Notes

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Studies on Preparation of 3-Hydroxy-4-phenyl-1,2,5-thiadiazole in Various Solvents

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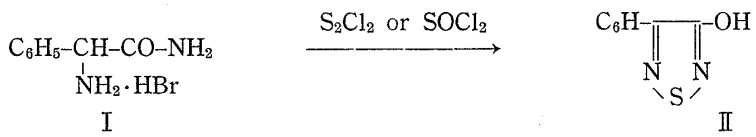
Recently Weinstock and associates[2] have synthesized 3-hydroxy-1,2,5-thiadiazoles including the 4-phenyl derivative by ring closure of α-amino acid amides with sulfur chloride in dimethylformamide. On the other hand, Mizsak and Perelman[3] have reported that α-amino acid amides underwent condensation with thionyl chloride in chloroform to give 3-hydroxy-4-substituted 1,2,5-thiadiazoles in very low yield (1.2%).



In the course of preparation of pharmaceutically active substances, we have investigated this cyclization in various solvents with phenylglycinamide hydrobromide (I) to give 3-hydroxy-4-phenyl-1,2,5-thiadiazole (II). Table I and II show the data obtained by the reaction with thionyl chloride and sulfur monochloride, respectively.

The reaction with thionyl chloride in less- and non-polar solvents including chloroform which was used by Mizsak, *et al.*[3] gave a very small amount of the product (II). They obtained improved results (20—60% yield) when the α-amino acid amides were allowed to react with thionylaniline in pyridine. We have found that the cyclization with thionyl chloride gives the product (II) in about 80% yield by prolonged heating in nitromethane, acetonitrile or tetrahydrofuran as shown in Table I. The reaction in dimethylformamide

Table I. Preparation of 3-Hydroxy-4-phenyl-1,2,5-thiadiazole by Cyclization with Thionyl Chloride (3 mole eq.)

Solvent	Reaction condition		Yield of (II) (%)	Recovery of (I) (%)
DMF	60°C	5 hr	0	—
	room temp.	24	40	—
CH_3NO_2	reflux	24	84	—
	60—70°C	7	4.5	69
CH_3CN	reflux	24	79	—
	60—70°C	8	8.9	58
DMSO	60—70°C	8	0	—
THF	reflux	24	80	16
$C_6H_5CH_3$	reflux	24	1.7	96
C_6H_6	reflux	24	trace	79
$CHCl_3$	reflux	24	1.3	96

1) Location: *2-9-3, Shimo-meguro, Meguroku, Tokyo.*
2) L.M. Weinstock, P. Davis, B. Handelsman, and R. Tull, *Tetrahedron Letters*, **No. 12**, 1263 (1966).
3) S.A. Mizsak and M. Perelman, *J. Org. Chem.*, **31**, 1964 (1966).

Table II. Preparation of 3-Hydroxy-4-phenyl-1,2,5-thiadiazole by Cyclization with Sulfur Monochloride (3 mole eq.)

Solvent	Reaction condition		Yield of (II) (%)	Solvent	Reaction condition		Yield of (II) (%)
DMF	60°C	5 hr	95	CH_3CN	reflux	16 hr	13
	room temp.	6	44	THF	reflux	15	trace
CH_3NO_2	reflux	16	44	C_6H_6	reflux	16	3.2

gave the product in 40% yield at room temperature, but did not give any identified product under heating. Also, the reaction in dimethyl sulfoxide gave only an unidentified tarry product with unpleasant mercaptan-like odor. The best yield (95%) was obtained in the reaction with sulfur monochloride in dimethylformamide which was used by Weinstock, *et al.*[2] With this exception, the reaction with sulfur monochloride gave lower yield than that with thionyl chloride. This seems to be partly related with the following facts. The reaction mixture of sulfur monochloride and phenylglycinamide gave an oily precipitate which was difficult to be dispersed into the solution unless stirring was vigorous and prevented from sufficient contact of the reactants. In addition, when the reaction mixture was poured into water, a resulting viscous tar made difficult the extraction of the product with ether.

Experimental

Phenylgycinamide Hydrobromide (I)——The procedure for α-amino aliphatic acid amides described by Karmas and Spoerri[4] was slightly modified for the preparation of phenylglycinamide from ethyl α-bromophenylacetate.[5] To a solution of 240 g (1.0 mole) of ethyl α-bromophenylacetate in 700 ml of ethanol was added 600 ml of conc. ammonium hydroxide solution. Ammonia gas was passed to the mixture at 0° until a homogeneous solution was obtained. The reaction flask was stoppered tightly and allowed to stand for one week at room temperature, during which time phenylglycine separated as a white precipitate. It was removed by filtration and the filtrate was concentrated below 50° to precipitate phenylglycinamide hydrobromide, which was collected by filtration. Yield 131 g (57%). Recrystallized from dilute hydrobromic acid. mp 281—282° (decomp.). UV λ_{max}^{EtOH} mμ (ε): 252 (210), 257.5 (280), 262 (290), 268.5 (210). *Anal.* Calcd. for $C_8H_{11}ON_2Br$: C, 41.57; H, 4.36; N, 12.12; Br, 34.58. Found: C, 41.70; H, 4.82; N, 11.99; Br, 34.57.

3-Hydroxy-4-phenyl-1,2,5-thiadiazole (II)——1) Cyclization with thionyl chloride (Table I): Phenylglycinamide hydrobromide (0.02 mole) was added to a solution of thionyl chloride (0.06 mole) in 20 ml of an appropriate solvent and the mixture was heated. The reaction mixture was filtered to remove unchanged starting material and the filtrate was evaporated into dryness. The residue was dissolved in 25 ml of 5% sodium hydroxide solution, and treated with a small amount of active carbon. The alkaline solution was washed with ether and acidified with dilute hydrochloric acid to give 3-hydroxy-4-phenyl-1,2,5-thiadiazole. mp 168—169° (from ethyl acetate) (lit.[3], mp 166—168°). UV λ_{max}^{EtOH} mμ (ε): 223 (11800), 307 (17800). *Anal.* Calcd. for $C_8H_6ON_2S$: C, 53.91; H, 3.39; N, 15.72. Found: C, 54.04; H, 3.33; N, 16.17.

2) Cyclization with sulfur monochloride (Table II): Phenylglycinamide hydrobromide (0.02 mole) was added to a solution of sulfur monochloride (0.06 mole) in 20 ml of an appropriate solvent and the mixture was heated under vigorous stirring. The reaction mixture was cooled to room temperature, poured into ice water and extracted with ether. The ethereal extracts were back-extracted with 5% sodium hydroxide solution and the alkaline extracts acidified with dilute hydrochloric acid to give 3-hydroxy-4-phenyl-1,2,5-thiadiazole.

4) G. Karmas and P.E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).
5) E. Schwenk and D. Papa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).