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UMPOLUNG OF THE AZOMETHINE REACTIVITY IN THE REACTION OF ALDEHYDE HYDRAZONES WITH SULFONYL ISOCYANATES SUBSTITUENT EFFECTS[2]

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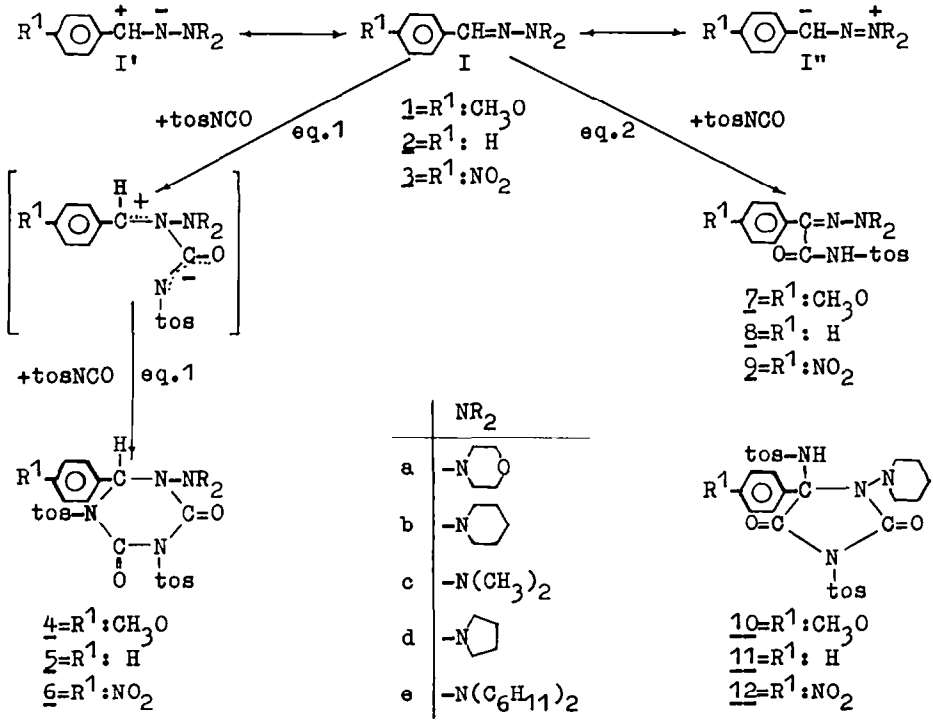
Abstract. Sulfonyl isocyanates attack the arylaldehyde N,N-dialkylhydrazones 1-3 at the nitrogen or carbon of the azomethine function leading to the formation of the hexahydro-1,3,5-triazine-2,4-diones 4-6 or arylglyoxylic acid sulfonamide-N,N-dialkylhydrazones 7-9 (scheme 1). Under equal experimental conditions the position of the electrophilic attack depends on the contribution of the dipolar structures I'↔I" determined by the electron withdrawing or donating potential of the substituents R^1 and NR_2. The normal reactivity of the >C=N-function is described by eq.1, the umpolung by eq.2. These different reactions correspond to the ^{13}C-chemical shifts of the azomethine carbon atoms.

Dependent on the substituents NR_2 resp. R^1 arylaldehyde N,N-dialkylhydrazones can react like enamines: as aza-enamines they are attacked in an umpolung reaction e.g. by sulfonyl isocyanates at the carbon of azomethine group forming the glyoxylic acid sulfonamide hydrazones 7-9 (eq.2). Otherwise arylaldehyde N,N-dialkylhydrazones like Schiff bases can be attacked by sulfonyl isocyanates at the nitrogen atom: via a not isolable dipolar intermediate the reaction with a second molecule of sulfonyl isocyanate yields a 5-amino-hexahydro-1,3,5-triazine-2,4-dione [1,3,4] 4-6 (eq.1).

This paper describes the courseof the electrophilic reactions of the 15 hydrazones 1a-e, 2a-e and 3a-e with p-tolylsulfonyl isocyanate under equal experimental conditions (molar ratio 1-3 / tosNCO = 1:2.5, in CCl_4 at same times) to find out the scope of the reactions according to eq.1 or eq.2.

