REACTION OF ISOTHIOCYANATES WITH DIAZOMETHANE*

M.UHER[a], A.RYBÁR[b], A.MARTVOŇ[a], and J.LEŠKO[c]

[a] *Department of Organic Chemistry, Slovak Institute of Technology, 880 37 Bratislava,*
[b] *Research Institute of Medicaments, 801 00 Bratislava and*
[c] *Laboratory of Mass Spectrometry, Slovak Institute of Technology, 880 37 Bratislava*

Received June 19th, 1975

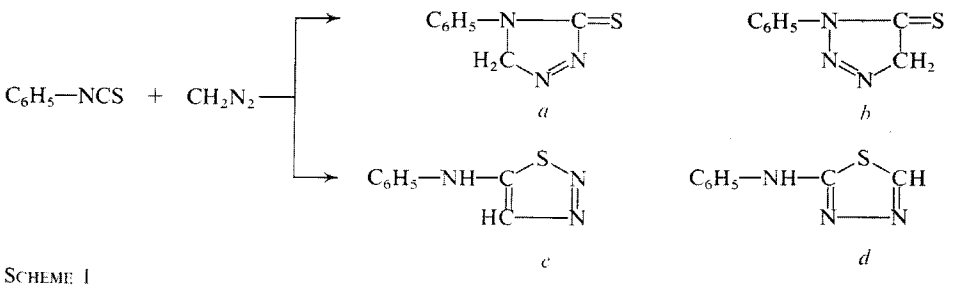
Preparation of 5-(substituted)amino-1,2,3-thiadiazoles from isothiocyanates and diazomethane is described and IR, UV, ^{1}H-NMR and mass spectra of the prepared compounds are discussed.

The reaction of phenyl isothiocyanate with diazomethane was first described by Pechmann and Nold[1] who assigned structure *c* (5-anilino-1,2,3-thiadiazole) to the product. These authors assumed that the reaction proceeds by one of the two possible reaction mechanisms under formation of four possible products, depending on whether diazomethane adds to the C=N or C=S bond (Scheme 1).

Sheenan and Izzo[2] confirmed the structure *c* and the possibility of its existence in imino and amino forms. According to IR spectra, the compound *c* exists preferentially in the form of 5-anilino-1,2,3-thiadiazole[3]. It was also found[3] that alkyl, arylalkyl and *ortho*-substituted phenyl isothiocyanates are unreactive. The reactivity of isothiocyanates increases with the increasing electrophilic character of the C atom in the —NCS group[4,5]. The reaction of methyl isothiocyanate with gaseous diazomethane affords in the first step 5-methylamino-1,2,3-thiadiazole which reacts with another isothiocyanate molecule to give N,N′-dimethyl-N-(1,2,3-thiadiazol-5-yl)thiourea[6]. According to Huisgen[7], all these reactions are 1,3-dipolar cycloadditions.

In the present study we reinvestigate the cycloaddition of isothiocyanates with diazomethane. In the series of aromatic isothiocyanates we chose substituents with different electronic as well as steric influence on the reaction centre. The aliphatic isothiocyanates used for the study had straight or branched chain. In order to obtain addition products with aliphatic isothiocyanates, several methods were tried. The reaction of isothiocyanates with diazomethane in ether at room temperature afforded the corresponding cycloadducts only in the case of aromatic isothiocyanates whereas the aliphatic derivatives did not react. The most reactive compounds were

* Part XLVI in the series Isothiocyanates and their Synthetic Producers; Part XLV: Chem. Zvesti *29*, 240 (1975).



SCHEME 1

4-nitro and 4-acetylphenyl isothiocyanates which after 10–15 minutes afforded crystalline products. The successful reaction of 2-methylphenyl isothiocyanate, confirmed by spectral measurements and elemental analysis, refutes the statements of several authors[3,5] about unreactivity of *ortho*-substituted aryl isothiocyanates.

It follows from the comparison of electronic effects of substituents on the cycloaddition course that the reaction rate is enhanced by electron-accepting substituents which lower the electron density on the carbon of the —NCS group and create there a partial positive charge, required for the nucleophilic attack of the electron pair of the diazomethane methylene group (Table I). Aliphatic isothiocyanates were also treated with diazomethane at higher temperature in dioxane but even this method did not lead to the corresponding thiadiazoles. The only one successful result was the reaction of methyl isothiocyanate with gaseous diazomethane leading to N,N'-dimethyl-N-(1,2,3-thiadiazol-5-yl)thiourea[6]. Other studied aliphatic isothiocyanates did not react under these conditions and were recovered from the reaction mixture.

