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A Novel General Synthesis of 2-Substituted 1,2-Benzisothiazolin-3-ones. Cyclization of N-Substituted 2-Methoxycarbonylbenzenesulfenamides

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Reaction of methyl 2-mercaptobenzoate (2) or dimethyl 2,2′-dithiodibenzoate (3) with bromine, chlorine, or sulfuryl chloride gave 2-methoxycarbonylbenzenesulfenyl halides (4), which were not isolated. Halides 4 reacted with primary aliphatic, aromatic, and heterocyclic amines to yield N-substituted 2-methoxycarbonylbenzenesulfenamides 5. The latter underwent catalytic cyclization by strong bases, providing 2-substituted 1,2-benzisothiazolin-3-ones (6) in good to excellent overall yields. Evidence supports a general base catalyzed mechanism initiated by the abstraction of a proton from the sulfenamide nitrogen, and followed by intramolecular attack on the ester carbonyl group and expulsion of methoxide ion. This route is simple and presented as a new general method for the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones.

The first preparation of 1,2-benzisothiazolin-3-one was reported[1] by McKibben and McClelland in 1923. A few years later the synthesis of 2-substituted 1,2-benzisothiazolin-3-ones (6) was achieved.[2] The chemistry of 6 was reviewed[3] in 1947. Since that time, it has been discovered that structure 6 possesses high antibacterial and antifungal activity,[4,5] which have also been reviewed recently.[6] A few years ago, the first commercial product (6, R = H) useful for the preservation of aqueous media containing organic matter was introduced.[7] It seems quite possible that other members of the benzisothiazolinone series will be introduced for similar commercial applications.

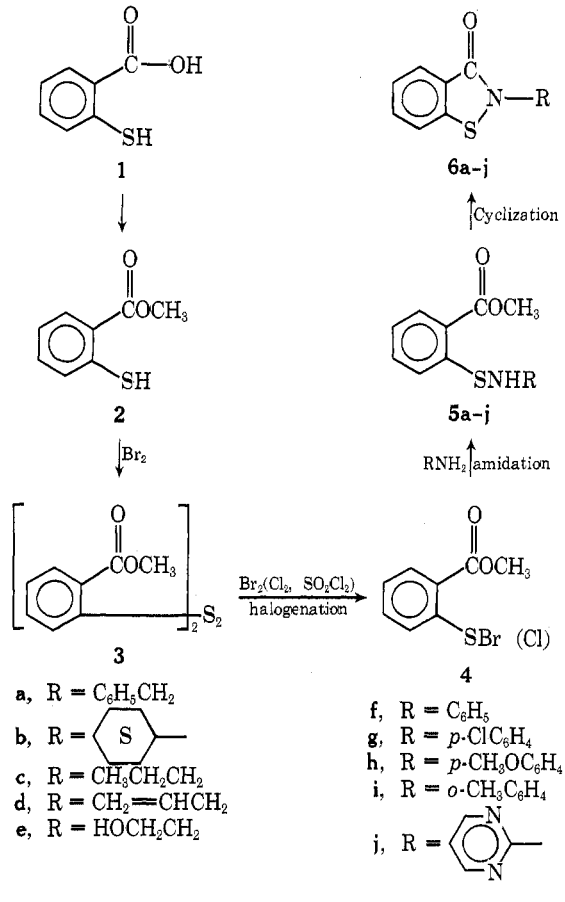
Benzisothiazolinones are prepared according to two well-established routes,[8] both of which use 2,2′-dithiodibenzoic acid as starting material. The acid is firstly[9] treated with thionyl chloride to give 2,2′-dithiodibenzoyl chloride, which is converted into the desired diamide, treated with bromine, and cyclized in boiling glacial acetic acid. Alternatively, halogenation of the acid chloride can precede amidation and cyclization. In this report, a third general synthesis utilizing methyl 2-mercaptobenzoate for starting material is presented.

Results and Discussion

Our continued interest in the chemistry of benzisothiazolinones led to a search for a different synthetic route, possibly circumventing the key intermediate 2,2′-dithiodibenzoyl chloride. For this purpose methyl 2-mercaptobenzoate (2), obtained directly by the Sandmeyer reaction on methyl anthranilate, was chosen as the starting material. It was thought that 2, or its oxidation product 3, could be easily converted into sulfenamides 5, which might subsequently undergo cyclization to 6 (Scheme I).

