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SYNTHESIS OF SUBSTITUTED PYRAZOLO[4, 5-d]THIAZOLES

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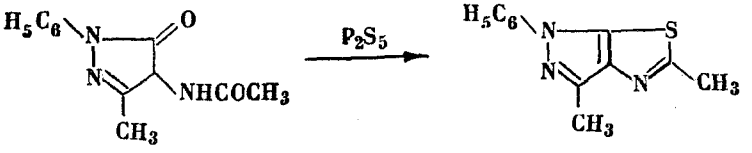
With phosphorus pentasulfide 1-phenyl-3-methyl-4-acetylaminopyrazol-5-one and 1, 3-diphenyl-4-acetylamino-5-acetoxypyrazole give, respectively, 2, 4-dimethyl-6-phenylpyrazolo[4, 5-d]thiazole and 2-methyl-4, 6-diphenylpyrazolo[4, 5-d]thiazole.

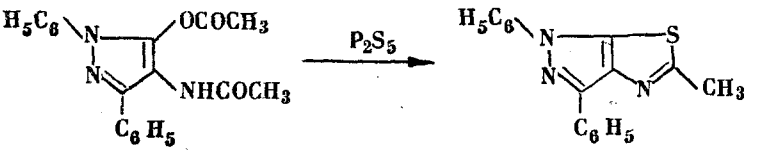
Gabriel's reaction [1], the reaction of phosphorus pentasulfide with α-acylaminocarbonyl compounds, has been successfully extended to preparing thiazoles condensed with pyrimidine [2], thionaphthene [3], and thiazoline [4] rings.

The reaction has now been used to synthesize the hitherto undescribed condensed system pyrazolo[4, 5-d]thiazole. Heating 1-phenyl-3-methyl-4-acetylaminopyrazol-5-one (I) with phosphorus pentasulfide at 175-180°, gave 2, 4-dimethyl-6-phenylpyrazolo[4, 5-d]-thiazole (II) in 93% yield.



I II

It was further shown that reaction of 4-acetylamino-5-acetoxy- derivatives of pyrazole with phosphorus pentasulfide, results in closing of the thiazole ring. Thus, on melting 1, 3-diphenyl-4-acetylamino-5-acetoxypyrazole (III) with phosphorus pentasulfide at 130°, 2-methyl-4, 6-diphenylpyrazolo[4, 5-d]thiazole (IV) was obtained in good yield:



III IV

Base II is quite soluble in alcohol, benzene, ether, and acetone, less soluble in petroleum ether, and insoluble in water, distills in steam, readily gives a picrate on heating with a solution of picric acid in alcohol, and forms quaternary compounds with alkylating agents. Base IV cannot be steam-distilled, and unlike II does not readily give a picrate or quaternary salt. Evidently, this is due to lowering of the basicity of the pyrazole-thiazole system when a methyl group is substituted for phenyl at position 3 in the pyrazole ring.

EXPERIMENTAL

1-Phenyl-3-methyl-4-isonitrosopyrazol-5-one is prepared by nitrosating 1-phenyl-3-methylpyrazol-5-one [5].

1, 3-Diphenyl-4-isonitrosopyrazol-5-one is synthesized by nitrosating 1, 3-diphenylpyrazol-5-one [6].

1-Phenyl-3-methyl-4-acetylaminopyrazol-5-one (I) has previously been prepared by acetylating 4-amino-1-phenyl-3-methylpyrazol-5-one [7] with acetic anhydride. Here it is synthesized by treating 1-phenyl-3-methyl-4-isonitrosopyrazol-5-one in a mixture of acetic acid and acetic anhydride with zinc dust. A finely ground mixture of 5 g (25 mmole) 1-phenyl-3-methyl-4-isonitrosopyrazolone and 10 g zinc dust is added with vigorous stirring to a mixture of 30 ml glacial acetic acid and 5 ml acetic anhydride at 50°, and the stirring then continued for 2 hr at the same temperature. The acetic acid and excess acetic anhydride are distilled off in a vacuum. The crystalline residue is ground with chloroform, filtered, and washed with chloroform. Yield 4.7 g (80.2%), mp 201-204°. Recrystallized from water it forms colorless needles, mp 213-214° (201°-203° [7]).

1, 3-Diphenyl-4-acetylamino-5-acetoxypyrazole (III). A finely-ground mixture of 5 g (19 mmole) 1, 3-diphenyl-4-isonitrosopyrazolone and 10 g zinc is gradually added to a stirred mixture of 30 ml acetic acid and 20 ml acetic anhydride at 65°, after which the reaction mixture is stirred for two hours at 65-70°, then filtered, and the filtrate diluted with 3 vols. water. The precipitate is filtered off, washed with water, and air-dried. Yield 5.5 g (87.3%), mp 138-140°. Recrystallization from m-xylene gives colorless needles, mp 145-146°. Found: N 12.75, 12.76%. Calculated for $C_{19}H_{17}N_3O_3$: N 12.53%.

