Azole Chemistry. X.[1] Silaazoles

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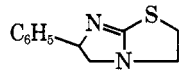
2-Mercaptoimidazoles and -benzimidazoles react with bromomethyldimethylchlorosilane in tetrahydrofuran to give the respective bromomethyldimethylchlorosilane derivates. Cyclodehydrohalogenation of the latter by 1,8-bis(dimethylamino)naphthalene affords 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazoles and 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazoles in good yields. The spectral properties of the new heterocycles are discussed.

A number of fused azoles exhibit important pharmacological activity (*e.g.*, **1**, tetramisole, is a commercial, broad spectrum anthelmintic).[3-7]



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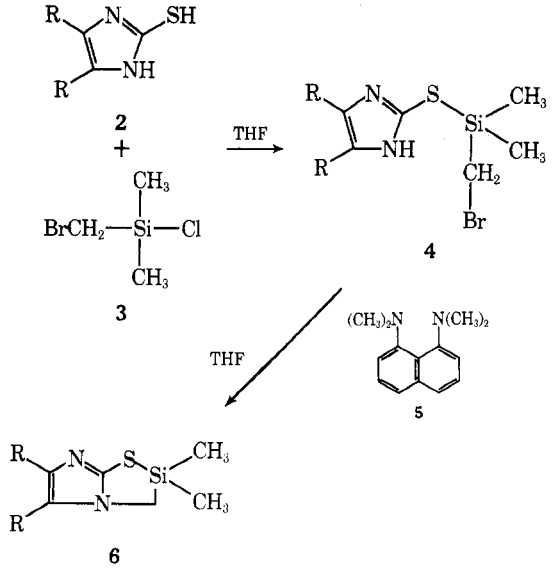
It was of considerable interest to learn what effect the replacement of a ring carbon by silicon would have on the activity of azoles of structural type **1**. The preparation of these heterocycles was required as a first step in attempting to answer this question. We now wish to report a simple and convenient synthesis of the 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazoles and 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazoles.

Results and Discussion

Reaction of 2-mercaptoimidazole (**2a**, R = H) or 4,5-diphenyl-2-mercaptoimidazole (**2b**, R = C_6H_5) with bromomethyldimethylchlorosilane (**3**) in anhydrous tetrahydrofuran (THF) afforded the bromomethyl silylated imidazoles (**4a** (R = H), **4b** (R = C_6H_5)), characterized on the



basis of analytical data and spectral results (Table I). Previous studies using α-halo carbonyls[8] and epoxy bromides[9] showed that condensation occurs at the mercapto group of 2-mercaptoimidazoles or 2-mercaptobenzimidazoles.

The infrared (ir) spectra of **4** (KBr disk) were characterized by an NH stretching band at 3400 cm^{-1}; a weak absorption at 1427–1433 cm^{-1} due to asymmetric deformation of the methyl groups bound to silicon.[10] The nmr spectra (DMSO-d_6) of **4a** and **4b** showed singlets at δ 0.20 and 0.22, respectively, corresponding to the *gem*-dimethyl group, and singlets at δ 2.87 and 2.97, respectively, for the methylene group.

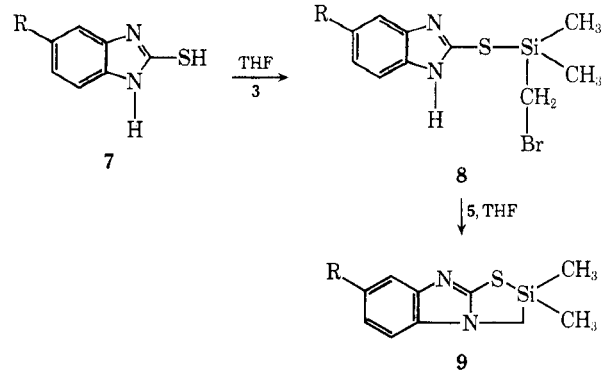
Table I
Yields and Melting Points for 4, 6, 8, and 9