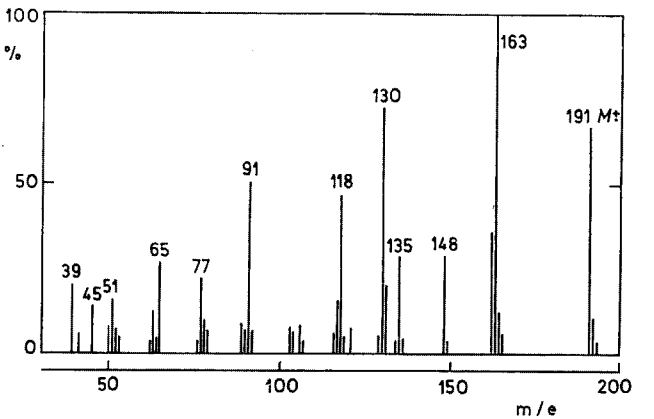
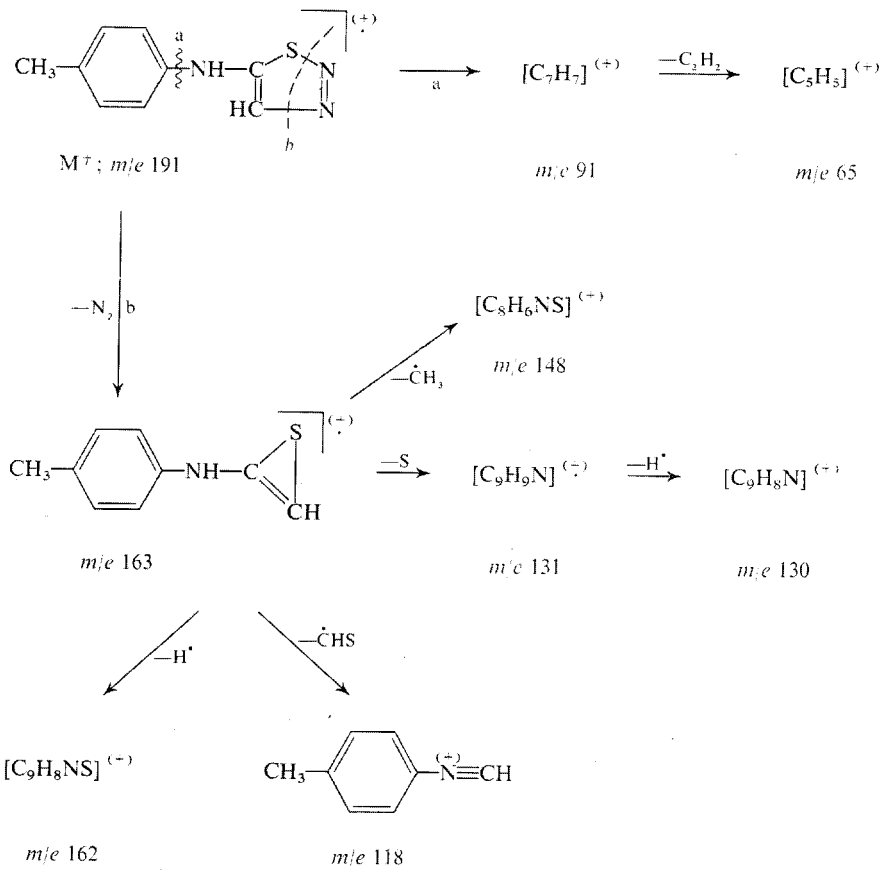


FIG. 1

Mass Spectrum of 5-(4-Methylphenyl)amino-1,2,3-thiadiazole

In order to confirm the structures of the synthesised compounds we measured their mass spectra. In all cases the molecular ion was in accord with the calculated molecular weight. The mass spectrum of 5-(4-methylphenyl)amino-1,2,3-thiadiazole is shown in Fig. 1. The base peak in the spectrum corresponds to the ion *m/e* 163, arising from the molecular ion by loss of nitrogen molecule from the 1,2,3-thiadiazole ring[9]. Further fragmentation paths are depicted in Scheme 2. ^{1}H-NMR spectra of 5-phenylamino-1,2,3-thiadiazole proved that the prepared thiadiazoles have the structure *c*.



SCHEME 2

[a] Reported[4] m.p. 180°C; [b] reported[4] m.p. 172–174°C; [c] reported[3] m.p. 144°C; [d] reported[3] m.p. 159°C; [e] reported[4] m.p. 168–170°C; [f] reported[4] m.p. 187–189°C; [g] reported[4] m.p. 206–209°C; [h] reported[4] m.p. 161–162°C; [i] substituent on the NH group.

