Thiohydrazides and Acetylene Esters, A New Route to 1,3,4-Thiadiazoles

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Aromatic thiohydrazides react with dimethyl acetylenedicarboxylate or methyl propiolate to yield carbomethoxymethyl-substituted 1,3,4-thiadiazoles. In a 2:1 ratio of methyl propiolate to aromatic thiohydrazide, 1,3,4-thiadiazoles with acrylate ester side chains are formed.

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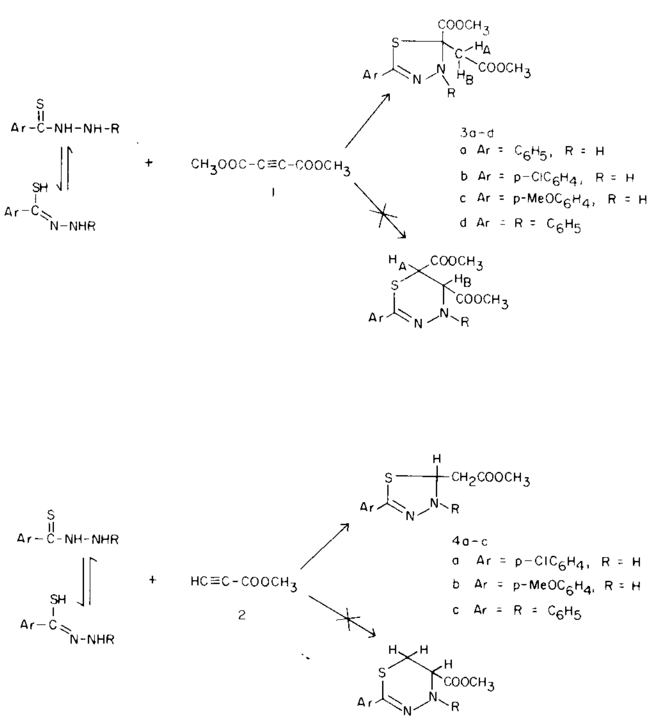
The utility of acetylene esters in formation of heterocyclic systems by bridging of nucleophilic centers in acyclic precursors has been exploited as a synthetic method in earlier papers from these laboratories (2,3,4). Two modes of cyclization of bis-nucleophiles have been observed. Examples are known in which Michael addition to the triple bond and displacement upon an ester generate the heterocycle (3,5) and others in which two Michael-like additions to the alkyne produce the product (6,7). With such a multitide of cyclization modes there are often ambiguities in product structure assignment (8).

We have investigated the condensation of aromatic thiohydrazides with dimethyl acetylenedicarboxylate (**1**) and methyl propiolate (**2**) in refluxing methanol and have observed the formation in 50-65% yields of 1:1 adducts whose infrared spectra reveal only non-conjugated ester carbonyls (1728-1745 cm^{-1}). Elemental and mass spectral analyses clearly eliminate the possilibity of an addition-displacement cyclization but do not clearly distinguish between the two possible double addition products (1,3,4-thiadiazoles and 1,3,4-thiadiazines) Scheme I.

An N-H linkage was characterized by a single sharp absorption in the infrared between 3300 and 3320 cm^{-1}. In the nmr its resonance fell between 6.5 and 7.5 ppm δ and was too broad to ascertain coupling, if any, to vincinal carbon-bound protons as might be expected in the 1,3,4-thiadiazoles. As has been noted for the heterocyclic products derived from thiohydroxamic acids (9) with **1** as well as from hydroxamic acids and **1** or **2** (10) definitive structural proof rests in the observed coupling constant of the H_A and H_B protons. In either option, the thiadiazoles or the thiadiazines, an AB quartet would be expected from H_A and H_B but when these protons are vincinal a maximum coupling of 12Hz would be anticipated (9) while J values of 16-18 Hz would be expected for the geminal methylene (9,10). In compounds **3a-c** coupling constants of 16-17 Hz were observed.