Although in most cases the reaction had been completed after some hours all reaction mixtures were allowed to stand over a period of 28 days, since only after this time the hydrazones 3b and 3c had reacted completely. 3a reacted even more slowly and only a small portion was converted after five months. Since most of the reaction products crystallized very well yields were determined gravimetrically.

The results are summarized in table 1. The majority of the aldehyde hydrazones shows a selective reaction. Thus the synoptic table may be subdivided into three limited regions. The hydrazones 1a-c, 2a and 2b in the upper left section are preferentially converted to the compounds 4 and 5; the hydrazones 1e, 2d and 2e and 3a-e standing at the bottom and on the right side are converted to the compounds 7-9. In most cases, the yields are considerable higher than 50%.



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The central section is the transition region; here the compounds 4d/7d and 5c/8c are formed as well in comparable quantities from 1d or from 2c.

Table 1[a]) Survey of reactive behaviour and the ^{13}C-chemical shifts of the azomethine carbon atoms of the aldehyde hydrazones [4e] 1-3.

NR_2	1=R^1:CH_3O			2=R^1: H			3=R^1:NO_2		
	N %4	C %7	ppm	N %5	C %8	ppm	N %6	C %9	ppm
a	83		136.6	+		136.1		+	131.5
b	84		135.0	22		134.5		50	129.3
c	69		133.5	6.5	10	132.7		84	126.9
d	+	54	132.9		86	132.0		90	126.5
e		76	125.1		75	124.5		100	121.1

[a]) N %.. or C %.. are the isolated yields of the corresponding compounds 4-6 or 7-9 obtained by attack of the isocyanate on the nitrogen or carbon of the azomethine group (mean values: cf.experimental part); + the yield was not exactly determined.

DISCUSSION*

For the hydrazones I, the dipolar canonical structures I' and I" can be formulated, the normal polarization of an imine structure is described by I', the umpolung of the imine structure by I".

In the anisaldehyde hydrazones 1a-e the methoxy group as an electron donor substituent R^1 delocalizes the formal positive charge on the azomethine carbon of I' and thus favours the imine like reactivity. The donor potential of the morpholino, piperidino and dimethylamino residues NR_2 is not sufficient to overcome the opposite influence of R^1=OMe. Thus the electrophilic attack takes place at the nitrogen of the azomethine group. However the pyrrolidino and the dicyclohexylamino substituents NR_2 as strong electron donors cause umpolung and thus an attack on carbon.

Umpolung is favoured in the reactions of benzaldehyde hydrazones 2 lacking the influence of the methoxy substituent.

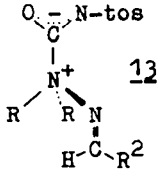
The strong electron acceptor substituent NO_2 in the hydrazones 3a-e increases the contribution of the dipolar structure I" and thus favours umpolung i.e. the aza-enamine reactivity. According the table 1 only the C-acyl products 9a-e were isolated.

The great difference in the electron donor potential of the cyclic six membered morpholino and piperidino substituents NR_2 resp. the five membered pyrrolidino substituent NR_2 in the anisaldehyde hydrazones 1a and 1b resp. 1d repeatedly was explained by steric effects [5,6,7,8].

The remarkable difference in the behaviour of the hydrazones 1c resp. 1e with non cyclic amino substituents NR_2 can be explained by different steric hindrance caused by the methyl resp. the bulky dicyclohexyl groups.

Scheibe [9] attributes the different resonance interaction between the amino groups and the double bonds in open chain cyanine dyes to the state of hybridization of the nitrogen atom which depends on the bond angles at the nitrogen atom. They might be larger in 1e than in 1c because of the great bulk difference of the residues R.

Furthermore, it is possible that a loose addition complex 13 is formed between the hydrazone and the isocyanate, by which the normal imine resonance structure I' is favoured due to blocking the lone pair and the strong -I-effect caused by the ammonium group. Corresponding to the results obtained in this study, the formation of 13 should be sterically hindered to a greater extent in 1e than in 1c.



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* In some cases, imidazolidine diones 10-12, not specified in table 1, are formed additionally [1]. Since it could not yet be elucidated whether the compounds 7-9 are intermediates in the formation of the imidazolidine diones this reaction is not included in the following considerations. It should be mentioned that 2b gave rise to a mixture of 5b and 11b with a total yield of 71% which could be separated with yields of 22% 5b and 35% 11b, respectively. In the same way, the reaction of 3b gave rise to a mixture of an average of 50% of 9b and 32% of 12b. In the reactions of 1c and 1b, a small amount of a substance could be detected or isolated which had the two characteristic C=O bands of the imidazolidine diones in the ir spectra.

