4-Amino-3-mercapto-4*H*-1,2,4-triazoles and Propargyl Aldehydes: A New Route to 3-*R*-8-Aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines

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The pendant amino and mercapto groups on 4-amino-3-mercapto-4*H*-1,2,4-triazoles can be cyclized by phenylpropargyl aldehydes. The aldehydes experience Michael addition of the SH to the alkyne linkage and imine formation between the NH_2 and the aldehyde carbonyl to produce 3-*R*-8-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines.

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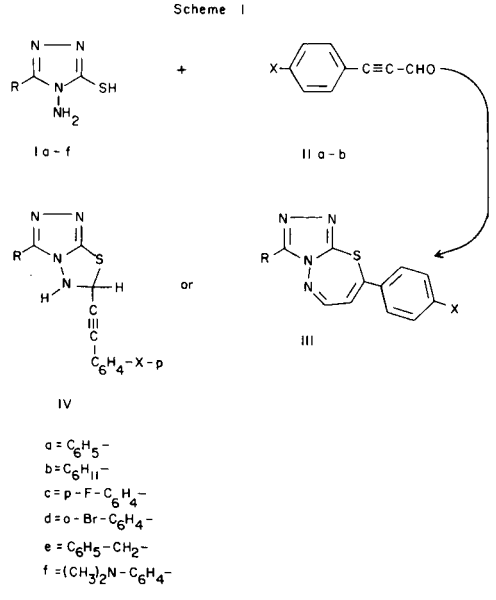
The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drug candidates including H_1/H_2 histamine receptor blockers (1), cholinesterase-active agents (2), CNS stimulants (3), anti-anxiety agents (4), and sedatives (5). An ideal heterocyclic upon which to build fused-ring heterocyclics is the 4-amino-3-mercapto-4*H*-1,2,4-triazole system (I). We have published two improved syntheses of this class (6) which, by virtue of its vicinal amino and mercapto groups constitutes a ready-made building block for such difunctional electrophiles as alkynyl aldehydes. A recent study has shown how the mercapto and amino groups can be bridged with dimethyl acetylenedicarboylate to give 7-carbomethoxymethylene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-6-one (7). We wish to report a convenient synthesis of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines by condensation of I with arylpropargyl aldehydes (II, X = H or X = Br), see Scheme 1.

Brief reflux in ethanol under a nitrogen atmosphere brought about a condensation of the aminomercaptotriazoles and the alkynyl aldehydes in 18 to 69% yields. Tarry, ethanol-soluble, highly colored by-products were present in every case but these could easily be separated from the crystalline products. All products displayed two characteristic vinyl resonances at 6.80 ± 0.10 ppm and 8.27 ± 0.10 ppm with a coupling constant of J = 4 Hz. No resonances were exchangeable with deuterium oxide and no N-H or acetylenic bands were evident in the infrared spectrum, thereby eliminating IV as a possible product.

Black, viscous, multi-component mixtures resulted from the attempted condensation of 5-(4-pyridyl)-4-amino-3-mercapto-4*H*-1,2,4-triazole (6) and the phenylpropargyl aldehyde. Earlier reports have indicated that reactive alkynes yield labile condensation products with the N=C linkage of the pyridine ring (8).

Scheme I



EXPERIMENTAL

Melting points, determined in capillaries on a Thomas-Hoover apparatus, are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 257 infrared spectrophotometer as 1-2% potassium bromide disks. The pmr spectra were obtained in the indicated solvents on a Perkin Elmer Hitachi R20A spectrometer. The combustion analyses were supplied by the G. I. Robertson Microanalytical Laboratory, Florham Park, New Jersey.

5-*R*-4-Amino-3-mercapto-4*H*-1,2,4-triazoles (Ia-f).