Scheme I



The thiadiazoles derived from methyl propiolate, *i.e.*, **4a-c**, must of necessity possess three interacting proton spin systems and a typical ABX pattern was observed. Analysis of the apparent eight-line methylene multiplet and the four-line methinyl signal by standard methods (11,12) extracted a J_{AB} of 16-17 Hz again confirming the 1,3,4-thiadiazole structural alternative.

Evans has reported the facile addition of the N-H proton of 1,3-thiazoles across the alkynyl function of acetylenic esters (13) and the 1,3,4-thiadiazoles prepared herein readily underwent addition to methyl propiolate. With a 2:1 excess of **2** benzothiohydrazide and p-methoxybenzothiohydrazide gave **5a** and **5b** (Scheme II) in 61 and 63% yields respectively. Similarly, the inter-

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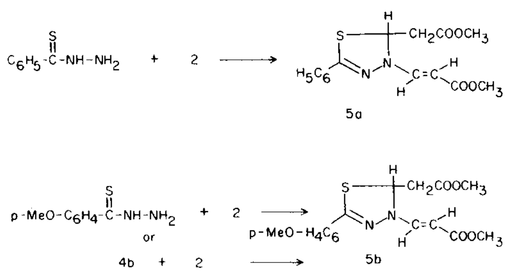
Table I

Analytical and Spectral Data on 1,3,4-Thiadiazoles

Compound	M.p. °C	Yield %	Formula	Analysis Calcd. C	 H	 N	 Found C	 H	 N	Pmr (a) λ ppm (multiplicity, relative area, assignment, coupling)
3a	110-112	52	$C_{13}H_{14}N_2O_4S$	53.06	4.79	9.52	53.20	5.02	9.38	3.69, 3.79 (s, 3H each, OCH_3's) 3.41 (q, 2H, CH_2, J = 16) 6.0-7.8 (m, 6H, ArH + NH)
3b	113-115	60	$C_{13}H_{13}ClN_2O_4S$	47.50	3.98	8.52	47.51	3.98	8.28	3.76, 3.84 (s, 3H each, OCH_3's) 3.71 (q, 2H, CH_2, J = 16) 6.8-7.8 (m, 5H, ArH + NH)
3c	149-150	65	$C_{14}H_{16}N_2O_5S$	51.85	4.97	8.64	51.95	5.08	8.87	3.74, 3.84, 3.88 (s, 3H each, OCH_3's) 3.42 (q, 2H, CH_2, J = 17) 6.8-7.7 (m, 5H, ArH + NH)
3d	127-129	52	$C_{19}H_{18}N_2O_4S$	61.62	4.89	7.56	61.88	4.91	7.45	3.70, 3.76 (s, 3H each, OCH_3's) 3.52 (q, 2H, CH_2) 7.1-7.9 (m, 10H, ArH)
4a	80-81	54	$C_{11}H_{11}ClN_2O_2S$	48.82	4.09	10.35	48.52	4.17	10.27	3.71 (s, 3H, OCH_3) 2.72 δ_B, 2.90 δ_A (8 lines, 2H, CH_2, J_{AB} = 16, J_{AX} = 16, J_{BX} = -2.0) 5.66 δ_X (4 lines, 1H, -CH-, $J_{AX} + J_{BX}$ = 14) 6.40 (s, 1H, NH) 7.2-7.8 (m, 4, ArH)
4b	63-64	58	$C_{12}H_{14}N_2O_3S$	54.13	5.30	10.52	54.22	5.39	10.52	3.70, 3.79 (s, 3H each, OCH_3's) 2.70 δ_B, 2.87 δ_A (8 lines, 2H, CH_2, J_{AB} = 16, J_{AX} = 16, J_{BX} = -2.0) 5.55 δ_X (4 lines, 1H, -CH-, J_{AX} + J_{BX} = 14) 6.49 (br s, 1H, NH) 6.7-7.7 (m, 4, ArH)
4c	92.5-95	41	$C_{17}H_{16}N_2O_2S$	65.37	5.16	8.97	65.25	5.13	8.76	3.63 (s, 3H, OCH_3) 2.75 δ_B, 2.97 δ_A (8 lines, 2H, CH_2, J_{AB} = 17, J_{AX} = 15, J_{BX} = -2.0) 6.25 δ_X (4 lines, 1H, -CH-, $J_{AX}+J_{BX}$ = 13) 6.7-7.8 (m, 10H, ArH)
5a	124-126	61	$C_{15}H_{16}N_2O_4S$	56.24	5.03	8.75	56.35	5.02	8.49	3.53, 3.65 (s, 3H each, OCH_3's) apparent ABX pattern incapable of complete analysis: 2.9 (m, 2H, CH_2) and 6.22 (m, 1H, -CH-) 5.32 (d, 1H, =CH, J = 14) 7.78 (d, 1H, =CH, J = 14) 7.3-7.7 (m, 5H, ArH)
5b	127-128	63	$C_{16}H_{18}N_2O_5S$	54.84	5.18	7.99	54.93	5.27	7.77	3.75, 3.78, and 3.85 (s, 3H each, OCH_3's) 2.90 δ_B, 3.17 δ_A (8 lines, 2H, CH_2, J_{AB} = 17, J_{AX} = 15, J_{BX} = -1.0) 6.00 δ_X (4 lines, -CH-, $J_{AX} + J_{BX}$ = 15) 5.19 (d, 1H, =CH, J = 14) 7.97 (d, 1H, =CH, J = 14) 6.9-7.9 (m, 4H, ArH)

