

Synthesis of Some *N*,1- and *N'*,1-Diaryl-1*H*-1,2,4-triazole-3,5-diamines

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Two novel methods for the preparation of *N*,1- and *N'*,1-diaryl-1*H*-1,2,4-triazole-3,5-diamines are described.

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In connection with a general study of the chemistry of heterocyclic compounds, we became particularly interested in the synthesis of 1,2,4-triazoles (1). This paper describes the synthesis of some *N*,1- and *N'*,1-diaryl-1*H*-1,2,4-triazole-3,5-diamines (2) by the reaction of *N*-cyanocarbodiimide and *N*-substituted cyanoguanidine with aryl hydrazines.

S,S'-Dimethyl *N*-cyanodithioimidocarbonate (I) (3), prepared by the reaction of cyanamide, carbon disulfide and methyl iodide in the presence of alkali, was treated with 4-chloroaniline and 4-chlorophenylhydrazine to yield *N*-(4-chlorophenyl)-*N'*-cyano-*S*-methylisothiurea (II) and 1-(4-chlorophenyl)-3-(methylthio)-1*H*-1,2,4-triazole-5-amine (V), respectively.

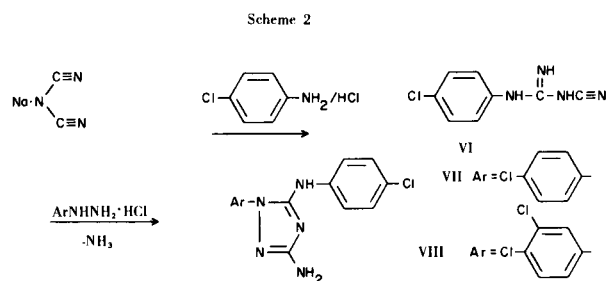
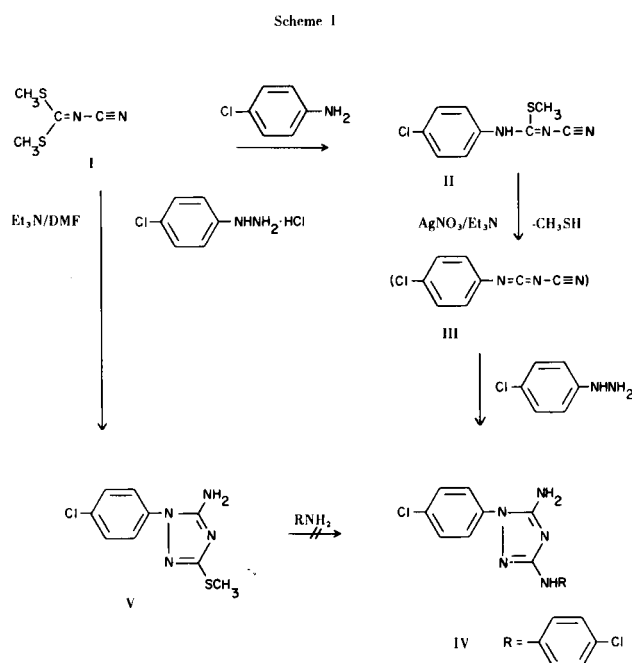
When II was reacted with silver nitrate and triethylamine in *N,N*-dimethylformamide, *N*-cyanocarbodiimide (III) was produced. Although the intermediate III could not be isolated (4), subsequent addition of 4-chlorophenylhydrazine to the solution led to the formation of *N*,1-bis-(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (IV).

All attempts to prepare IV by the reaction of V with amines or II with arylhydrazines were unsuccessful.

1-Cyano-3-(4-chlorophenyl)-guanidine (VI) is easily prepared from sodium dicyanamide and 4-chloroaniline (5). It seemed to us that VI might react with 4-chlorophenylhydrazine hydrochloride, which, it was expected, would be readily cyclized by elimination of ammonia to give *N'*,1-bis(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VII).

In a similar manner, *N'*-(4-chlorophenyl)-1-(3,4-dichlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VIII) was obtained from VI by reaction with 3,4-dichlorophenylhydrazine hydrochloride.