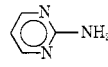
In this work, methyl 2-mercaptobenzoate (2) was prepared from commercially available 1 by passing dry hydrogen chloride through a solution of 1 in methanol.[10] Oxidation of 2 by the theoretical amount of bromine gave solid 3, which was also used extensively as starting material. In fact, oxidation of 2 to 3 by bromine was found to be a more convenient laboratory preparation as compared to the known preparation of 3 by esterification[11] of 2,2′-dithiodibenzoic acid or methanolysis[12] of its acid chloride. Furthermore, the isolation of 3 in high yield confirmed existing evidence[13] that nearly all of the thiol is converted into disulfide before the latter is cleaved into sulfenyl halide by halogenating agents. Attempts to prepare 6a from 2 by treating 4 with an equimolar amount of benzylamine in pyridine gave 7.

Scheme I



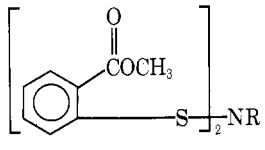
The fact that 7 (mp 131–132°) was not disulfide 3 (mp 131–133°) was shown conclusively by elemental analysis, mixture melting point, and the appearance of the methylene signal (singlet at 4.62 ppm) in the NMR spectrum. When an excess of benzylamine or triethylamine was used instead of pyridine, amidation of 4 to 5a proceeded

Table I
2-Methoxycarbonylbenzenesulfenamides (2, 3 → 4 → 5)

Reactants			Final Product[a]			
Compd brominated	Amine	HBr Binder[b]	Compd	Mp, °C	Recrystn solvent[c]	Yield, %
2	$C_6H_5CH_2NH_2$	Et_3N	5a	61–62.5	B	80
3		Et_3N	5b	*d, e*		95[h]
3	$CH_3CH_2CH_2NH_2$	A	5c	*d, f*		95[h]
2	$CH_2{=}CHCH_2NH_2$	A	5d	*g*		90[h]
2	$HOCH_2CH_2NH_2$	Et_3N	5e	*g*		95[h]
3	$C_6H_5NH_2$	A	5f	154–155.5	B	85
3	p-$ClC_6H_4NH_2$	A	5g	152–153	C	82
3	p-$CH_3OC_6H_4NH_2$	A	5h	106–107	C	79
3	o-$CH_3C_6H_4NH_2$	Et_3N	5i	113–114	C	85
3		Et_3N	5j	157–158	B	88

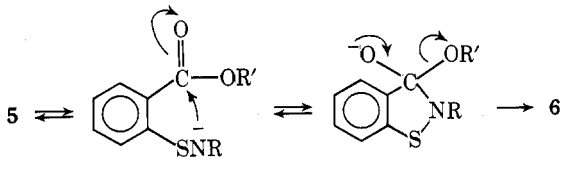
[a] All sulfenamides are new compounds. Acceptable microanalyses (±0.3% for C, H, N, S) for all **5** except **5d** and **5e** were obtained. [b] A = excess of RNH_2. [c] B = MeOH; C = CH_2Cl_2–MeOH: crude product was dissolved in CH_2Cl_2, clarified, concentrated, diluted with MeOH, concentrated to a small volume, and cooled. [d] Thick liquids, decomposing near 200° (0.1 mm). Purified by column chromatography only. [e] $n^{25}D$ 1.5833. [f] $n^{25}D$ 1.5764. [g] Compound was not purified. [h] Crude yield.

smoothly. Pure **5a** was thus isolated in 60% yield although conversions better than 90% (**2** → **3** → **4** → **5a**) were indicated (TLC).



7, R = $CH_2C_6H_5$
8, R = H

A few attempts to effect cyclization in nonpolar solvents were unsuccessful. Crude **5a**, for example, remained virtually unchanged (TLC) in carbon tetrachloride at reflux for several hours. On the other hand, heating under reflux in 2-propanol for 7 hr did give **6a** in 20% yield. It was then discovered that complete cyclization occurred when crude **5a** was heated on a steam bath for 4–6 hr or allowed to stand at room temperature over 4 weeks, but a melt of pure **5a** was partially (50%) converted into **6a** even after 20 hr at 95°. The difference in reactivity between crude and pure **5a** was finally traced to a small amount of residual benzylamine present in the former. The catalytic effect of bases was subsequently demonstrated by the high-yield cyclization of pure **5a** in methanol in the presence of sodium methoxide. Experiments with a few common bases such as sodium alkoxides, potassium or sodium hydroxide, and tetramethylammonium hydroxide in lower alcohols proved that strong bases are essential in effecting fast and complete cyclization. The rate of cyclization increased with increasing base strength and concentration, both of which are compatible with a general base catalyzed mechanism initiated by the abstraction of a proton from the sulfenamide nitrogen. This proton abstraction is also indicative of the weakly acidic but not basic[14] nature of sulfenamides. The remarkable drop in basicity of nitrogen bonded to bivalent sulfur may be explained in terms of a $(p\text{–}d)_\pi$ overlap resulting in a significantly reduced negative charge on nitrogen.