(a) All pmr spectra were obtained in deuteriochloroform on a Perkin-Elmer Hitachi R20A and are calibrated against TMS.

Scheme II



mediate thiadiazole (such as **4b**) prepared from the 1:1 combination of the alkyne ester and the thiohydrazide could be converted to acrylate-pendant analog by re-exposure to a second equivalent of **2**. In accord with the claims that secondary amines often display a cis stereochemistry of addition to alkynes (14), both **5a** and **5b** appear to be the products of a cis addition. The two vinyl protons show a coupling constant of 14 Hz in agreement with a transoid orientation (15).

EXPERIMENTAL

Combustion analyses were provided by Dr. G. I. Robertson, Florham Park, N. J. Melting points are reported uncorrected as obtained on a Fisher-Johns apparatus. Infrared spectra were obtained as thin films or nujol mulls on a Perkin Elmer 257 or Beckman Model 33 infrared spectrophotometer.

Preparation of Thiobenzohydrazides.

All of the thiobenzohydrazides utilized in this study were known compounds prepared as described by Jensen (16,17) from condensation of hydrazine and carbomethoxymethyl dithiobenzoate. The *N*-phenylthiobenzohydrazide has been described by Jensen utilizing phenylhydrazine in the condensation (18).

Preparation of the 2-Carbomethoxy-2-carbomethoxymethyl-5-aryl-2,3-dihydro-1,3,4-thiadiazoles (**3a-c**) and the 3,5-Diphenyl Analog (**3d**).

A solution of 5.0 mmoles of the requisite thiobenzohydrazide and 5.0 mmoles of dimethyl acetylenedicarboxylate (**1**) was stirred at reflux in 25 ml. of anhydrous methanol for 3 hours, evaporated to virtual dryness, chilled, and the precipitated solid recrystallized from methanol to yield the title compounds. See Table I for data and constants.

Preparation of the 2-Carbomethoxymethyl-5-aryl-2,3-dihydro-1,3,4-thiadiazoles (**4a-b**) and the 3,5-Diphenyl Analog (**4c**).

A solution of 4.5 mmoles of the thiohydrazide and 4.5 mmoles of methyl propiolate (**2**) was refluxed in anhydrous methanol (30 ml.) for 2 hours, evaporated, and the residue recrystallized from methanol to analytical purity. Initially obtained as an oil, **4c**, crystallized on standing 3 months. Attempted distillation under *vacuo* decomposed **4c**; see Table I for data.

Preparation of 1,3,4-Thiadiazoles with Acrylate Side-chains (**5a-b**).

Three hours reflux in 25 ml. of methanol of 11.0 mmoles of **2** and 5.0 mmoles of either thiobenzohydrazide or *p*-methylbenzothiohydrazide gave, upon evaporation and recrystallization from methanol the **5a** and **5b** compounds.

REFERENCES AND NOTES

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