TABLE I

Synthesised 5-(R-phenyl)amino-1,2,3-thiadiazoles

R	Formula (mol.w.)	M.p., °C (yield, %)	Calculated / Found % N	Calculated / Found % S	$\lambda_{1\,max}$, nm (log ε)		$\lambda_{2\,max}$, nm (log ε)
H	$C_8H_7N_3S$ (177·2)	174—176[a] (42·5)	—	—	247 (3·91)	286sh	322 (4·22)
2-CH_3	$C_9H_9N_3S$ (191·2)	106—108 (14·7)	22·19 21·87	16·75 16·69	247 (3·84)	285sh	320 (4·13)
3-CH_3	$C_9H_9N_3S$ (191·2)	128—129 (31·4)	22·19 21·92	16·75 16·61	248 (3·90)	287sh	324 (4·23)
4-CH_3	$C_9H_9N_3S$ (191·2)	170—172[b] (43·5)	—	—	249 (3·95)	287sh	325 (4·21)
4-CH_3O	$C_9H_9NO_3S$ (207·2)	144—145[c] (26·2)	—	—	251 (4·14)	276sh	323 (3·76)
4-C_2H_5O	$C_{10}H_{11}NO_3S$ (221·3)	158—159[d] (21·8)	—	—	250 (3·98)	286sh	323 (4·17)
4-CH_3S	$C_9H_9N_3S_2$ (223·3)	149—150 (27·5)	18·82 18·94	28·72 28·94	265 (3·99)		331 (4·30)
4-C_2H_5S	$C_{10}H_{11}N_3S_2$ (237·3)	130—132 (22·8)	17·70 17·62	26·98 26·70	266 (3·92)		330 (4·32)
4-$CH_3(CH_2)_9S$	$C_{18}H_{27}N_3S_2$ (349·5)	122—124 (17·5)	12·02 12·30	18·34 18·42	268 (3·92)		331 (4·30)
4-$(CH_3)_2N$	$C_{10}H_{12}N_4S$ (220·3)	166[e] (36·2)	—	—	266 (4·05)	306sh	326 (4·08)
4-CH_3CO	$C_{10}H_9N_3OS$ (219·3)	183—184 (64·2)	19·17 19·27	14·67 14·80	233 (3·97)	280 (3·84)	342 (4·50)
4-Br	$C_8H_6BrN_3S$ (256·1)	186—187[f] (52·6)	—	—	255 (4·03)		325 (4·28)
4-CH_3OOC	$C_{10}H_9N_3O_2S$ (235·3)	196—198 (48·2)	17·86 17·96	13·68 13·61	272 (3·87)		336 (4·46)
4-C_2H_5OOC	$C_{11}H_{11}N_3O_2S$ (249·3)	182—184 (45·7)	16·86 16·83	12·86 12·82	271 (3·84)		336 (4·47)
4-NO_2	$C_8H_6N_4O_2S$ (222·2)	207—209[g] (58·4)	—	—	234r	296 (3·70)	365 (4·32)
1-Naphthyl[i]	$C_{12}H_9N_3S$ (227·3)	160—161[h] (21·2)	—	—	246 (4·18)		342 (4·11)
2-Naphthyl[i]	$C_{12}H_9N_3S$ (227·3)	188—189 (20·5)	18·50 18·73	13·55 13·74	251 (3·44) 286 (4·04)	278 (4·03)	332 (4·29)

Derivatives of 1,2,3-thiadiazole absorb in the regions ~900, 1100–1150, ~1190, 1280–1350 and 1470–1580 cm^{-1}. Since the system is conjugated, an unequivocal assignment of the absorption bands due to C=C and N=N stretching vibrations in the region ~1600 cm^{-1} is not possible[4,8]. The spectra of the prepared compounds exhibit several strong absorption bands in the region 1280–1500 cm^{-1} which are ascribed to skeletal vibrations. In the region of bending δ(CH) vibrations, absorption bands at 895 ± 4 cm^{-1}, 1125 ± 4 cm^{-1} and 1184–1204 cm^{-1} are present in all compounds.

In the UV spectra of 1,2,3-thiadiazoles we can find two characteristic regions (Table I): the first, 233–272 nm, contains a variable maximum, the second is 320 to 365 nm. In the latter region a marked bathochrome shift (20–40 nm) was observed in compounds with electron-accepting substituents; this can be explained by a better involvement of *p*-electron pair of the sulphur atom in the conjugation with the π-electron system of the ring.