These structures were established on the basis of analyses and spectra. The nmr spectra of compounds IV, V, VII and VIII are consistent with the assigned



structures and show exchangeable peaks integrating for two protons at approximately 6.58-6.60 and 5.40-5.46 ppm. The peaks are assignable to the $\text{C}_5\text{-NH}_2$ and the $\text{C}_3\text{-NH}_2$, respectively (6).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were obtained as Nujol mulls using a Perkin-Elmer Model 137 infracord spectrophotometer. The nuclear magnetic resonance spectra were obtained in DMSO- d_6 with a Varian T-60A spectrometer using tetramethylsilane as an internal standard. The electron-impact mass spectra were determined with a LKB-9000 mass spectrometer (70eV). Microanalyses were determined under the supervision of Mr. J. P. Gilbert of Analytical Section, Merck Sharp and Dohme Research Laboratories.

S,S'-Dimethyl-*N*-cyanodithioimidocarbonate (I).

This compound was prepared in yields of approximately 92% by the method of Suyama and Odo (3). The crude product was recrystallized from aqueous methanol to yield I, m.p. 52-53° [lit. (3), m.p. 49-52°]; $\text{ir } \lambda \text{ max (Nujol): } 4.60 \mu (\text{C}\equiv\text{N})$.

Anal. Calcd. for $\text{C}_4\text{H}_6\text{N}_2\text{S}_2$: C, 32.85; H, 4.14; N, 19.16; S, 43.85. Found: C, 32.84; H, 4.18; N, 19.06; S, 43.83.

N-(4-Chlorophenyl)-*N'*-cyano-*S*-methylisothiourea (II).

A mixture of I (5.85 g., 0.04 mole), 4-chloroaniline (5.10 g., 0.04 mole) and 40 ml. of ethanol was heated under reflux for 18 hours. The mixture was then reduced by evaporation to a small volume. The colorless solid which separated on cooling were recrystallized from ethanol to yield 4.8 g. (53%) of *N*-(4-chlorophenyl)-*N'*-cyano-*S*-methylisothiourea (II), m.p. 190-191°; $\text{ir } \lambda \text{ max (Nujol): } 3.12 (\text{NH}), 4.60 (\text{shoulder}) \text{ and } 4.64 (\text{C}\equiv\text{N}) \text{ and } 6.32 \mu (\text{C}=\text{N})$.

Anal. Calcd. for $\text{C}_9\text{H}_8\text{ClN}_3\text{S}$: C, 47.89; H, 3.57; N, 18.62; Cl, 15.71. Found: C, 47.66; H, 3.46; N, 18.06; Cl, 15.43.

N,1-*Bis*(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (IV).

A solution of 3.62 g. (0.0213 mole) of silver nitrate in 20 ml. of *N,N*-dimethylformamide was added to a solution of II (4.80 g., 0.0213 mole) and 2.16 g. (0.0213 mole) of triethylamine in 50 ml. of *N,N*-dimethylformamide. A yellow precipitate of silver mercaptide formed immediately. After the mixture was stirred for 2 hours at room temperature, the yellow precipitate was removed by filtration (a quantitative yield of silver mercaptide) and washed with *N,N*-dimethylformamide. 4-Chlorophenylhydrazine (3.04 g., 0.0213 mole) was then added to the solution. The mixture was heated on the steam bath for 0.5 hours. After cooling, the mixture was poured onto cracked ice water and the solid which separated was collected, washed with water and recrystallized from ethanol to obtain 1.0 g. (16%) of *N*,1-*bis*(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (IV), m.p. 250-253°; $\text{ir } \lambda \text{ max (Nujol): } 2.92, 3.08 \text{ and } 3.20 \mu (\text{NH}, \text{NH}_2)$; nmr (DMSO- d_6): δ 6.60 (s, 2H, NH_2 , deuterium oxide exchangeable), 7.2-7.72 (m, 8H, arom.), 9.80 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{N}_5$: C, 52.52; H, 3.46; N, 21.87; Cl, 22.15. Found: C, 52.70; H, 3.23; N, 21.44; Cl, 21.81.

1-(4-Chlorophenyl)-3-(methylthio)-1*H*-1,2,4-triazole-5-amine (V).