Finally, it can be assumed that not only the nitrogen of the substituent NR_2 but also the adjacent nitrogen of the azomethine group is much more shielded by the bulky cyclohexyl residue R than by the methyl group R, so that the carbon becomes the preferred point of attack.

Bending of the amino moiety NR_2 out of the C=N-plane and therefore reduced resonance interaction between NR_2 and the adjacent C=N [5,7,8] seems to be of little account, since this effect should result in opposite behaviours of the two aldehyde hydrazones 1c resp. 1e.

In the product determining electrophilic step the hydrazones in the upper left section of table 1 preferentially are attacked at nitrogen, whereas those on the right and below at the carbon of the azomethine groups. This can be correlated with the ^{13}C-chemical shifts of the azomethine carbons in table 1: the ^{13}C-values decrease from top to bottom and from the left to the right side. This decrease corresponds to an increase of the π-electron densities at the azomethine carbon atoms of the hydrazones, which means an increasing contribution of the dipolar structure I".

EXPERIMENTAL

Ir spectra: ir spectrophotometer UR 20 made by VEB Carl Zeiss, Jena. Thin layer chromatography: Merck plates (silica gel 60, F-254), mobil solvent: toluene/methanol 90:10 or 96:4 vol%. Preparative layer chromatography: plate size 20x20 cm, 30g of Merck silica gel G according to Stahl Type 60 + 0,2g of fluorescent indicator F-254. Column chromatography: silica gel 60 from Merck, granulation 0.063 - 0.2 mm.

General procedure for the reaction of the aldehyde hydrazones 1-3 with 4-methylphenylsulfonyl isocyanate and work up of the formed products 4-9 (for variations, concerning reaction and work up, details are given with the numbers of the starting hydrazones).

2 mmol of aldehyde hydrazone 1-3 was suspended [3,4c,10] or dissolved together with 5 mmol of 4-methylphenylsulfonyl isocyanate in 2 ml of CCl_4 (cleaned by boiling for 20 h over phosphorus pentoxide and subsequent distillation) and allowed to stand for 28 d at room temp. in the absence of moisture. In general, the hydrazones dissolved quickly, at the latest during the following hours. The reaction product usually crystallized from the solution after some hours or days.

After 28 d the solvent was removed by decanting and the crystalline residue washed with 2 ml of CCl_4 and then triturated with 2 to 5 ml (depending on the solubility of the reaction product) of alcohol-free ethyl acetate (first crystallizate). To obtain a further yield, some water was added to the combined filtrates in order to decompose excessive sulfonyl isocyanate, solvents and water were removed by evaporation and the residue was dissolved or suspended in the lowest possible amount of ethylacetate (in general, 0.2 to 0.5 ml). After standing overnight at a temperature of +6°C, the second crystallizate mostly precipitated and was separated from the solution and washed with a small amount of ice cold ethyl acetate. The yields given below (1st and 2nd crystallizate, vacuum-dried at 60°C) were determined after the purity test proved by thin layer chromatography and ir spectrum (in KBr). Yields of at least 2 up to 5 experiments refer to the starting hydrazones.

Results.

From 0.44g 4-methoxybenzaldehyde-N,N-(ß,ß'-oxy-diethylene)hydrazone 1a [11] 1.02g=83% resp. 1.03g=84% 4a [12] were formed.

From 0.437g 4-methoxybenzaldehyde-N,N-pentamethylene hydrazone 1b [11] 1.05g=86% resp. 1.04g=85% resp. 1.0g=82% 4b [12] were formed.

From 0.356g 4-methoxybenzaldehyde-N,N-dimethylhydrazone 1c [11] 0.764g=67% resp. 0.802g=70% resp. 0.81g=71% 4c [12] were formed.

From 0.409g 4-methoxybenzaldehyde-N,N-tetramethylene hydrazone 1d [11] 0.406g=51% resp. 0.420g=52% resp. 0.455g=57% resp. 0.463g=58% (4-methoxyphenyl)glyoxylic acid(4-methylphenyl-sulfonamide)N,N-tetramethylene hydrazone 7d [12] were formed.

