H6), 7.5 (m, 4H, H-bromophenyl), 7.4 (br. s, 2H, H-NH_2), 7.4 (m, 2H, H2 + H6 (anion)), 7.10 (m, 2H, H3 + H5 (anion)), 4.9 (s, 2H, CH_2), 2.37 (s, 3H, CH_3 (anion)); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ: 178.3, 142.6, 141.3, 138.2, 131.6 (2C), 131.4, 131.2 (2C), 128.5, 127.6 (C6), 127.5 (2C), 126.2, 124.7 (2C), 122.6, 122.0, 116.4, 34.9, 20.3; Anal. Calcd for $C_{21}H_{19}BrN_2O_3S_2$ (491.42): C, 51.33; H, 3.90; N, 5.70; S, 13.05. Found: C, 51.33; H, 3.90; N, 5.68; S, 13.17.

3-Amino-2-(4-chlorobenzyl)-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (5d)

Starting from **4d** (0.260 g), white crystals (0.410 g, 92%); mp 159-160 ºC; IR (KBr): 3170, 3070, 2914, 1493, 1463, 1220, 1177, 1034, 1011, 770, 681 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 8.31 (dd, J = 8.7, 1.1 Hz, 1H, H7), 8.23 (dd, J = 8.1, 1.0 Hz, 1H, H4), 7.89 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H, H5), 7.72 (ddd, J = 8.7, 7.3, 1.0 Hz, 1H, H6), 7.54 (m, 4H, H-chlorophenyl), 7.47 (br. s, 2H, H-NH_2), 7.42 (m, 2H, H2 + H6 (anion)), 7.10 (m, 2H, H3 + H5 (anion)), 4.85 (s, 2H, CH_2), 2.25 (s, 3H, CH_3 (anion)); ^{13}C NMR (DMSO-d_6) δ: 178.0 (C2), 142.6 (C1' (anion)), 141.0 (C3a), 137.7 (C4' (anion)), 133.8 (C4'), 133.5 (C1'), 130.6 (C3' + C5'), 128.4 (C3 + C5 (anion)), 128.0 (C5), 127.2 (C6), 127.1 (C2 + C6 (anion)), 126.0 (C7a), 124.4 (C2' + C6'), 122.6 (C7), 116.1 (C4), 34.5 (CH_2), 20.1 (CH_3(anion)); ^{15}N NMR δ: -194.0 (N3), -314.0 (NH_2); Anal. Calcd for $C_{21}H_{19}ClN_2O_3S_2$ (446.97): C, 56.43; H, 4.28; N, 6.27; S, 14.35. Found: C, 56.21; H, 4.32; N, 6.34; S, 14.08.

3-Amino-2-(4-fluorobenzyl)-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (5e)

Starting from **4e** (0.240 g), white crystals (0.370 g, 87%); mp 150-151 ºC; IR (KBr): 3173, 3072, 2913, 1512, 1463, 1220, 1177, 1033, 1011, 770, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 8.25 (d, J = 8.5, 1H, H7), 8.11(d, J = 8.0 Hz, 1H, H4), 7.78 (m, 1H, H5), 7.7 (m, 1H, H6), 7.5 (m, 4H, H-fluorophenyl+ H2 + H6 (anion)), 7.45 (br. s, 2H, H-NH_2), 7.1 (m, 4H, H-fluorophenyl+ H2 + H6 (anion)), 4.9 (s, 2H, CH_2), 2.28 (s, 3H, CH_3 (anion)); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ: 178.6, 162.1 (d, $^{1}J_{C,F}$ = 249 Hz), 143.7, 141.5, 138.1, 131.6(2C, d, $^{3}J_{C,F}$ = 8 Hz) , 128.9, 128.7 (d, $^{4}J_{C,F}$ = 3.5 Hz), 128.0, 127.8 (2C), 126.7, 125.1 (2C), 123.5, 116.5, 115.7 (2C, d, $^{2}J_{C,F}$ = 21.5 Hz), 34.8, 20.6; Anal. Calcd for $C_{21}H_{19}FN_2O_3S_2$ (430.52): C, 58.59; H, 4.45; N, 6.51; S, 14.90. Found: C, 58.24; H, 4.63; N, 6.68; S, 15.10.