To a stirred solution of I (2.92 g., 0.02 mole) and 4-chlorophenylhydrazine hydrochloride (3.58 g., 0.02 mole) in 20 ml. of *N,N*-dimethylformamide was added 2.02 g. (0.02 mole) of triethylamine. The reaction mixture was heated on the steam bath for 16 hours. The solution was poured onto cracked ice and precipitated product was then crystallized from aqueous ethanol giving 3.6 g. (75%) of 1-(4-chlorophenyl)-3-(methylthio)-1*H*-1,2,4-triazole-5-amine (V), pale yellow prism, m.p. 153-155°; $\text{ir } \lambda \text{ max (Nujol): } 2.90, 3.04, 3.20 \text{ and } 6.05 \mu$; nmr (DMSO- d_6): δ 2.44 (s, 3H, SCH_3), 6.58 (s, 2H, NH_2 , deuterium oxide exchangeable), 7.56 (s, 4H, arom.); mass spectrum (electron impact, 70 eV):

Anal. Calcd. for $\text{C}_9\text{H}_9\text{ClN}_4\text{S}$: C, 44.90; H, 3.77; N, 23.27; S, 13.32; Cl, 14.73. Found: C, 44.97; H, 3.55; N, 23.44; S, 13.03; Cl, 14.48.

1-Cyano-3-(4-chlorophenyl)guanidine (VI).

A solution of 25.6 g. (0.2 mole) of 4-chloroaniline in 2.5 *N* hydrochloric acid (80 ml., 0.2 mole) at 40° was added to 17.8 g. (0.2 mole) of sodium dicyanamide in 100 ml. of water. The mixture was heated on the steam bath for a few minutes and the solid was separated by filtration. The crude product was recrystallized from ethanol to give colorless solid (28.2 g., 72.5%) of VI, m.p. 198-200° [lit. (5), m.p. 197-200°]; $\text{ir } \lambda \text{ max (Nujol): } 2.98, 3.05 \text{ and } 3.20 (\text{NH}, \text{NH}_2), 4.60 (\text{shoulder}) \text{ and } 4.65 \mu (\text{C}\equiv\text{N})$.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{ClN}_4$: C, 49.37; H, 3.62; N, 28.79; Cl, 18.22. Found: C, 49.67; H, 3.59; N, 28.53; Cl, 18.01.

N',1-*Bis*(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VII).

Compound VI (9.7 g., 0.05 mole), 4-chlorophenylhydrazine hydrochloride (9 g., 0.05 mole), ethanol (50 ml.), and water (10 ml.) were refluxed in an atmosphere of nitrogen for 4 hours. The reaction mixture was filtered hot and diluted with water. The semi-solid which separated on cooling was filtered and recrystallized from 50% ethanol to yield 2.1 g. (13%) of *N'*,1-*bis*(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VII) as light tan solid, m.p. 160-163°; $\text{ir } \lambda \text{ max (Nujol): } 2.94, 3.10 \text{ and } 3.20 \mu (\text{NH}, \text{NH}_2)$; nmr (DMSO- d_6): δ 5.40 (s, 2H, NH_2 , deuterium oxide exchangeable), 7.23-7.60 (m, 8H, arom.), 8.90 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{N}_5$: C, 52.52; H, 3.46; N, 21.87; Cl, 22.15. Found: C, 52.14; H, 3.42; N, 21.80; Cl, 22.01.

N'-(4-Chlorophenyl)-1-(3,4-dichlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VIII).

This compound was prepared in a manner similar to the synthesis of VII, except that 2-ethoxyethanol (50 ml.) was used. From 5.4 g. (0.025 mole) of 3,4-dichlorophenylhydrazine hydrochloride and 4.9 g. (0.025 mole) of VI, 3.2 g. (36%) of *N'*-(4-chlorophenyl)-1-(3,4-dichlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (VIII) was obtained upon recrystallization from 80% ethanol, m.p. 155-156°; $\text{ir } \lambda \text{ max (Nujol): } 2.90, 3.10 \text{ and } 3.20 \mu (\text{NH}, \text{NH}_2)$; nmr (DMSO- d_6): δ 5.46 (s, 2H, NH_2 , deuterium oxide exchangeable), 7.30-7.79 (m, 8H, arom.), 8.97 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{Cl}_3\text{N}_5$: C, 47.41; H, 2.84; N, 19.75; Cl, 29.99. Found: C, 47.21; H, 2.86; N, 19.75; Cl, 29.81.

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The author wishes to express his thanks to Dr. A. A. Patchett for his valuable discussions.

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- (5) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).
- (6) Our unpublished results showed that the nmr (DMSO- d_6) of 1-(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine had δ 5.20 (s, 2H, $\text{C}_3\text{-NH}_2$, deuterium oxide exchangeable), 6.30 (s, 2H, $\text{C}_5\text{-NH}_2$, deuterium oxide exchangeable) and 7.52 (s, 4H, arom.):