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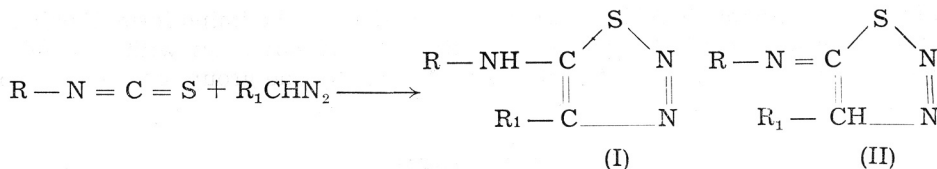
Formation of 1,2,3-Thiadiazole Derivatives from Isothiocyanates and Aliphatic Diazo Compounds

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Among different methods for the preparation of 1,2,3-thiadiazole derivatives^{1,2} a relatively simple one consists in the reaction of an isothiocyanate and a diazoalkane. However, this reaction, first reported by Pechmann and Nold³ and later checked by Sheehan and Izzo⁴, was successfully performed only with phenyl isothiocyanate and diazomethane as representatives of both classes of reactants. Although the 1,2,3-thiadiazole structure of the reaction product (I) was confirmed, it seemed desirable to study the reaction with different isothiocyanates and diazo compounds. Furthermore, it was not fully established if the compound exists in the amino (I) or imino (II) form.

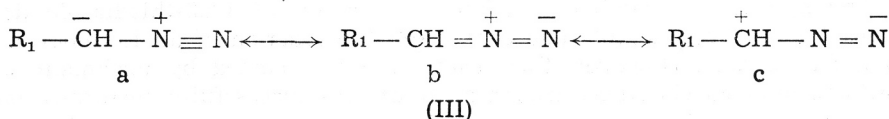


In order to examine the usefulness and possibilities of the above mentioned reaction, we studied the reaction of different alkyl and aryl isothiocyanates with diazomethane, diazoethane, phenyldiazomethane and ethyl diazoacetate. The addition of diazoalkanes on a thiocarbonyl group is known to proceed with elimination of nitrogen and formation of ethylene sulfide derivatives in the case of thioesters⁵ or trimethylene-1,3-disulfides in the case of thioketones^{6,7,8}. Phenyl isothiocyanate underwent the reaction with diazomethane in equimolecular proportions as indicated above and in a different way as isocyanates, which reacted with two molecules of a diazoalkane and the ring closure occurred on nitrogen instead on the carbonyl oxygen⁴.

An examination of the reactivity of different isothiocyanates toward diazomethane and diazoethane revealed that the reaction proceeded well with aromatic isothiocyanates, but different alkyl or arylalkyl isothiocyanates failed to react in an ethereal solution at room temperature. In all cases where an *o*-substituted phenyl isothiocyanate (*o*-methyl, *o*-chloro- or 2,5-dimethyl-) was used the reaction failed to produce a 1,2,3-thiadiazole derivative and an unchanged starting isothiocyanate was recovered after steam distillation of the reaction mixture or, in some cases, the reaction proceeded with evolution of nitrogen leading to compounds of unidentified structure.

Another important fact to be considered, is the structure of the diazo compound used in the reaction. Thus diazoethane, bearing an electron-donating group, reacted by far readily than ethyl diazoacetate where the electron-withdrawing group hinders the reaction. Also diazomethane appears to be somewhat less reactive than diazoethane where the additional +I effect of the methyl group influences the reactivity and makes the reaction more favorable. Ethyl diazoacetate did not react at room temperature, when refluxing an ethereal solution of both components, or even operating at elevated temperatures (110—120°C) without solvent. The same unreactivity was observed with phenyldiazomethane where no 1,2,3-thiadiazole derivatives could be obtained.

The above findings are in accordance with the electronic interpretation of this reaction, formulated as a nucleophilic attack of (III) (the contribution of forms IIIa and b being the most important) on the carbon atom of a thiocarbonyl



group with subsequent stabilization through ring closure on sulfur.

