FUSED PYRAZOLE SYNTHESIS BY N-N BOND FORMATION: THE PYRAZOLO[5,1-*b*]BENZOTHIAZOLE SYSTEM

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Abstract: Treatment of (benzothiazol-2-yl)acetone oxime **1** with excess trifluoroacetic anhydride (TFAA) at room temperature produces 2-methyl-3-trifluoroacetylpyrazolo[5,1-*b*]benzothiazole **11** in 71-92 % yield depending on the purity of the oxime. Compound **11** is reduced by $NaBH_4$ to the corresponding alcohol **12** and hydrolyzed to the corresponding carboxylic acid **13** under alkaline conditions. Other reagents commonly used to promote Beckmann rearrangement of oximes cause only decomposition of **1** to intractable materials.

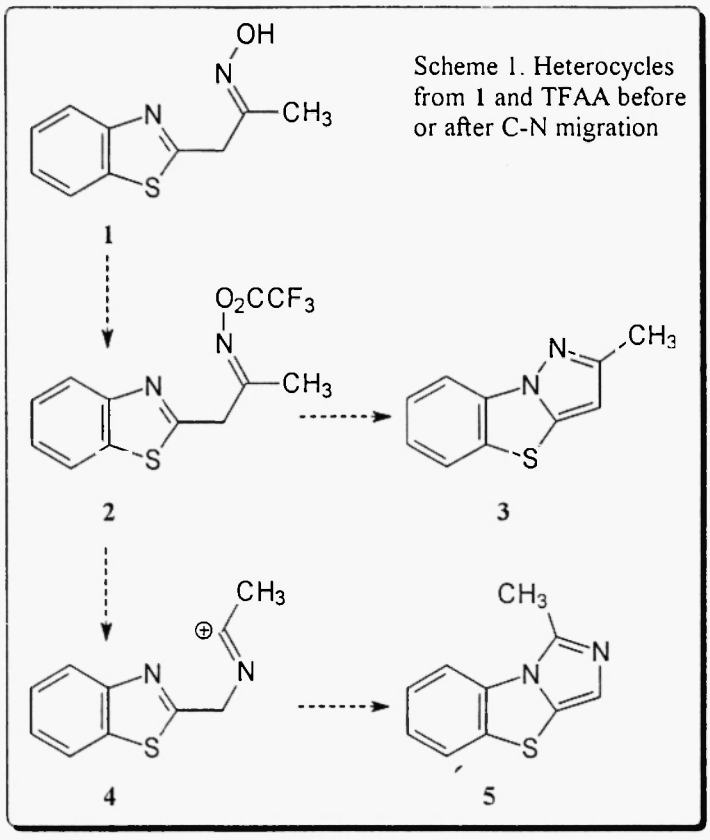
Introduction

As part of a program to examine structure-activity relationships in fused benzothiazole heterocycles, we wished to prepare, in addition to the pyrrole derivatives previously reported (1), compounds containing two nitrogen atoms in the fused ring: pyrazolo[5,1-*b*]benzothiazole **3** and imidazo[5,1-*b*]benzothiazole **5**. Derivatives of **3** substituted in the 3-position (pyrazole numbering) had been prepared in low yield previously (2). Derivatives of **5** substituted in the 2- and 4- positions (imidazole numbering) have also been reported, but the reaction sequence was tedious (3).

It seemed plausible that the skeleton of **3** and/or **5** could be prepared via capture by the benzothiazole nitrogen of electron deficient species generated during the Beckmann rearrangement (4) of oxime **1**. This process is shown in Scheme 1 with **2** and **4** formally representing the intermediates capable of being trapped. There is literature precedence for selective capture of Beckmann rearrangement intermediates both before (5) and after (6) C→N migration and at least one example in which products derived from both intermediates were isolated (7). We now report selective formation of the pyrazolo[5,1-*b*]benzothiazole nucleus **3** based on this approach.