3-Amino-2-(4-nitrobenzyl)benzothiazol-3-ium 4-methylbenzenesulfonate (5f)

Starting from **4f** (0.270g), yellow crystals (0.370 g, 81%); mp 172-173 ºC; IR (KBr): 3300, 3120, 2915, 1521, 1352, 1220, 1170, 1032, 1010, 772, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 8.3 (d, J = 8.5 Hz, 1H, H7), 8.25 (m, 2H, H-nitrophenyl), 8.2 (d, J = 8.0 Hz, 1H, H4), 7.8 (m, 2H, H-nitrophenyl), 7.8 (m, 1H, H5), 7.7 (m, 1H, H6), 7.5 (br. s, 2H, H-NH_2), 7.49 (m, 2H, H2 + H6 (anion)), 7. 0 (m, 2H, H3 + H5

(anion)), 4.11 (s, 2H, CH_2), 2.28 (s, 3H, CH_3 (anion)); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ: 178.3, 147.3, 143.9, 141.2, 140.5, 138.0, 131.0 (2C), 129.0, 128.1, 127.8 (2C), 126.8 (2C), 125.1 (2C), 123.8, 123.7, 116.5, 35.0, 20.6; Anal. Calcd for $C_{21}H_{19}N_3O_5S_2$ (457.52): C, 55.13; H, 4.19; N, 9.18; S, 14.02. Found: C, 55.01; H, 4.30; N, 9.00; S, 14.19.

General procedure for ring closure of 3-amino-2-benzylbenzothiazolium salts to pyrazolo[5,1-*b*][1,3]benzothiazoles.

A suspension of 3-aminobenzothiazolium salts (**5a-f**, 1 mmol) in triethyl orthoformate (5 mL) was heated to 120 ^{o}C (oil bath temperature) and stirred for 4h. The obtained dark brown solution was evaporated to dryness *in vacuo*, and the residue was suspended in water (10 mL). This suspension was neutralized by conc. NH_4OH and extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried (Na_2SO_4) and evaporated, the residue was treated with methanol (5 mL) and the precipitated product was filtered off and crystallized from MeCN.

3-Phenylpyrazolo[5,1-*b*][1,3]benzothiazole (6a)

Starting from **5a** (0.410 g), beige crystals (0.082 g, 33%); mp 139-140 ºC; IR (KBr): 3025, 1603, 1550, 1471, 1400, 1377, 748, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.2 (s, 1H, H2), 8.0 (d, *J* = 8.0, 1H, H8), 7.7 (d, *J* = 8.0 Hz, 1H, H5) 7.6-7.2 (m, 7H, H-phenyl, H6,7); ^{13}C NMR ($CDCl_3$) δ: 141.6, 134.7, 134.0, 131.5, 130.0, 129.0 (2C), 126.6, 126.2, 124.9 (2C), 124.8, 124.0, 114.5, 112.8; Anal. Calcd for $C_{15}H_{10}N_2S$ (250.32): C, 71.97; H, 4.03; N, 11.19; S, 12.81. Found: C, 71.55; H, 3.91; N, 10.98; S, 12.72.

3-(4-Methylphenyl)pyrazolo[5,1-*b*][1,3]benzothiazole (6b)

Starting from **5b** (0.430 g), beige crystals (0.180 g, 68%); mp 149-150 ºC; IR (KBr): 3020, 2913, 2854, 1556, 1473, 1460, 1373, 808, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.17 (s, 1H, H2), 8.0 (dd, *J* = 8.1, 1.1 Hz, 1H, H8), 7.72 (dd, *J* = 8.0, 1.1 Hz, 1H, H5), 7.52 (ddd, *J* = 8.1, 7.5, 1 Hz, 1H, H7), 7.46 (m, 2H, H2'+H6'), 7.37 (ddd, *J* = 8.0, 7.5, 1.1 Hz, 1H, H6), 7.28 (m, 2H, H3'+H5'), 2.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 141.8 (C2), 136.3 (C4'), 134.6 (C3a), 134.4 (C8a), 130.3 (C4a), 130.0 (C3'+C5'), 128.9 (C1'), 126.9 (C7), 125.2 (C2'+C6'), 125.0 (C6), 124.3 (C5), 114.9 (C3), 113.0 (C8), 21.4 (CH_3); Anal. Calcd for $C_{16}H_{12}N_2S$ (264.34): C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.64; H, 4.50; N, 10.68; S, 12.07.

3-(4-Bromophenyl)pyrazolo[5,1-*b*][1,3]benzothiazole (6c)

Starting from **5c** (0.490 g), beige crystals (0.184 g, 56%); mp 200-201 ºC; IR (KBr): 3087, 1593, 1545, 1471, 1459, 1391, 812, 746 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 8.53 (s, 1H, H2), 8.1 (d, *J* = 8.0, 1H, H8), 7.9 (d, *J* = 8.0 Hz, 1H, H5) 7.66, 7.54 (m, 4H, H-bromophenyl), 7.60 (m, 1H, H7), 7.60 (m, 1H, H6); ^{13}C NMR (DMSO-d_6) δ: 143.0, 135.1, 133.9, 132.8 (2C), 131.0, 130.0, 128.0, 127.3 (2C), 126.1, 125.9, 119.5, 113.5, 113.1; Anal. Calcd for $C_{15}H_9BrN_2S$ (329.21): C, 54.72; H, 2.76; N, 8.51; S, 9.74. Found: C, 54.48;

H, 2.60; N, 8.50; S, 9.62.