Triazoles Ia-d were prepared by Method A in our previous publication (6). The benzyl derivative (Ie) was obtained by the method of Potts (9) and the *p*-dimethylaminophenyl compound (If) was obtained as described below. A solution of 35.8 g. (0.20 mole) of *p*-dimethylaminobenzhydrazide, 11.2 g. (0.20 mole) of potassium hydroxide pellets, and 500 ml. of anhydrous ethanol was treated to the addition of 40 ml. of carbon disulfide in a single portion. The reaction was exothermic and application of ice-water bath was necessary to hold the temperature under reflux. Upon inception of precipitation of the product, the medium was diluted with an additional 100 ml. of absolute ethanol and stirred overnight. Chilling in an ice-water bath, dilution with 250 ml. of ether, filtration, and washing of the filtrate with 50 ml. of ether gave a 43.6 g. (75%) yield of the crude dry potassium 3-(*p*-dimethylaminobenzoyl)dithiocarbazinate (m.p. 241-246° dec.) which was used without purification. A solution of 15 ml. of cold water and 12.8 g. (0.40 mole) of anhydrous hyrazine was treated to the addition of the 43.6 g. (0.15 mole) of the dithiocarbazinate. The medium, initially a suspension, was stirred at reflux for 3 hours, diluted with 200 ml. of cold water, and adjusted to neutrality by the dropwise addition of concentrated hydrochloric acid. The white precipitate was filtered, recrystallized from 1:1 ethanol:water to give 18.6 g. (53%) of If, m.p. 263-265°; ir (potassium bromide): 3200-2800 (br), 1600, 1500-1430 (br), 1230, 1195, 1065, 925, 815 and 730 cm^{-1}; nmr (DMSO-d_6): δ 2.92 (s, 6, $N(CH_3)_2$), 5.72 (s, 2, NH_2), 6.78 (d, 2,

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Table 1

Preparation of 3-*R*-8-Aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines

R =	X =	Formula	% Yield	M.p. (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5-	H	$C_{17}H_{12}N_4S$	28	247-250	67.10	3.96	18.40	67.06	4.20	18.33
C_6H_{11}-	H	$C_{17}H_{18}N_4S$	18	204-207	65.78	5.84	18.05	66.03	6.08	17.90
p-F-C_6H_4-	H	$C_{17}H_{11}FN_4S$	57	218-220	63.34	3.44	17.38	63.50	3.72	17.12
o-Br-C_6H_4-	H	$C_{17}H_{11}BrN_4S$	65	200-202	53.27	2.89	14.62	53.00	3.15	14.66
C_6H_5-CH_2-	H	$C_{18}H_{14}N_4S$	69	201-203	67.90	4.43	17.60	67.64	4.38	17.38
p-$Me_2NC_6H_4$-	H	$C_{19}H_{17}N_5S$	60	196-198	65.68	4.93	20.16	65.70	5.14	19.96
C_6H_5-	Br	$C_{17}H_{11}BrN_4S$	36	212-214	53.27	2.89	14.62	53.42	2.99	14.53
C_6H_5-CH_2-	Br	$C_{18}H_{13}BrN_4S$	44	172-175	54.42	3.30	14.10	54.65	3.26	14.04

Ar*H*), 7.92 (d, 2, Ar*H*), and 13.60 ppm (s, 1, NH).

Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.48; H, 5.61; N, 30.01. Found: C, 51.22; H, 5.65; N, 29.77.

General Procedure for Preparation of 3-*R*-8-Aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines (III).

A solution of 20.0 mmoles of the triazole (Ia-f) in 30 ml. of anhydrous ethanol was refluxed for 10 minutes under a slow stream of nitrogen. To this was added, with stirring and continued nitrogen blanket, a solution of arylpropargyl aldehyde (20.0 mmoles), IIa-b, in 10 ml. of ethanol. Reflux was continued for 2 hours but in many cases solid product began to appear within minutes of mixing the reagents. The solution/suspension was chilled in ice-water bath, the solid removed by filtration, washed with 30 ml. of 10% aqueous potassium hydroxide, and recrystallized from ethanol to analytical purity. Yields and physical properties are given on Table 1.

p-X-Phenylpropargyl Aldehydes (IIa, X = H) and (IIb, X = Br).

Phenylpropargyl aldehyde (IIa, X = H) was prepared by hydrolysis of its diethyl acetal which was obtained by condensation of phenylacetylene and triethyl orthoformate under zinc nitrate catalysis as published by Houk and Sauer (10). *p*-Bromophenylpropargyl aldehyde (IIb, X = Br) was prepared in 43% yield by the Houk procedure from *p*-bromophenylacetylene (11) and was obtained as a crude oil which was used *in situ* for the preparation of bromophenyl thiadiazepines; ir (thin film): 2960, 2880, 2240, 1660, 1585, 1470, 1250, 1100, and 820 cm^{-1}; nmr (deuteriochloroform): δ 7.48 (m, 4, Ar*H*) and 9.39 ppm (s, 1, C*H*O).

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