Synthesis and Identification of 4-Methyl-*N*-(4*H*-1,2,4-triazol-4-yl)-2-benzothiazolamine, an Impurity in the Synthesis of Tricyclazole

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The synthesis of 4-methyl-*N*-(4*H*-1,2,4-triazol-4-yl)-2-benzothiazolamine, **4**, a by-product in the synthesis of tricyclazole, **1**, by oxidative cyclization of the corresponding thiourea, **12**, with thionyl chloride, is described.

J. Heterocyclic Chem., **26**, 1735 (1989).

Introduction.

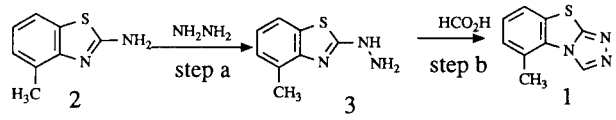
Tricyclazole, **1**, the major constituent of the rice blast fungicide Beam[R] [1], is synthesized in two steps [2] (see Scheme 1) from 4-methyl-2-benzothiazolamine, **2**, by reacting it with hydrazine to form the hydrazino intermediate **3**, and heating in formic acid to accomplish formylation and cyclization in one step.

During a scale-up of the synthesis of **1**, a minor impurity was discovered, present in $<0.3\%$, which, based on spectral data, was assigned structure **4**. Since compounds like **4** were unknown in the literature, and since a sizable sample was required for analytical purposes, an effort was made to synthesize structure **4** unequivocally. Herein we confirm the structural assignment of the impurity.

An examination of the reactions leading to the synthesis of tricyclazole, **1**, (Scheme 1), suggested that **4** could have

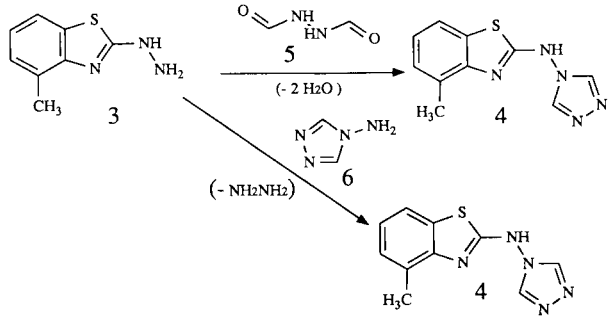
Scheme 1

(Tricyclazole synthesis)

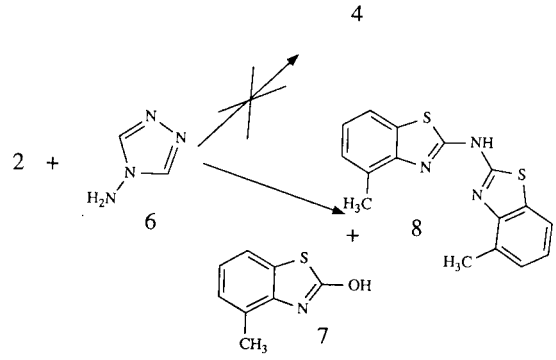


Scheme 2

(Possible routes to 4)



Scheme 3

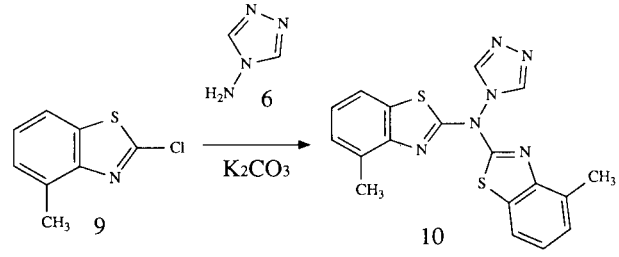


formed in step b of Scheme I by two possible routes, as outlined in Scheme 2. Since a slight excess of hydrazine was known to be present in the conversion of **3** to **1**, hydrazine could have reacted with the formic acid to form diformylhydrazide, **5**, [3] which could then have reacted directly with **3** to form the impurity **2**. Similarily, the reaction of hydrazine with formic acid is known to form 4*H*-1,2,4-triazol-4-amine **6** [4], but at higher temperatures than were employed in Scheme 1. If some of **6** did form under the conditions of the tricyclazole reaction, it could have reacted with **3** to displace the hydrazino group to form **4** (Scheme 2).