2,4-Dimethyl-6-phenylpyrazolo[4,5-d]thiazole (II). A finely-ground mixture of 0.58 g (2.5 mmole) I and 0.6 g (2.7 mmole) phosphorus pentasulfide is heated at 175-180° (in a bath) until evolution of hydrogen sulfide ceases (20 min), 10 ml water and 2 ml 25% aqueous sodium hydroxide solution are added to the resultant melt, and the base steam is distilled off. Yield 0.54 g (93.1%), mp 89-90°. Recrystallized from 1:1 alcohol-water it forms long colorless needles, mp 90-91°. Found: N 18.08, 18.14%. Calculated for $C_{12}H_{11}N_3S$: N 18.34%. Picrate. Yellow needles (from ethanol), mp 106-107°. Found: N 18.34, 18.44%. Calculated for $C_{12}H_{11}N_3S(NO_2)_3C_6H_2OH$: N 18.34%.

2,4-Dimethyl-6-phenylpyrazole[4,5-d]thiazole ethiodide. 0.12 g (0.05 mmole) II and 0.08 g (0.5 mmole) diethyl sulfate are heated together for 20 min at 130°. 0.2 g (1.2 mmole) potassium iodide is added to a solution of the resultant quaternary compound in 2 ml water. The precipitate formed is filtered off, washed with 1 ml water, and recrystallized from acetone. Yield 0.12 g (63.1%) of almost colorless needles, mp 167-169°. Found: N 11.11, 10.91%. Calculated for $C_{14}H_{16}JN_3S$: N10.91%.

2,4-Dimethyl-6-phenylpyrazolo[4,5-d]thiazole ethylperchlorate. 2,4-Dimethyl-6-phenylpyrazolo[4,5-d]thiazole diethylsulfate is prepared by heating 0.22 g (1 mmole) II and 0.16 g (1 mmole) diethyl sulfate at 130°/20 min, and the product dissolved in 5 ml water. 0.5 g (4 mmole) sodium perchlorate is added to the solution, and the precipitate formed is filtered off, washed with 5 ml water, and dried. Yield 0.28 g (82.3%), mp 170-172°. Recrystallization from ethanol gives pale yellow needles, mp 186-187°. Found: N 12.34, 12.37%. Calculated for $C_{14}H_{16}ClN_3O_4S$: N 12.45%.

2-Methyl-4,6-diphenylpyrazolo[4,5-d]thiazole (IV). A finely-ground mixture of 1 g (3 mmole) III and 1 g (4.5 mmole) phosphorus pentasulfide is heated at 130° (in a bath) until evolution of hydrogen sulfide ceases (10 min). The resultant melt is ground with 25 ml 5% aqueous sodium hydroxide solution. The base is extracted from the reaction mixture with benzene (30 ml thrice). The benzene extracts are united, washed with water (30 ml twice), and dried over calcium chloride. The benzene solution is evaporated to 20 ml, and then run through an activated alumina column. After the benzene has been evaporated off, there remains 0.63 g (85.3%) of colorless crystals, mp 114-115°. Colorless needles from petroleum ether, mp 115°. Found: N 14.24, 14.34%. Calculated for $C_{17}H_{13}N_3S$: N 14.43%.

2-Methyl-4,6-diphenylpyrazolo[4,5-d]thiazole dimethylsulfate. 0.15 g (0.5 mmole) IV and 0.15 g (1.2 mmole) dimethyl sulfate are heated together for one hour on a steam bath. The resultant colorless crystalline mass crystallizes from 10 ml water. Yield 0.08 g (38.1%) mp 184-185° (decomp.). Colorless needles. Found: N 9.99, 10.0%. Calculated for $C_{19}H_{19}N_3O_4S_2$: N 10.07%.

2-Methyl-4,6-diphenylthiazolo[4,5-d]thiazole ethiodide. 0.29 g (1 mmole) IV and 0.16 (1 mmole) diethyl sulfate are heated together at 130° (in a bath) for 45 min. The resultant quaternary salt is dissolved in 10 ml water, and 1 g (6 mmole) potassium iodide added. The resultant precipitate is filtered off, washed with water, and crystallized from acetone. Yield 0.11 g (24.4%). Pale yellow fine needles, mp 162-163°. Found: N 9.09, 9.17%. Calculated for $C_{19}H_{18}IN_3S$: N 9.39%.

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