In order to expand the scope of this reaction, a number of new sulfenamides (**5a–j**) were prepared[15] in good yields by employing primary aliphatic, aromatic, and heterocyclic amines. Bromine, sulfuryl chloride, and chlorine were used as halogenating agents, but yields of **5** or **6** decreased in the same order, the best yields being obtained with bromine. Sulfenamides **5a** and **5f–j** were easily purifiable and stable solids. On the other hand, attempted purification of liquids **5b** and **5c** by distillation at reduced pressure (0.05–0.1 mm) caused decomposition and cyclization. Analytical samples were, therefore, prepared by column chromatography without subsequent distillation. No attempts to purify **5d** and **5e** were made. They were employed in the crude form for the preparation of the corresponding **6** by cyclization. These experiments have been summarized in Table I. All **5** exhibited ir and NMR spectra consistent with their assigned structures. The ν(NH) and ν(C=O) vibrations appeared as sharp peaks at 3300–3400 and 1700–1710 cm^{-1}, respectively. In $CDCl_3$, the NMR signals showed the ester methyl group at 3.85–3.92 ppm and the nitrogen proton at 2.54–2.85, 4.94–5.14, and 8.19 ppm, when R in **5** was an aliphatic, aromatic, and 2-pyrimidyl group, respectively. Moreover, all NH assignments were secured by deuterium exchange determinations.

The cyclization step proceeded smoothly in every case in lower aliphatic alcohols and in the presence of strong bases, to give the corresponding benzisothiazolinones[16] in good to excellent yields. These products were identified by mixture melting point, ir, and NMR spectra against authentic samples prepared according to published methods. Table II represents a summary of the cyclization reactions.

A cursory investigation of the effect of strong acids on **5a** showed that methanolic sulfuric acid ruptures the sulfur–nitrogen bond depending on the acid concentration to yield **7** or **3**. A similar behavior of sulfenamides toward hydrochloric or acetic acid has been reported.[18] In contrast, p-toluenesulfonic acid did promote cyclization. For example, heating **5a** at 90° for 22 hr gave **6a** in 50% yield (TLC); the same conditions in the presence of 10 mol % of p-toluenesulfonic acid resulted in 85% cyclization (TLC), from which **6a** was isolated in 65% yield. In 2-propanol at reflux for 52 hr a 1 mol % acid caused a threefold acceleration of the cyclization, from 20% to 60%. The mechanism for an acid-catalyzed cyclization may be initiated by proton attachment on one of the ester oxygens, but since the sulfenamide ni-

Table II
Preparation of 1,2-Benzisothiazolin-3-ones (5 → 6)

Compd 5	Solvent	Catalyst	Product 6	Recrystn solvent[a]	Mp[b] (bp), °C	Lit. mp (bp), °C	Ref	Yield, %
5a	MeOH	NaOMe	6a	A	86–89	89	17	92
5b	EtOH	NaOMe	6b	B	86–88	87–88	5b	82
5c	MeOH	KOH	6c		(126–128)[c] (0.2 mm)	(170–172) (0.8 mm)	5b	72[d]
5d	MeOH	KOH	6d	B	49–50.5[c,e]			56[d,e]
5e	MeOH	Triton B	6e	C	112–114[c]	104–106	5b	72[d]
5f	Me_2CHOH	$NaOCHMe_2$	6f	D	142–143.5	143–144	20	82
5g	MeOH	NaOMe	6g	D	129–130	130–131	8	93
5h	EtOH	NaOMe	6h	D	147–149	148–149	5b	85
5i	MeOH	NaOMe	6i	E	122–123	124	5b	87[d]
5j	EtOH	NaOMe	6j	D	237–238	236	5b	70[d]

[a] A, 2-propanol; B, ether–hexane; C, acetone; D, ethanol; E, methylene chloride–methanol. [b] After a single crystallization. [c] Satisfactory microanalysis for C, H, N, S, (±0.3%) was obtained. [d] Overall yield (2 → 3 → 4 → 5 → 6). [e] Product was purified by distillation under reduced pressure before final crystallization.

trogen is a poor nucleophile the catalytic effect of acids is small, which is in accord with our experiments.