1. Synthetic Approaches Related to the Tricyclazole Synthesis Route.

Our first approaches involved altering the reaction conditions in step b (Scheme 1) in order to optimize the for-

Scheme 4



+ 4 (TRACE)

mation of **4**. Three approaches were tried: 1) the concentration of free hydrazine in step b was increased, 2) freshly prepared diformylhydrazine was reacted with **3** in a variety of solvents and under various temperature regimens, and 3) some 4*H*-1,2,4-triazol-4-amine, **6**, was added to the reaction. None of these protocols successfully increased the small amount of **4** present in the reaction product.

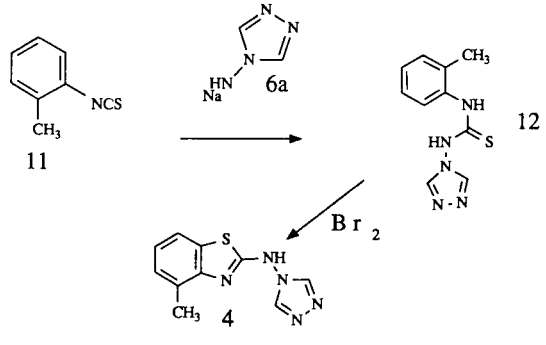
The next approach was to synthesize **4** by the replacement of the amino group in **3** with 4*H*-1,2,4-triazol-4-amine, **6**, under the conditions used in Scheme 1 to achieve substitution of the amino by hydrazine [2]. After numerous attempts, the only products isolated from the reaction were 4-methyl-2-benzothiazolol, **7**, and the dimer **8** (see Scheme 3). Further, there was no evidence from thin-layer chromatography (tlc) comparisons with the impurity **4** that any of it was formed in the reaction.

2. Reactions of 2-Halo-4-methylbenzothiazole with 4-*H*-1,2,4-Triazole-4-amine, **6**.

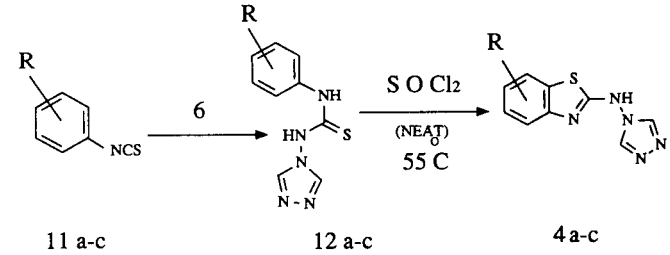
We next tried to form **4** directly from the reaction of 2-halo-4-methylbenzothiazole with **6**. First, a synthetic route to either the 2-bromo or 2-chloro-4-methylbenzothiazole was needed. Although unsubstituted 2-benzothiazolamine is known to form 2-bromobenzothiazole under Sandmeyer conditions [5], albeit in low yield, 4-methyl-2-benzothiazolamine, **3**, could not be made to undergo a similar transformation. Conditions were found, however [6], that allowed the ready conversion of the hydrazine intermediate **3** to 2-chloro-4-methylbenzothiazole **9** in good yield using *neat* thionyl chloride at 55%.

With **9** in hand, nucleophillic displacements of the chlorine with aminotriazole **6** were attempted. A variety of conditions were used, ranging from no added base to strong bases, but the chlorine atom proved to be very resistant to displacement or the products were unstable. However, by using potassium carbonate in DMF, compound **4** apparently formed during the reaction but continued to react with additional **9** to form mainly the bis addition product **10** (Scheme 4). By performing the reaction with an excess of aminotriazole **6**, a small quantity of **4** could be isolated, enough to confirm the structure of the impurity but not enough for use as an analytical standard or for biological evaluation.

Scheme 5



Scheme 6



11 a-c 12 a-c 4 a-c

R	YIELD (12)	M.P.	YIELD (4)	M.P.
a. CH_3	71 %	156-158 °C	61 %	262-264 °C
b. H	73 %	164-166 °C	64 %	278-279 °C
c. Cl	30 %	162-163 °C	21 %	245-247 °C

3. Oxidative Cyclization of Thiourea.

Finally, with the lack of success in either forming the triazole last or coupling the triazole to the benzothiazole, an approach was developed that formed the benzothiazole last. This involved oxidatively cyclizing thiourea **12** with bromine to give **4** (Scheme 5). Compound **11**, 1-isothiocyanato-2-methylbenzene, readily formed from the reaction of *o*-toluidine with thiophosgene, reacted with either aminotriazole, **6**, or its sodium salt **6a** to form the thiourea **12** in moderate-to-good yield.