Compd	Formula[a]	Mp, °C	Yield,[b] %
4a, R = H	$C_6H_{11}BrN_2SiS$	177–178	46
4b, R = C_6H_5	$C_{18}H_{19}BrN_2SiS$	205–206	50
6a, R = H	$C_6H_{10}N_2SiS$	128–133	80–85
6b, R = C_6H_5	$C_{18}H_{18}N_2SiS$	150 dec	80–90
8a, R = H	$C_{10}H_{13}BrN_2SiS$	218–219	47
8b, R = NO_2	$C_{10}H_{12}BrN_3O_2SiS$	>177 dec	31
9a, R = H	$C_{10}H_{12}N_2SiS$	181–182	>80
9b, R = NO_2	$C_{10}H_{11}N_3O_2SiS$	165 dec	65

[a] All compounds except **4a** (R = H) (*Anal.* Calcd: C, 28.69. Found: C, 29.42.) and **9a** (R = H) (*Anal.* Calcd: C, 54.50. Found: C, 53.93.) gave C, H, and N analysis within 0.4 of the calculated values. [b] No attempt was made to optimize yields.

Cyclodehydrohalogenation of **4** to **6** was effected in high yield by use of the powerful but nonnucleophilic base, 1.8-bis(dimethylamino)naphthalene (**5**, "proton sponge").[11] Nucleophiles, such as hydroxide or methoxide ion, cleaved the sulfur–silicon bond of **4**. The ir spectra of 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazole (**6**, R = H) and its 5,6-diphenyl derivative (**6**, R = C_6H_5) showed the expected asymmetric and symmetric deformation bands for the methyl groups attached to silicon, but lacked any absorption due to an NH group. In the nmr spectrum, the signal for the methyl groups of **6a** (R = H) and **6b** (R = C_6H_5) appeared at almost the same chemical shift as noted for **4**, while the methylene groups of **6** displayed a singlet at higher field than observed for the corresponding protons of **4** (*i.e.*, δ 2.56–2.59 for methylene protons of **6**).

Condensation of 2-mercaptobenzimidazole (**7a**, R = H) or 2-mercapto-5-nitrobenzimidazole (**7b**, R = NO_2) with **3** in THF gave **8a** (R = H) and **8b** (R = NO_2), which on exposure to 1,8-bis(dimethylamino)naphthalene afforded 2-dimethylsila-3*H*-thiazolo[3,2-*a*]benzimidazole (**9a**, R = H) and its 7-nitro derivative (**9b**, R = NO_2)[12] in good yields (Table I). The ir and nmr spectral properties for **8** and **9** were completely analogous to data discussed for the related



systems, **4** and **6**. In addition, a parent molecular ion peak was observed in the mass spectrum of **9a**, R = H, at *m/e* 220.

In summary, condensation of mercaptoazoles with bromomethyldimethylchlorosilane, followed by cyclodehydrohalogenation, constitutes a simple two-step entry into fused silaazoles. This synthetic pathway should be applicable to other azoles such as mercaptotriazoles and mercaptotetrazoles. Compounds **4**, **6**, **8**, and **9** are currently being screened for pharmacological activity.

Experimental Section

General. Elemental analyses were determined by Hoffmann-La Roche, Nutley, N. J., Pascher Microanalytical Laboratory, Bonn, Germany, and by Heterocyclic Chemical Corp., Harrisonville, Missouri. Infrared spectra were determined using a Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. All mass spectra were obtained from an AEI MS-902 spectrometer.

Bromomethyldimethylchlorosilane and 1,8-bis(dimethylamino)-naphthalene were purchased from Pierce and Aldrich Chemical Co., respectively, and were used as received. The mercaptoazoles were commercially available and were recrystallized from aqueous ethanol and then oven dried, prior to use.