An extremely slow cyclization of pure liquid sulfenamides **5b** and **5c** at room temperature over prolonged periods of time, and the sluggish cyclization of **5a** in 2-propanol, have already been mentioned. An additional example of cyclization in the absence of catalysts was provided with the preparation of **6c** from **5c** above 130° under reduced pressure. In that **5c** suffered concurrent decomposition, the 42% yield of **6c** isolated was significant. The mechanistic path here could involve protonation of the ester group by the sulfenamide hydrogen (autocatalysis). Again, the low nucleophilicity of the sulfenamide nitrogen precludes fast rates of cyclization, or requires such high temperatures that side reactions become significant.

Finally, basic cyclization is the method of choice. The reaction mechanism should operate with any ortho ester groups capable of acyl–oxygen cleavage, and substitution at any of the four positions of the sulfenamide phenyl ring may not be expected to alter cyclization rates significantly. Isolation of intermediates **4** and **5** is not necessary and overall yields (**2** → **3** → **4** → **5** → **6**) are good to excellent. On the other hand, a few attempts to prepare **5** (R = H) by treating **4** with ammonia failed, since disulfenamide **8** was obtained instead in good yield. A similar behavior for ammonia has been reported.[18]

Experimental Section[19]

Dimethyl 2,2′-Dithiodibenzoate (3). A solution of bromine (80 g, 0.5 mol) in carbon tetrachloride (350 ml) was added dropwise with stirring and cooling to a solution of methyl 2-mercaptobenzoate (**2**, 168.2 g, 1 mol) in carbon tetrachloride (150 ml) over a period of 40 min. The reaction took place with the evolution of hydrogen bromide. After the addition had been completed, the reaction mixture was stirred at room temperature for 1 hr, and the precipitated product was filtered off and dried to give 140.5 g (84%) of very pure **3**: mp 131.5–133° (lit.[12] mp 131–133°); NMR ($CDCl_3$) δ 3.85 (s, 6, OCH_3), 7–7.3 (m, 4, aromatic H), 7.74 (d, 2, aromatic H), 8.01 (d, 2, aromatic H); ir ($CHCl_3$) 1710 cm^{-1} (C=O).

***N,N*-Bis(2-methoxycarbonylphenylthio)benzylamine (7).** Dry chlorine was bubbled through a stirred solution of methyl 2-mercaptobenzoate (5 g, 0.03 mol) in carbon tetrachloride (25 ml) at 15–20° until detected at the outlet with potassium iodide–starch paper. Dry nitrogen was then bubbled through to remove excess of chlorine and the red solution obtained was added dropwise with stirring to benzylamine (3.2 g, 0.03 mol) in pyridine (25 ml) at 25–30° over a period of 20 min. After the addition had been completed, the mixture was heated at 75–80° for 30 min and added warm with stirring to 3 *N* HCl (125 ml) and ice. The solvent layer was separated, dried ($MgSO_4$), and evaporated to dryness in vacuo, yielding an oil. Addition of ether (10 ml) followed by hexane (2 ml) caused the crystallization of almost pure product (mp 129–130.5°, 2.8 g, 42.5%), which was recrystallized once from acetone–hexane: mp 131–132°; NMR ($CDCl_3$) δ 3.85 (s, 6, OCH_3), 4.63 (s, 2, CH_2N), 7–7.6 (m, 12, aromatic H), 7.97 (d, 2, aromatic H); ir (Nujol) 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{21}NO_4S_2$: C, 62.85; H, 4.82; N, 3.19; S, 14.59. Found: C, 62.94; H, 4.84; N, 3.27; S, 14.94.

Mixture melting point with diester **3** (mp 131.5–133°) was depressed. In a larger scale experiment crude **7** was obtained in 59% yield.