Bromine oxidation of **12**, normally successful in the formation of 2-benzothiazolamines from the corresponding thioureas [7], failed to form more than a trace of **4**, accompanied by a great deal of decomposition product. Using conditions developed by Papenfuhs [8], to cyclise phenylthiourea to 2-benzothiazolamine by heating the thiourea in *neat* thionyl chloride at 50°, we were able to carry out the conversion of **12** to **4** in good yield. The reaction proved general enough for both the unsubstituted phenylthiourea **12b** and the 2-chlorophenylthiourea **12c** to be converted to the corresponding 4*H*-1,2,4-triazol-4-yl-benzothiazolamines, **4b** and **4c** (Scheme 6).

This route allowed us to synthesize quantities of **4** and to screen **4** and its analogs **4b** and **4c** for biologically activity. None of these triazolylbenzothiazolamines exhibited any biological activity in our screens.

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Nuclear magnectic resonance spectra for proton (^{1}H) nmr were recorded on a Varian T-60 and a Bruker 360 MHz; chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference and were assigned on integral information and coupling patterns. Mass spectra were taken on a Hewlett-Packard 5985 GC/MS.

Formation of 2-Chloro-4-Methylbenzothiazole **9**.

To a round-bottomed three-necked flask, fitted with a mechanical stirrer was added 118.97 (1.0 mole) of thionyl chloride. This was slowly heated to 55° and, with stirring, 98.5 g (0.50 mole) of 2-hydrazino-4-methylbenzothiazole, **3**, was slowly added over 6 hours, keeping the temperature at 55°. After addition, the reaction mixture was stirred an additional hour then cooled to room temperature. A solid formed upon cooling which was distilled (130°/9mm) to yield 44.7 g (48% yield) of **9** as a yellow liquid which solidified on cooling, mp 47-48°; ^{1}H nmr (deuteriochloroform): δ = 2.71 (s, 3H), 7.25-7.33 (m, 2H), 7.54-7.62 (m, 1H); ms: m/e 183.

Anal. Calcd. for C_8H_6ClNS: C, 52.32; H, 3.27; N, 7.63. Found: C, 52.29; H, 3.19; N, 7.77.

Formation of **2** and **11** from 2-Chloro-4-methylbenzothiazole.

A mixture of 1.87 g (0.01 mole) of 2-chloro-5-methylbenzothiazole **10**, 1.64 g (0.02 mole) of 4*H*-1,2,4-triazol-4-amine **5** and 1.38 g (0.01 mole) of potassium carbonate was combined with 50 ml of dimethylformamide and the stirred at 150° until tlc (1:1 toluene/ethyl acetate on silica gel) indicated the absence of **10** (about 3 hours). The cooled solution was poured into water and an off-white solid formed which, when recrystallized from methanol gave 1.5 g of compound **11** as off-white needles, mp 250-261°; ^{1}H nmr (DMSO-d_6): δ = 2.67 (s, 6H), 7.25-7.29 (m, 4H), 7.60-7.67 (m, 2H), 8.58 (s, 2H, triazole protons); ms: m/e 378.

Anal. Calcd. for $C_{18}H_{14}N_6S_2$: C, 57.14; H, 3.70; N, 22.22. Found: C, 56.99; H, 3.80; N, 22.45.

The mother liquor was concentrated and a 0.15 g of **4**, crystallized, mp 262-264°; H^1 nmr (DMSO-d_6): δ = 2.38 (s, 3H), 7.0-7.16 (m, 3H), 8.66 (s, 2H, triazole protons), 11.8-12.25 (b, 1H, amino proton); ms: m/e 231; tlc, r_f 0.7 (1:1 toluene/ethyl acetate eluent, silica gel).

Anal. Calcd. for $C_{10}H_9N_5S$: C, 51.95; H, 3.90; N, 30.30. Found: C, 52.15; H, 3.91; N, 30.15.

Formation of 1-Isothiocyanato-2-methylbenzene, **11**.