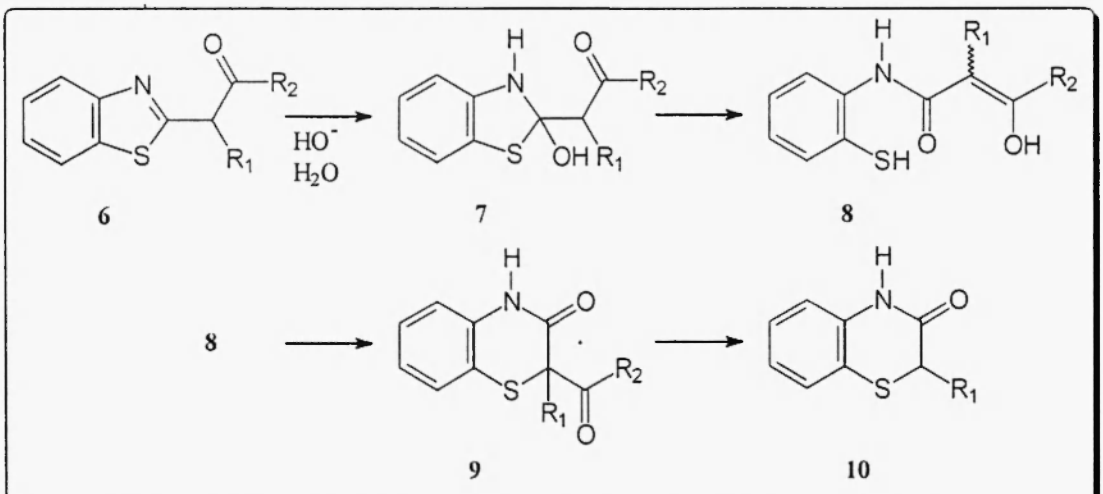
Results and Discussion

Oxime **1** is readily prepared from (benzothiazol-2-yl)acetone (**8**) by standard methods. ^{1}H nmr analysis indicated the compound to be roughly a 1.8:1 ratio of *E*- and *Z*-oxime isomers. The ^{13}C nmr also supports the presence of *E/Z* isomers, with the two oxime carbon sp^2 resonances present in unequal intensities. The more intense resonance (167.1 ppm) represents the *E*-oxime while the more sterically compressed *Z*-oxime shows a smaller peak shifted upfield (165.8 ppm) (9).



Scheme 1. Heterocycles from 1 and TFAA before or after C-N migration

Although this oxime is readily prepared, care must be exercised in the preparation of related compounds. For example, we were unable to obtain an oxime from **6** (R_1 = H, R_2 = Ph); the only isolable product was 1,4-benzothiazin-3-one (**10**, R_1 = H). Similar treatment of **6** (R_1 = R_2 = CH_3) produced mixtures of the desired oxime and a product tentatively identified as the benzothiazinone **9** (R_1 = R_2 = CH_3). As outlined in Scheme 2, attack of hydroxide (or H_2O on a protonated species at low pH) at C-2 followed by ring opening (to **8**), oxidative cyclization (to **9**), and subsequent