EXPERIMENTAL

Phenyl isothiocyanates were prepared by the thiophosgene method from free amines or their hydrochlorides according to ref.[10–12]. Ethereal solution of diazomethane was obtained by the alkaline decomposition of N-methyl-N-nitroso-*p*-toluenesulphonamide (Diazald)[13], gaseous diazomethane was prepared from N-methyl-N-nitrosourea[14].

The IR spectra were taken in the region 800–3600 cm^{-1} on a double-beam UR-20 (Zeiss, Jena) spectrophotometer. Since some of the derivatives were not sufficiently soluble in chloroform, nujol technique was used. The UV spectra were measured on a recording photometer Specord UV VIS in the region 200–800 nm (10 mm cells, concentration 3–5 . 10^{-5}M) in spectroscopically pure dioxane. Mass spectra were obtained on an MS 902 S instrument using direct inlet system; electron energy 70 eV, trap current 100 μA, temperature of the ionisation chamber 80–150°C, depending on the volatility of the sample. ^{1}H-NMR spectrum of 5-phenylamino--1,2,3-thiadiazole was measured at 25°C on a 80 MHz NMR Tesla BS 847 C spectrometer in a mixture of deuteriochloroform and hexadeuteriodimethyl sulphoxide.

Reaction of Isothiocyanates with Ethereal Diazomethane

An ethereal solution of diazomethane (0·01 mol) was added dropwise to a solution of the corresponding isothiocyanate (0·01 mol) in ether (10 ml) and the reaction mixture was allowed to stand for two days at room temperature. The crystalline products were separated, the ethereal solution was allowed to evaporate and in the course of 2–5 days it deposited crystalline products. The obtained 5-(substituted) amino-1,2,3-thiadiazoles were purified by crystallisation from various solvents. For 5-phenylamino-1,2,3-thiadiazole ^{1}H-NMR (δ): 6·9–7·5 p.p.m. (5 H, m, aromatic H); 8·26 p.p.m. (1 H, s, CH); 10·32 p.p.m. (1 H, s, NH).

Reaction of Aliphatic Isothiocyanates

a) *With diazomethane at higher temperature*: A solution of the aliphatic isothiocyanate (0·02 mol) and diazomethane (0·025 mol) in dioxane (50 ml) was refluxed for 10 hours. Samples were withdrawn during reflux and their UV spectra were measured. Steam-distillation of the mixture recovered the unreacted isothiocyanates.

b) *With gaseous diazomethane*: Diazomethane was bubbled in a stream of nitrogen through the given isothiocyanate during two hours. The reaction flask was then stoppered and set aside at room temperature for 2 days. The crystals which were formed in the case of the methyl derivative were separated. Steam distillation of the reaction mixtures from other isothiocyanates recovered the unreacted isothiocyanates. The isolated N,N'-dimethyl-N-(1,2,3-thiadiazol-5-yl)thiourea melted at 220°C (ref.[6] reports m.p. 222°C).

REFERENCES

1. von Pechmann H., Nold A.: Ber. Deut. Chem. Ges. *25*, 2588 (1896).
2. Sheenan J. C., Izzo P. T.: J. Amer. Chem. Soc. *71*, 4059 (1949).
3. Tišler M., Hrovat H., Machiedo M.: Croat. Chem. Acta *34*, 183 (1962).
4. Lieber E., Calvanico M., Rao C. N. R.: J. Org. Chem. *28*, 257 (1963).
5. Martin D., Mücke W.: Z. Chem. *3*, 347 (1963); Justus Liebigs Ann. Chem. *673*, 128 (1964).
6. Martin D., Mücke W.: Justus Liebigs Ann. Chem. *682*, 90 (1965).
7. Huisgen R.: Angew. Chem. *75*, 742 (1963).
8. Rao C. N. R., Venkataraghavan R.: Can. J. Chem. *42*, 43 (1964).
9. Zeller K. P., Meier H., Müller E.: Tetrahedron *28*, 1353 (1972).
10. Uher M., Kristián P., Antoš K., Drobnica Ľ.: Chem. Zvesti *21*, 44 (1967).
11. Uher M., Jendrichovský J.: This Journal *38*, 289 (1973).
12. Uher M., Antoš K.: Chem. Zvesti *22*, 439 (1968).
13. De Boer T. J., Backer H. J.: Rec. Trav. Chim. Pays-Bas *73*, 229, 582 (1954).
14. Urry W. H., Bilow N.: J. Amer. Chem. Soc. *86*, 1817 (1964).

Translated by M. Tichý.