Considering the possibility of the above mentioned compounds to exist in the amino (I) or imino (II) form, the infrared spectra of different compounds were recorded as mulls in hexachlorobutadiene and exhibited bands at about 3270 cm^{-1} assignable to NH group⁹ and thus excluding the imino form. Furthermore the compound I (R = *p*-Cl-C₆H₄-; R₁ = H) did not react with benzaldehyde as it would be expected in the case of a methylene group, *e. g.* the imino form.

EXPERIMENTAL

Melting points were determined on a Kofler block. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics.

Reagents

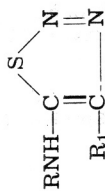
Diazomethane¹⁰ and diazoethane¹¹ were prepared as ethereal solutions from *N*-nitroso-*N*-methylurea and *N*-nitroso-*N*-ethylurethan. Ethyl diazoacetate¹² was prepared from glycine ethyl ester hydrochloride and phenyldiazomethane from azibenzil¹³ by an improved method according Yates and Shapiro¹⁴. Isothiocyanates (*o*-, *m*- and *p*-tolyl-, *o*-, *m*- and *p*-chlorophenyl, 2,5-dimethylphenyl-, *p*-methoxyphenyl-, *p*-ethoxyphenyl-, 2-phenylethyl- and cyclohexyl-) were prepared from the corresponding amines using a generally applicable procedure¹⁵, except for methyl-, ethyl- and 2-phenylethyl isothiocyanate which were prepared by a modified procedure¹⁶.

Formation of 1,2,3-Thiadiazole derivatives. General procedure

To the corresponding isothiocyanate (0.02 mole) an ethereal solution of 0.02 mole of the diazo compound (40 ml.) was added at room temperature and the mixture left overnight. In some cases, particularly with diazoethane, the reaction was vigorous and external heating was applied. The separated crystals were collected and recrystallized from ethanol or aqueous ethanol. Yields were 30—55%. The melting points and analytical data of the compounds obtained are presented in Table I.

Acknowledgment. The authors are indebted to Dr. S. Detoni for recording and interpreting the infrared spectra.

TABLE I
5-Arylamino-1,2,3-thiadiazoles



Compound No.	R	R ₁	M. p. °C	Formula	Analyses					
					Calcd.	Found				
				%C	%H	%N	%C	%H	%N	
1.	<i>p</i> -methylphenyl-	H	168	C ₉ H ₉ N ₃ S	56.54	4.75	21.98	56.87	4.96	21.68
2.	<i>p</i> -methoxyphenyl-	H	144	C ₉ N ₃ O ₃ S	52.17	4.38	20.28	52.37	4.76	20.17
3.	<i>p</i> -ethoxyphenyl-	H	159	C ₁₀ H ₁₁ N ₃ O ₃ S	54.29	5.01	19.00	54.45	5.14	18.86
4.	<i>m</i> -chlorophenyl-	H	158	C ₈ H ₆ ClN ₃ S	45.40	2.85	19.85	45.38	2.63	19.78
5.	<i>p</i> -chlorophenyl-	H	180	C ₈ H ₆ ClN ₃ S	45.40	2.85	19.85	45.53	2.70	19.76
6.	<i>p</i> -methylphenyl-	methyl-	163	C ₁₀ H ₁₁ N ₃ S	58.53	5.40	20.48	58.88	5.30	20.23
7.	<i>p</i> -methoxyphenyl-	methyl-	172	C ₁₀ H ₁₁ N ₃ O ₃ S	54.29	5.01	19.00	54.28	4.78	18.98
8.	<i>p</i> -ethoxyphenyl-	methyl-	176	C ₁₁ H ₁₃ N ₃ O ₃ S	56.16	5.57	17.86	56.28	5.61	17.76
9.	<i>p</i> -chlorophenyl-	methyl-	169	C ₉ H ₈ ClN ₃ S	47.90	3.57	18.60	48.00	3.41	18.39

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IZVLEČEK

Tvorba derivatov 1,2,3-tiadiazola iz izotiocianatov in alifatskih diazo spojin

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Od različnih alkil, arilalkil in aromatskih izotiocianatov reagirajo samo slednji z diazometanom ali diazoetanom tvoreč derivate 1,2,3-tiadiazola, čóčim s fenildiazometanom in diazoocetnim estrom reakcija ne poteka. Dobljeni derivati 1,2,3-tiadiazola obstajajo najverjetneje v aaminski obliki.

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