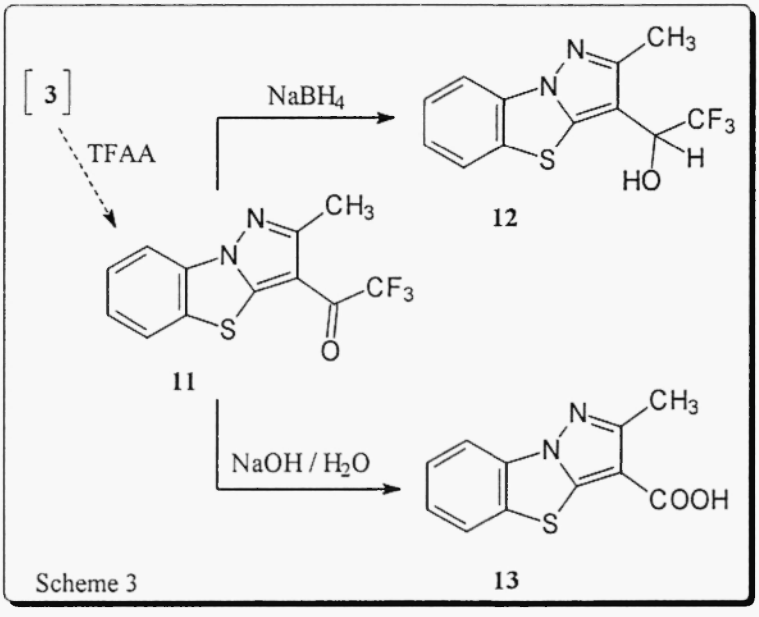


Scheme 2. Suggested mechanism for ketone decomposition during attempted oximation

deacylation could produce **10**. There is ample evidence for reaction of nucleophiles at C-2 of benzothiazoles (10) and oxidative addition of thiols to enols is also well known (11).

Treatment of **1** with trifluoroacetic anhydride at room temperature for 30 min gave a high melting solid in excellent yield. The presence of a trifluoroacetyl group in this product was apparent from the mass spectrum, which showed a strong molecular ion at m/z 284, and major peaks at m/z 215 (base peak, $-CF_3$), 187 ($-CF_3CO$), 174 ($-CF_3$ and CH_3CN), and 146 ($-CF_3CO$ and CH_3CN). The trifluoroacetyl group was definitely carbon bound. Reduction with $NaBH_4$ to an alcohol and alkaline hydrolysis (12) to a carboxylic acid clearly rule out any structure in which the CF_3CO group is bonded to N, O, or S. Unlike 1-pyrrolo[2,1-*b*]benzothiazole carboxylic acid, which readily decarboxylates, this carboxylic acid sublimed under vacuum essentially without decomposition. 4-Pyrazole carboxylic acids are known to be quite thermally stable (13).

Differentiating pyrazole nucleus **3** from the imidazole skeleton **5** on a purely chemical basis favors **3** since imidazole derivatives are generally resistant to acylation (3-phenylimidazo[5,1-*b*]benzothiazole does not acetylate with hot $Ac_2O/AlCl_3$ (14)). On the other hand, simple pyrazoles undergo acylation with the approximate facility of benzene (15). This analysis is supported by the lack of reactivity of independently prepared **5** (16) with TFAA. The imidazole skeleton is therefore ruled out for the product of reaction of oxime **1** with TFAA.

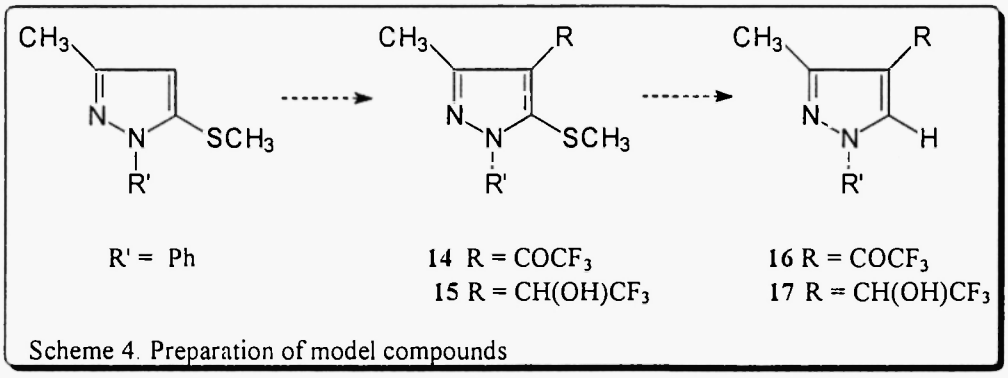


Scheme 3

Pyrazole **11**, the alternative product, could arise from trifluoroacylation of initially formed **3** by excess TFAA. Structure **11** (and therefore **12** and **13**) was confirmed by desulfurization with Raney nickel to either **16** or **17** depending on reaction conditions. Authentic samples were prepared via **14** and **15** derived from 4,4'-bis(methylthio)-3-buten-2-one (17, 18) (Scheme 4).