3-(4-Chlorophenyl)pyrazolo[5,1-*b*][1,3]benzothiazole (6d)

Starting from **5d** (0.450 g), beige crystals (0.182 g, 64%); mp 182-183 ºC; IR (KBr): 3087, 1547, 1472, 1459, 1391, 814, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.2 (s, 1H, H2), 8.0 (d, J = 8.0, 1H, H8), 7.7 (d, J = 8.0 Hz, 1H, H5) 7.6- 7.3 (m, 6H, H-chlorophenyl, H6,7); ^{13}C NMR ($CDCl_3$) δ: 141.6, 134.8, 134.2, 131.8, 130.2, 129.2 (2C), 127.8, 126.8, 126.2 (2C), 125.0, 124.0, 113.5, 112.9; Anal. Calcd for $C_{15}H_9ClN_2S$ (284.76): C, 63.27; H, 3.19; N, 9.84; S, 11.26. Found: C, 63.12; H, 3.08; N, 9.90; S, 11.18.

3-(4-Fluorophenyl)pyrazolo[5,1-*b*][1,3]benzothiazole (6e)

Starting from **5e** (0.460 g), beige crystals, (0.240 g, 91%); mp 150-151 ºC; IR (KBr): 3070, 1552, 1502, 1472, 1373, 1238, 830, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 8.3 (s, 1H, H2), 8.0 (m, 2H, H5,8), 7.6-7.4 (m, 4H, H-Fphenyl, H6,7), 7.3-7.1 (m, 2H, H-Fphenyl); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ: 162.0 (d, $^{1}J_{C,F}$ = 239 Hz), 141.2, 134.3, 133.8, 129.6, 127.5 (d, $^{4}J_{C,F}$ = 3 Hz), 126.5, 126.3 (2C, d, $^{3}J_{C,F}$ = 8 Hz), 124.8, 123.9, 115.8 (2C, d, $^{2}J_{C,F}$ = 22.5 Hz), 113.4, 112.5; Anal. Calcd for $C_{15}H_9FN_2S$ (268.31): C, 67.15; H, 3.38; N, 10.44; S, 11.95. Found: C, 66.97; H, 3.40; N, 10.45; S, 12.10.

3-(4-Nitrophenyl)pyrazolo[5,1-*b*][1,3]benzothiazole (6f)

Starting from **5f** (0.460 g), yellow crystals (0.160 g, 53%); mp > 256 ºC; IR (KBr): 3076, 2924, 1595, 1550, 1513, 1489, 1340, 1320, 841, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$+TFA) δ: 8.5 (s, 1H, H2), 8.3, 7.7 (m, 4H, H-NO_2phenyl), 8.0 (d, J = 8.1, 1H, H8), 7.9 (d, J = 8.0 Hz, 1H, H5) 7.6- 7.5 (m, 26H, H6,7); ^{13}C NMR ($CDCl_3$+TFA) δ: 146.1, 140.6, 136.9, 132.5, 129.5, 128.0, 126.8, 125.5 (2C), 124.9 (2C), 124.5, 117.2, 113.4, 111.5; Anal. Calcd for $C_{15}H_9N_3O_2S$ (295.32): C, 61.01; H, 3.07; N, 14.23; S, 10.86. Found: C, 60.88; H, 3.12; N, 14.15; S, 10.86.

(2*Z*)-2-[(4-Nitrophenyl)methylidene]-1,3-benzothiazol-3(2*H*)-amine (7)

To a suspension of 3-amino-2-(4-nitrobenzyl)-1,3-benzothiazol-3-ium 4-methylbenzenesulfonate (**5e**, 1 mmol, 0.460 g) in MeCN (15 mL), TEA (1 mL) was added and the mixture was refluxed for 5 min. The formed deep red solution was cooled to rt, and the precipitated crystals were filtered off to give **7** (0.220 g, 77%) as deep red crystals; mp 193-194 ºC; IR (KBr): 3330, 3065, 1589, 1579, 1552, 1478, 1316, 1190, 1114, 840, 742 cm^{-1}; MS: 285, 269, 223; ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ: 8.1 and 7.3 (m, 4H, H-NO_2phenyl), 7.5 (d, J = 8.0, 1H, H7), 7.3-7.1 (m, 2H, H4,5), 7. 0 (m, 1H, H6), 6.4 (s, 1H, H(=CH)), 5.5 (s, 2H, H-NH_2); ^{13}C NMR (DMSO-d_6+$CDCl_3$) δ: 148.5, 145.0, 142.0, 140.7, 126.6, 124.0 (2C), 123.9 (2C), 121.5, 121.2, 118.4, 109.8, 90.5; Ms: m/z 285, 269, 223; Anal. Calcd for $C_{14}H_{11}N_3O_2S$ (285.32): C, 58.93; H, 3.89; N, 14.73; S, 11.24. Found: C, 58.81; H, 3.76; N, 14.70; S, 11.28.

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