THE "HILBERT-JOHNSON" REACTION OF 3,5-DIETHOXY-1,2,4-THIADIAZOLE

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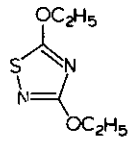
Alkylation of 3,5-diethoxy-1,2,4-thiadiazole via a Hilbert-Johnson type reaction results in the formation of N(2)-substituted derivatives.

The replacement of a carbon-carbon double bond by a sulfur atom has been recognized as an interesting type of modification in view of the electronic and steric similarities between the two structural elements[1,2]. Such a replacement in case of pyrimidine would lead to the 1,2,4-thiadiazole system. In view of the fact that pyrimidine derivatives are involved in the structure of nucleic acid components, it would be of interest to design thiadiazole analogues of nucleosides and nucleotides. In this communication we describe the N(2)-alkylation of 3,5-diethoxy-1,2,4-thiadiazole via the Hilbert-Johnson reaction[3].

3,5-Diethoxy-1,2,4-thiadiazole 1 was obtained by oxidation of ethyl thiocarbamate[4] and purified by vacuum sublimation (50-60°/10 mm). The sulfur-free product showed a melting point of 49-50°. Reaction of 1 with benzyl bromide 2a, in refluxing CH_3CN, proceeded slowly and even after a week both the starting materials

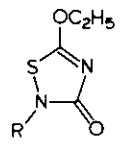


1

R—X

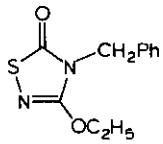
2

a R=CH_2Ph, X=Br
b R=CH_2OCH_2Ph, X=Cl



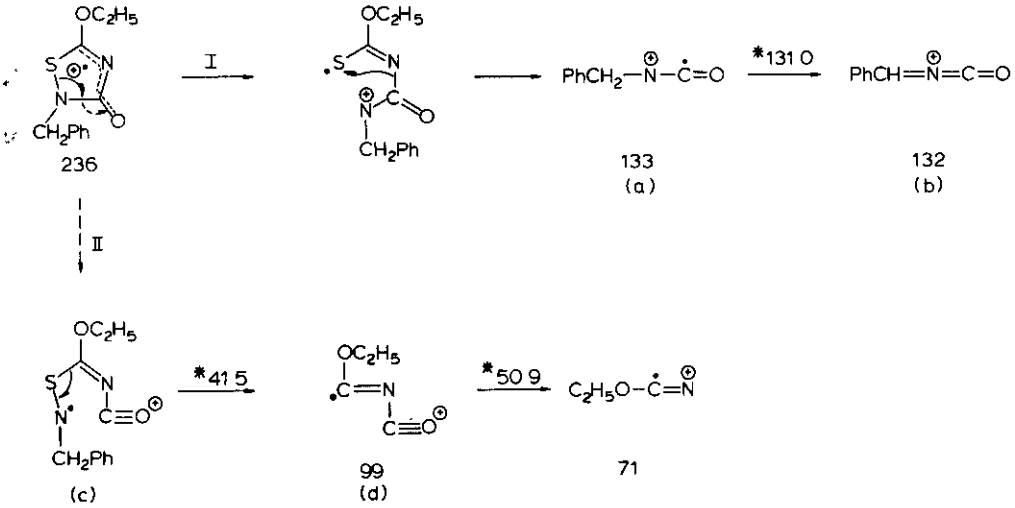
3

a R=CH_2Ph
b R=CH_2OCH_2Ph



4

Scheme A



could be detected in the mixture. The latter fact attests to the lower nucleophilicity of the thiadiazole system in comparison to the corresponding pyrimidine. The product of the reaction which was isolated in a pure state by chromatography over a silica column (eluent: $CHCl_3$) showed the following spectral data: IR(pure) 1690, 1590, 1550 cm^{-1}; PMR(CCl_4) δ 1.42 t and 4.53 q ($C\underline{H}_3C\underline{H}_2O$-), 4.74 s ($PhC\underline{H}_2$), 7.27 (aromatic protons). These data do not, however, allow a distinction between the N(2)-benzyl and the N(4)-benzyl derivatives 3a and 4, respectively. Assignment of structure 3a to the benzylated product is based upon the electron-impact fragmentation of the compound (Scheme A). The mass spectrum shows the following significant peaks: m/e 236 (73%, M^+), 175 (12%), 133 (21%), 132 (43%), 99 (2%), 91 (100%, $C_7H_7^+$). While formation of ions a and b are consistent with structure 3a, they can also be explained on the basis of 4. The formation of ion d, on the other hand, is only possible from the N(2)-isomer 3a. The genesis of d may be rationalized by the loss of a C_6H_5-CH_2N=S molecule from ion c (m/e 236). This is supported by the observation of a strong meta-stable peak at m/e 41.5, corresponding to the process 236 ⟶ 99.

1 reacted with chloromethyl benzyl ether[5] (2b) at room temperature (24h, CH_3CN) to yield 3b in 80% yield. IR(pure): 1690, 1600, 1100 cm^{-1}; PMR($CDCl_3$), δ 1.38 t and 4.49 q ($C\underline{H}_3C\underline{H}_2O$-), 4.65 s($PhC\underline{H}_2$-), 5.13 s(-O-$C\underline{H}_2N$), 7.34 (aromatic protons); MS m/e 266 (15% M^+), 236 (24%, M-CH_2O), 160 (6%, M-C_6H_5CHO), 91 (100%, $C_7H_7^+$). The positional assignment of the alkyl group in 3b is based upon analogy of the reaction of 1 with benzyl

bromide. Attempts to debenzylate 3b by treatment with HBr/ CH_3COOH or catalytic hydrogenation led to the degradation of the heterocyclic system. Similarly, hydrolysis of either 3a or 3b gave reaction mixtures in which free sulfur could be demonstrated. The aforementioned results indicate that the 3-oxo-1,2,4-thiadiazoles are relatively unstable under acidic, basic and hydrolytic conditions.

The application of the Hilbert-Johnson reaction of 1 with ribosyl halides with the objective of preparing novel nucleosides is being investigated.

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