Oxime **1** was treated with other reagents used to promote Beckmann rearrangement (4) in an attempt to prepare **3** directly. These reactions led either to recovery of starting material or total decomposition. The oxime from **6** ($R_1 = R_2 = CH_3$) produces only polymeric material upon treatment

with TFAA under conditions used to prepare **11** (19). The apparent uniqueness of this reaction may be due to the instability of **3** and related compounds under the acidic reaction conditions of Beckmann rearrangement. Electron deficient compounds such as **11** would be less prone to acid catalyzed decomposition. This would also explain why **3** could not be isolated from reactions of **1** with small quantities of TFAA. In these cases only **11** was isolated in lower yield and poorer purity.



R' = Ph

14 R = $COCF_3$
15 R = $CH(OH)CF_3$

16 R = $COCF_3$
17 R = $CH(OH)CF_3$

Scheme 4. Preparation of model compounds

Experimental Section

Reagents and solvents were used as received. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Chemical shifts are reported relative to TMS (^1H, ^{13}C) or 1,2-dichloro-1,1-difluoroethane (^{19}F).

(Benzothiazol-2-yl)acetone

A mixture of 2-aminobenzenethiol (Aldrich technical grade, 20 g, 0.16 mole) and ethyl acetoacetate (20.8 g, 0.16 mole) in 200 mL of mixed xylenes was heated to reflux under a Dean/Stark trap for azeotropic ethanol removal. After 7 h at reflux, the volume was reduced *in vacuo* to about 50 mL and the orange liquid was diluted with absolute ethanol (75 mL) and placed in the freezer. The yellow solid which formed was collected and washed with cold ethanol (6.6 g, 22 %). Recrystallization from ethanol gave a gray solid: mp 113 °C (lit. (8a) mp 117 °C): ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, J = 8.25 Hz, 1H), 7.92 (d, J = 8.00 Hz, 1H), 7.48-7.37 (m, 2H), 4.23 (s, 2H), 2.32 (s, 3H) [the spectrum also contains peaks at 5.63 (s, 1H) and 2.10 (s, 3H) corresponding to about 20 % of the enol.]; IR(KBr): 2200-3200 cm^{-1} (no carbonyl is present); partial ^{13}C NMR ($CDCl_3$, 50 MHz): Keto form: δ 162.8 (S-C=N), 48.3 (CH_2), 29.9 (CH_3); enol form: 92.6 (CH=), 22.1 (CH_3).

(Benzothiazol-2-yl)acetone oxime (1)

Hydroxylamine hydrochloride (19.3 g, 0.28 mole) in water (115 mL) was neutralized with 10% aqueous NaOH (76.6 mL) and 3.0 g (0.016 mole) of recrystallized (benzothiazol-2-yl)acetone was added followed by absolute ethanol (200 mL). The solution was refluxed on a steam bath for 3 h during which time the color changed from green to greenish yellow. The cooled reaction mixture was extracted with chloroform (2 x 100 mL). The combined organic layer was washed with water then dried (Na_2SO_4). Solvent removal produced a yellow oil which crystallized in the freezer; trituration with ethanol and filtration gave a yellow solid (2.78 g, 86%). Recrystallization from ethanol gave an analytically pure sample as white needles: mp 83-85 °C, ^1H NMR ($CDCl_3$, 200 MHz, mixture of *E/Z* isomers): δ 9.84 and 9.67 (br s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.50-7.31 (m, 2H), 4.28 and 4.05 (both s, 2H, ratio is 1:1.8, respectively), 2.00 (s, 3H), ^{13}C NMR (DMSO-d_6, 50 MHz): (*E*-isomer) δ 167.1, 154.6, 153.2, 135.7, 126.1, 125.2,122.9,121.3,

40.7, 13.6; (*Z*-isomer) δ 165.8, 153.0, 152.7, 135.6, 126.1, 125.1, 122.8, 121.5, 33.6, 19.9; IR (KBr): 3180, 3060, 1660, 1010, and 940 cm^{-1}, MS (70 ev): m/z 206 (17), 149 (100), 45(100). Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.34; H, 4.98; N, 13.51.

