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2-Amino-5-alkyl and 2-amino-5-aryl-1,3,4-thiadiazoles were prepared by the dehydration of 2-acylthiosemicarbazides with molar equivalents of methanesulfonic acid in refluxing toluene. The synthesis appears to be general.

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The standard route to 2-amino-1,3,4-thiadiazoles **2** involves the acylation of a thiosemicarbazide followed by dehydration (Equation 1). The acylation is usually carried out with an acid chloride and the resulting acylthiosemicarbazide **1** is cyclized with a dehydrating reagent. Common reagents for this cyclization have been neat sulfuric acid, neat polyphosphoric acid or mixtures thereof (1,2). Phosphorus halides have been used when R₂ is alkyl but the reaction fails when R₂ is aryl (3,4). In contrast to these procedures which require a large molar excess of acid and cumbersome volumes of ice, water and base, we wish to report a convenient and general cyclization technique (where R₂ = alkyl or aryl) that requires only molar equivalents of dehydrating agent.

Thus, treatment of **1a-e** with 1.5 moles of methanesulfonic acid in refluxing toluene for four to six hours afforded on cooling, good yields of the thiadiazoles **2a-e** as their sulfonate salts. The free bases were isolated by

filtration after neutralization of the salts in water. In the case of **2c**, the sulfonate salt was soluble in the cooled reaction mixture, and the sulfonic acid was readily separated by extraction with aqueous base.

Other sulfonic acids gave comparable results but methanesulfonic was the reagent of choice based on ease of handling, crystallinity of salts, and relative cost. Interestingly, a stoichiometric amount of sulfonic acid was required to effect complete cyclization and 1.5 moles afforded the maximum yield. For example, the use of a catalytic amount of sulfonic acid and attempted azeotropic water removal afforded only starting material.

The reaction appears general for the preparation of 2-amino-5-alkyl or 2-amino-5-aryl-1,3,4-thiadiazoles.

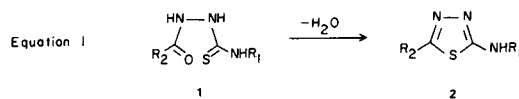
EXPERIMENTAL

General Procedure (2a-e).

To a slurry of the appropriate acylthiosemicarbazide (0.05 mole) in 150

Table I

Synthesis of Some 2-Amino-1,3,4-thiadiazoles.
Dehydrations with Methanesulfonic Acid



Compound	R ₁	R ₂	Isolated % Yield	M.p.	Formula	Analysis		Pmr Chemical Shifts (δ)	
						Calcd.	Found		
a	H	<i>p</i> -CF ₃ Ph	89	238-240.5	C ₉ H ₆ F ₃ N ₃ S	C	44.08	43.85	CDCl ₃ , 7.56 (br s, 2, NH ₂), 7.86 (q, 4, phenyl)
						H	2.46	2.61	
						N	17.14	16.95	
b	H	<i>p</i> -ClPh	75	224.5-226	C ₈ H ₆ ClN ₃ S	C	45.39	45.55	DMSO, 7.46 (br s, 2, NH ₂), 7.66 (q, 4, phenyl)
						H	2.86	3.05	
						N	19.85	20.04	
c	CH ₃	-C(CH ₃) ₃	83	81-82.5 [lit. value (3) 80-82]				CDCl ₃ , 7.13 (s, 1, NH), 2.97 (s, 3, CH ₃), 1.37 (s, 9, <i>t</i> -butyl)	
d	H	-CH ₂ Ph	84	201-203.5	C ₉ H ₉ N ₃ S	C	56.52	56.28	DMSO, 4.13 (s, 2, CH ₂), 7.00 (br s, 2, NH ₂), 7.27 (s, 5, phenyl)
						C	4.90	4.65	
						N	15.72	15.43	
e	H	-CH(Ph) ₂	80	202-206	C ₁₅ H ₁₃ N ₃ S	C	67.39	67.68	DMSO, 7.43 (s, 1, CH), 7.20 (br s, 2, NH ₂), 7.27 (s, 10, phenyl rings)
						H	4.90	4.65	
						N	15.72	15.43	

ml. of toluene at 25°, was added dropwise over 15 minutes, 7.2 g. (0.075 mole) of methanesulfonic acid. The mixture was stirred at reflux for 4 hours. After cooling to 10° in all cases except **2c**, the crystallized sulfonate salt was filtered and dried. The salt was placed in water, the solution was adjusted to pH 8 with concentrated ammonium hydroxide and the resulting solid was filtered, washed with water and dried. Tlc (silica gel-acetonitrile) showed one spot. In the case of **2c**, to the cooled reaction mixture, water was added with good agitation and the pH adjusted to 8 with concentrated ammonium hydroxide. The toluene layer was separated and the solvent was removed *in vacuo* affording the product.

REFERENCES AND NOTES

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