General Laboratory Procedure for the Preparation of Sulfenamides 5. A solution of bromine (16 g, 0.1 mol) in carbon tetrachloride (100 ml) was added dropwise at ambient temperature to a stirred suspension of dimethyl 2,2′-dithiodibenzoate (**3**, 16.7 g, 0.1 mol) in the same solvent (100 ml) over a period of 30 min. After the addition had been completed, the red solution of bromide **4** obtained was stirred for 30 min and added dropwise with stirring to a solution of the desired primary amine (0.41 mol) or to a stoichiometric amount of the amine (0.2 mol) and triethylamine (0.21 mol) in carbon tetrachloride (200 ml) at 25–30° in 30 min. The reaction mixture was stirred at room temperature for 1 hr or refluxed briefly and the precipitated hydrobromide was filtered off. Depending on solubility, product **5** may partially precipitate along with the amine hydrobromide. The latter was removed by dissolving in water, in which **5** is insoluble. The filtrate of carbon tetrachloride was concentrated to a small volume and cooled or evaporated to dryness in vacuo to give another crop of crude **5**, which can be purified or used as such in the subsequent cyclization step. All compounds had ir bands at 3300–3400 (ν_{NH}) and 1700–1710 cm^{-1} ($\nu_{C=O}$); δ ($CDCl_3$) 3.85–3.90 (s, 2). A specific example of such a preparation is as follows.

***N*-(*o*-Tolyl)-2-methoxycarbonylbenzenesulfenamide (5i).** A solution of bromine (80 g, 0.5 mol) in carbon tetrachloride (100 ml) was added dropwise with stirring to disulfide **3** (167.2 g, 0.5 mol) in carbon tetrachloride (400 ml) over a period of 30 min. The red solution of sulfenyl bromide **4** obtained was stirred at ambient temperature for 30 min and added to a stirred solution of *o*-toluidine (113 g, 1.05 mol) and triethylamine (106 g, 1.05 mol) in carbon tetrachloride (1000 ml) at 20–25° within 90 min. The reaction mixture was stirred at room temperature for 1 hr, heated under reflux for 1 hr, cooled, and filtered from a solid. The solid was stirred in water (1000 ml) to dissolve triethylamine hydrobromide, leaving a small amount of crude product (**5i**, mp 111–112°, 6.9 g, 2.5%). The filtrate was concentrated to about one-half volume, cooled, and filtered to give 225 g (82.5%) of nearly pure **5i** (mp 112–113.5°). The analytical sample was obtained by recrystallization from CH_2Cl_2–MeOH: mp 113–114°; NMR ($CDCl_3$) δ 2.26 (s, 3, CCH_3), 3.90 (s, 3, OCH_3), 4.98 (s, 1, NH), 6.6–8 (m, 8, aromatic H); ir (CS_2) 3380 (NH), 1703 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53; N, 5.12; S, 11.72. Found: C, 65.79; H, 5.45; N, 5.03; S, 11.83.

General Method for the Preparation of 2-Substituted 1,2-Benzisothiazolin-3-ones (6). A concentrated solution of sulfenamide **5** in methanol containing 1–10 mol % of NaOMe, KOH, or

NaOH was refluxed until cyclization was completed (10 min–3 hr) as shown by TLC. Silica gel plates and mixtures of benzene–chloroform or chloroform–methanol of suitable polarity were used. When solid, the crude product was obtained by concentrating and cooling, or by bringing the reaction mixture to dryness. Liquids **6** were isolated by evaporation of the reaction mixture to dryness and distillation at reduced pressure. The catalyst used can be neutralized by an equivalent amount of hydrochloric acid before working up the reaction mixture or extracted with water. Following are two examples of the cyclization method.

2-Cyclohexyl-1,2-benzisothiazolin-3-one (6b). An ethanolic solution of sodium hydroxide (80 mg, 2 mmol, in 2 ml of ethanol) was added to a stirred solution of crude **5b** (5.3 g, 20 mmol) in ethanol (25 ml). A mild exothermic reaction raised the temperature to 40°. The reaction mixture was stirred at ambient temperature for 1 hr and evaporated to dryness under reduced pressure to yield an oil residue. This residue was dissolved in chloroform, washed with water, and evaporated to dryness, giving crude **6b** as an oil which solidified upon standing. The product (mp 83–86°) was purified by crystallization from ether–hexane, mp 86–88° (lit.[5b] mp 87–88°), yield 82%.

2-Phenyl-1,2-benzisothiazolin-3-one (6f). Sulfenamide **5f** (2.6 g, 10 mmol) in 2-propanol (8 ml) containing 0.1 mmol of sodium isopropoxide (obtained by addition of the calculated amount of sodium hydride) was heated under reflux for 2 hr. Upon cooling **6f** (2.3 g, mp 135–139°) crystallized out, and was filtered off and purified by recrystallization from ethanol and then acetone, mp 142–143.5° (lit. mp^{20} 143–144°).