2-Methyl-3-trifluoroacetylpyrazolo[5,1-*b*]benzothiazole (11)

The oxime (0.2 g, 0.97 mmole) was suspended in benzene (2 mL) and TFAA (1.13 mL; 8 mmole) was added in one portion. The brown mixture was stirred at room temperature for 30 min at which time all volatiles were removed *in vacuo*. Addition of a little ether to the brown oil produced a solid. Washing with several portions of ether gave a cream colored solid (0.2 g, 73%). Depending upon the purity of the oxime used, yields varied from 71 to 92%. Recrystallization from ethanol gave an analytical sample: mp 204-205 °C; IR (KBr): 1645 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz): δ 8.33-7.97 (m, 2H), 7.90-7.53 (m, 2H), 2.88 (s, 3H); (DMSO-d_6): δ 7.88 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.58-7.49 (m, 2H), 2.93 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.1 (q, J_{C-F} = 34.9 Hz), 144.0, 141.5, 132.9, 131.1, 127.4, 125.4, 123.0, 116.7 (q, J_{C-F} = 290 Hz), 115.2, 15.2; ^{19}F NMR (DMSO-d_6): δ -73.9 (s); MS (70 ev): m/z 284 (rel. int. 66, M^+), 215 (100). Anal. Calcd for $C_{12}H_7F_3N_2OS$: C, 50.75; H, 9.86; N, 2.46; Found: C, 50.62; H. 9.78; N, 2.53.

2-methyl-3-pyrazolo[5,1-*b*]benzothiazolecarboxylic acid (13)

A mixture of **11** (2 g, 7.04 mmole) and 0.6 M NaOH in 50% aqueous ethanol (100 mL) was refluxed for 4 h. The cooled solution was poured into 100 mL water and acidified to pH 2 with 5% HCl solution. After cooling on ice, a white precipitate was collected and dried under vacuum (1.43 g, 88%): mp 245 °C, IR (KBr): 3120-2200, 1665 cm^{-1}, MS (70 ev): m/z 232 (M^+), 161 (100 %).

Reduction of 2-methyl-3-trifluoroacetylpyrazolo[5,1-*b*]benzothiazole with sodium borohydride

A solution of $NaBH_4$ (79 mg, 2.1 mmole) in water (1 mL) was mixed with a solution of **11** (300 mg, 1.05 mmole) in absolute ethanol (6.5 mL) and the mixture refluxed for 20 min. The solvent was evaporated *in vacuo* and chloroform was added to the residue. The mixture was washed once with water, dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give alcohol **12** as a white solid (250 mg, 83%): mp 190-192 °C: IR (KBr): 3050 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz): δ 8.13-7.77 (m, 2H), 7.63-7.30 (m, 2H), 7.08 (br s, 1H,), 5.07 (q, J = 3.8 Hz, 1H), 2.72 (s, 3H); (DMSO-d_6): δ 7.72 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.45-7.25 (m, 2H), 5.13 (q, J = 6.9 Hz, 1H), 2.82 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 138.0, 133.5, 132.0, 126.7, 125.5, 125.1, 124.1, 114.7, 67.43 (q, J = 30.9 Hz), 15.6; ^{19}F NMR: δ -78.6 (d, J = 6.6 Hz), MS (70 ev): 286 (36), 217 (100). Anal. Calcd for $C_{12}H_9F_3N_2OS$: C, 50.34, H, 3.17; N, 9.79; Found: C, 50.23; H, 3.35, N, 9.67.

Acknowledgments

Financial support from the Dow Chemical Co. is gratefully acknowledged. H.S. Folk wishes to thank Michigan Technological University for a de Vlieg Summer Fellowship. An NSF award (CHE-9512445) provided partial support for acquisition of the Varian Inova 400 spectrometer.

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Received on March 9, 1997