Solvents were purified by standard techniques. All reactions were run under a nitrogen atmosphere. All weighings and reaction work ups were carried out in a glove bag (N_2 atmosphere).

General Procedure for Reactions of Mercaptoazoles (2, 7) with Bromomethyldimethylchlorosilane (3). To a solution of the mercaptoazole in THF (40–70 ml) was added, by syringe techniques, an approximately equimolar amount (7–15 mmol) of bromomethyldimethylchlorosilane. The mixture was stirred at room temperature for 1 day and filtered, and the white solid was washed well with the THF and then dried *in vacuo*. The yields, melting points, and analytical data for **4** and **8** are listed in Table I.

General Procedure for Cyclodehydrohalogenation of 4 and 8. A suspension of **4** or **8** (5–12 mmol) in THF (50–80 ml) containing 1,8-bis(dimethylamino)naphthalene (1.0–1.5:1.0 mol ratio of **5**:**4**,**8**) was stirred for 1 day at room temperature. The solution was filtered to remove protonated **5** and any unreacted **4** or **8**, and the filtrate was evaporated *in vacuo*. The residue obtained was treated with hexane and filtered, and the product (**6**, **9**) was washed well with hexane and dried. The hexane washings contained unreacted **5** (if present). The yields, melting points, and analytical data for **6** and **9** are given in Table I.

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Registry No.—**2a**, 872-35-5; **2b**, 3718-54-5; **3**, 16532-02-8; **4a**, 53178-96-4; **4b**, 53279-97-5; **6a**, 53178-98-6; **6b**, 53178-99-7; **7a**, 583-39-1; **7b**, 6325-91-3; **8a**, 53179-00-3; **8b**, 53179-01-4; **9a**, 53179-02-5; **9b**, 53179-03-6; i, 53179-03-6.

References and Notes

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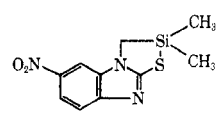
(11) R. W. Alder, P. S. Bowman, W. R. P. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).
(12) We cannot, at present, distinguish **9b**, R = NO_2, from i.



i

Benzimidazole Chemistry. I. Syntheses of the Three *N*-*n*-Propyl Isomers of 4-Amino-2,6-dimethylbenzimidazole

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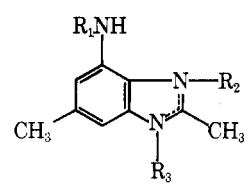
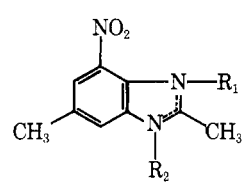
The specific preparations of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) are described. These methods make use of the regiospecific or highly regioselective acylation and alkylation possible in the substrates. A correlation of isomeric structure with nmr spectra is also presented.

The regiospecificity of acylation and alkylation at multiple sites available in substituted fused imidazoles has received the greatest attention with purine derivatives because of their importance in living systems.[1] These data have received only limited application to the prediction of the reactivity of substitution of benzimidazoles.[2] For this reason the syntheses of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) were attempted in order to obtain authentic examples of the three structures for comparison. Similarly 1-*n*-propyl-2,6-dimethyl-4-nitrobenzimidazole (**4**) was prepared and an unsuccessful attempt was made to synthesize 1-*n*-propyl-2,5-dimethyl-7-nitrobenzimidazole (**5**).



1, R_1 = H; R_2 = *n*-C_3H_7; R_3 =
2, R_1 = H; R_3 = *n*-C_3H_7; R_2 =
3, R_1 = *n*-C_3H_7; R_2 = H; R_3 =



4, R_2 = *n*-C_3H_7; R_1 =
5, R_1 = *n*-C_3H_7; R_2 =

The synthesis of authentic **1** could be accomplished from the symmetrical *N*-*n*-propyl-2,6-dinitro-*p*-toluidine (**6**) obtained from 2,6-dinitro-*p*-toluidine (**7**)[3] by a Sandmeyer