2-Propyl-1,2-benzisothiazolin-3-one (6c) by Heating Neat 5c at Reduced Pressure. A sample of crude **5c** (4 g) was heated at 0.1 mm by means of an oil bath in a flask connected for distillation. Near 130° an increase in pressure to 1 mm was recorded indicating thermal decomposition. Heating was continued until the temperature of the liquid bath increased to 230°. Nearly pure **6c** was distilled over. Redistillation gave pure **6c**: bp 126–128° (0.05 mm); yield 1.4 g (42%); NMR (CCl_4) δ 0.98 (t, 3, CH_2CH_3), 1.78 (sextet, 2, CH_2CH_3), 3.83 (t, 2, NCH_2), 7.2–7.6 (m, 3, aromatic H), 8.01 (d, 1, aromatic H); ir spectrum was identical with that of an authentic sample.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.14; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.02; H, 5.79; N, 7.09; S, 16.45.

***N*-2-Methoxycarbonylphenylthio-2-methoxycarbonylbenzenesulfenamide (8).** To a suspension of dimethyl 2,2′-dithiodibenzoate (**3**, 6.7 g, 0.02 mol) in carbon tetrachloride (60 ml), bromine (3.2 g, 0.02 mol) was added dropwise with stirring. The red solution obtained was added dropwise to a stirred solution of ammonium hydroxide (6.7 g, ~0.1 mol) in dioxane (100 ml), and the precipitated crude product was filtered off. The filtrate was diluted with water, yielding a second crop. The two crops were combined (5.3 g, 75%), washed with water, and recrystallized from methanol to give pure **8**: mp 200–202.5° dec; yield 5.3 g (75%); ir ($CHCl_3$) 3350 (NH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{15}NO_4S_2$: C, 55.00; H, 4.33; N, 4.01; S, 18.35. Found: C, 54.76; H, 4.25; N, 3.99; S, 18.35.

Action of Sulfuric Acid on *N*-Benzyl-2-methoxycarbonylbenzenesulfenamide (5a). A. Isolation of *N,N*-Bis(2-methoxycarbonylphenylthio)benzylamine (7). Concentrated sulfuric acid (0.14 ml, 0.0025 mol) was added to a suspension of **5a** (2.7 g, 0.01 mol) in methanol (20 ml), and the mixture was heated under reflux for 1 hr and cooled. The precipitated crude product was filtered off, dissolved in chloroform (100 ml), extracted with water (3 × 50 ml), and dried ($MgSO_4$). Evaporation of the solvent gave almost pure **7**, which was purified by one crystallization from methanol and identified by mixture melting point and ir and NMR spectra, mp 130–132°, yield 1.2 g (54%).

B. Isolation of Bis(2-methoxycarbonylphenyl) Disulfide (3). To a suspension of **5a** (2.7 g, 0.01 mol) in methanol (10 ml) was added concentrated sulfuric acid (0.28 ml, 0.005 mol), and the mixture was heated under reflux for 10 min. Upon cooling pure **3** (mp 129–130°, 1.1 g, 66%) crystallized out and was identified by mixture melting point with an authentic sample and ir and NMR spectra.

Registry No.—**1**, 147-93-3; **2**, 4892-02-8; **3**, 5459-63-2; **4**, 55255-07-7; **5a**, 34757-96-5; **5b**, 34757-97-6; **5c**, 34757-98-7; **5d**, 55255-08-8; **5e**, 55255-09-9; **5f**, 34757-99-8; **5g**, 55255-10-2; **5h**, 55255-11-3; **5i**, 55255-12-4; **5j**, 34758-00-4; **6a**, 2514-36-5; **6b**, 2527-02-8; **6c**, 4299-05-2; **6d**, 35159-81-0; **6e**, 4299-09-6; **6f**, 2527-03-9; **6g**, 2620-91-9; **6h**, 2514-33-2; **6i**, 4299-23-4; **6j**, 4337-41-1; **7**, 55255-13-5; **8**, 55255-14-6; $C_6H_5CH_2NH_2$, 100-46-9; cyclohexylamine, 108-91-8; $CH_3CH_2CH_2NH_2$, 107-10-8; $CH_2{=}CHCH_2NH_2$, 107-11-9; $C_6H_5NH_2$, 62-53-3; p-$ClC_6H_4NH_2$, 106-47-8; p-$CH_3OC_6H_4NH_2$, 104-94-9; o-$CH_3C_6H_4NH_2$, 95-53-4; 2-aminopyrimidine, 109-12-6; $HOCH_2CH_2NH_2$, 141-43-5; sulfuric acid, 7664-93-9.

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