A solution of 5.6 g (0.1 mole) of *o*-toluidine in 100 ml of chloroform was cooled to 0° and to it was added, simultaneously, with vigorous stirring, a solution of 21 g (0.2 mole) of potassium carbonate in 50 ml of water and a solution of 11.5 g (0.1 mole) of thiophosgene in 50 ml of chloroform. After addition, the solution was allowed to warm to room temperature. The chloroform solution was isolated, dried, and the solvent removed on a rotary evaporated and a mixture of solid and liquid resulted. This was slurried in hexane and filtered. The hexane was evaporated from the filtrate yielding 12.5 g (84%) of **11** as a yellow, mobile liquid with ir and nmr spectra consistent with the desired isothiocyanate. This compound was used without further purification in the formation of the thiourea **12**.

Formation of *N*-(2-Methylphenyl)-*N'*-(4*H*-1,2,4-triazol-4-yl)thiourea, **12**, from **11**.

4*H*-1,2,4-Triazol-4-amine, **6**, (8.4 g, 0.1 mole) was dissolved in 200 ml of dry dimethylformamide. The solution temperature was lowered to 0° by cooling with a dry ice/acetone bath and to it was then added, under nitrogen, 2.4 g (0.12 mole) of sodium hydride (4.8 g, 50% sodium hydride in mineral oil, washed with pentane) and the resultant mixture was stirred for 2 hours at room temperature. The mixture was then cooled to 0° and to it was slowly added 17.88 g (0.12 mole) of 1-isothiocyato-2-methylbenzene, with some foaming resulting. After addition, the reaction was stirred at 0° for 1 hour and then allowed to reach room temperature over 16 hours. The reaction mixture was then poured into 1.0 liter of ice-water and acidified to *p*H 1 with dilute hydrochloric acid. An off-white solid slowly formed on standing. This was filtered and about 17 g (71% yield) of **12** was formed. This was recrystallized from ethanol to yield a white solid, mp 156-158°; H^1 nmr (DMSO-d_6); δ = 2.83 (s, 3H), 7.16-7.25 (m, 4H), 8.67 (s, 2H, triazole protons), 10.1 (s, 1H), 10.8 (s, 1H); ms: m/e 233.

Anal. Calcd. for $C_{10}H_{11}N_5S$: C, 51.48; H, 4.75; N, 30.02; S, 13.74. Found: C, 51.26; H, 4.75; N, 29.77; S, 13.44.

Formation of **4** and from **12**.

To 25 ml of thionyl chloride, heated to 55° C with stirring, was added 5.0 g (0.02 mole) of the thiourea **12** slowly, over one hour. Heating was continued for 4 hours and the mixture cooled to room temperature. A solid formed which was added to 800 ml of water and filtered. The filtrate was collected and the *p*H raised to *p*H 8 with ammonium hydroxide. A white solid formed which was collected, dried and recrystallized from methanol to yield 1.67 g of **4** as white needles, mp 262-264°C, the elemental analysis was consistent with $C_{10}H_9N_5S$ and the tlc, nmr and mass spectra were identical to those obtained for both the impurity isolated from the synthesis of tricyclazole and for the formed from the reaction of 4*H*-1,2,4-triazol-4-amine and the 2-chloro-4-methylbenzothiazole.

Acknowledgements.

I would like to acknowledge the contributions of John Koons, who did much of the analytical evaluations of tricyclazole which led to the discovery of impurity **4**.

REFERENCES AND NOTES

[1] J. D. Froyd, C. J. Paget, L. R. Guse, B. A. Dreikorn and J. L. Pafford, *Phytopathology*, **66**, 1135 (1976).

[2] C. J. Paget, U.S. Patent 4,064,261 (1972); *Chem. Abstr.*, **79**, 18721B (1973).

[3] C. Ainsworth and R. Jones, *J. Am. Chem. Soc.*, **77**, 621 (1955).

[4] C. F. H. Allen and A. Bell, *Org. Synth.*, Coll Vol. **3**, 96 (1965).

[5] Y. Mizuno, K. Adachi and K. Nakamura, *Pharm. Bull.*, **1** 319 (1953).

[6] T. Papenfuhs, European Patent 43,013 (1982); *Chem. Abstr.*, **96**, 104299E (1982).

[7] D. R. Clark and H. S. Pridgen, U.S. Patent 4,363,913 (1982); *Chem. Abstr.*, **98**, 89352K (1983).

[8] T. Papenfuhs, *Angew. Chem. Int. Ed. Engl.*, **21**, 542 (1982).