As an increasing resin formation the reaction mixture was worked up not after 28d but already after 3d; because of high solubility the crystallizate was washed not with 2-5 ml but only with 0.6ml ethyl acetate. To isolate two further substances the solvent of mother and washing liquors of a 10mmol batch was evaporated and the residue chromatographed with toluene as eluent on a 250mm column (diameter 23mm). After recrystallization from i-propanol the first fraction yielded 0.091g 6-(4-methoxyphenyl)-1,3-di(4-methylphenyl-sulfonyl)-5-pyrrolidino-hexahydro-1,3,5-triazin -2,4-dione 4d: m.p.131°C; ir (KBr) ν_{CO}=1733 and 1757 cm^{-1}, both strong and sharp; m/e=204 (M+ minus tosNCO), 197 (tosNCO+),155,134 (characteristic values of the compounds 4-6) [1];

calc. C,56.17; H,5.05; N,9.36; found C,56.23; H,4.94; N,9.51. The 2.fraction was recrystallized from glacial acetic acid; m.p. 249°C to 251°C; ir (KBr) ν_{CO}= 1749cm^{-1} very strong and 1800cm^{-1} weak, both sharp (characteristic of compound typ 10-12[1]).

From 4-methoxybenzaldehyde-N,N-dicyclohexylhydrazone 1e[11] 7e[12] was formed. 7e did not crystallize from the reaction mixture within 28d. Therefore CCl_4 was removed at 20°C, the residue suspended in 5ml of acetonitrile+ 2 drops of water and the separated product recrystallized from the amount of ethyl acetate just necessary. Because of high solubility of 7e, the yields referred to 0.629g 1e were only 0.636g=62% resp. 0.638g=62% resp. 0.664g=65%. A further yield was isolated from the first-noted batch by means of prep. layer chromat. of the evaporated filtrates (6 plates, eluent toluene/methanol 93:7 vol%). After extraction with 140 ml of methanol further 0.146=14% 7e resulted after recrystallizing and washing with 0.3ml of ice-cold ethyl acetate. Total yield: 0.782g= 76% 7e.

From 0.38g benzaldehyde-N,N-(ß,ß'-oxy-diethylene)hydrazone 2a[11] 0.531g=45% resp. 0.365g=31% resp. 0.354g=30% 5a[12] were formed.

From 2b [11](benzaldehyde-N,N-pentamethylene hydrazone) a crystallizate was obtained on the basis of the general procedure consisting of a mixture of 5b[12] and 11b[12]. Two tests from 0.377g 2b yielded 0.769g=66% 5b+11b resp. 0.831g=71.3% 5b+11b, which were separated by prep. layer chromat. (eluent toluene/methanol 90:10 vol%). 5b had the higher Rf value and was completely extracted with hot dimethyl formamide, 11b with methanol at 20°C. 0.192g of the mixture of the second batch yielded 0.058g=21.6% 5b and 0.1g=37% 11b, and 0.144g of the same mixture resulted in 0.045g=22.3% 5b and 0.067g=33.2% 11b.

From benzaldehyde-N,N-dimethylhydrazone 2c[11] a mixture of 5c[12] and phenylglyoxylic acid(4-methylphenyl-sulfonamide)N,N-dimethylhydrazone 8c[11] was formed. The reaction products did not always crystallize, therefore the solution was evaporated to dryness at 20°C and the residue chromatographed on a column of 80g of Silasorb 600, granulation 30µm irregular, length 180mm, diameter 25mm, eluent 0.05-0.1vol% of methanol in CH_2Cl_2, 1 atm.overpressure, 10mg of raw product dissolved in 1ml of solvent, 80mg each applied per passage. Yields referred to 0.296g 2c: fraction 2: 0.070g=6.5% 5c; fraction 4: 0.22g consisted at first of three substances, the subsequent prep.layerchromat.(one plate, eluent toluene/methanol 90:10 vol%) yielded 0.070g=10% 8c.

From 0.348g benzaldehyde-N,N-tetramethylene hydrazone 2d[11] 0.635g=85% resp. 0.617g=83% phenylglyoxylic acid(4-methylphenyl-sulfonamide)N,N-tetramethylene hydrazone 8d[11] were formed. In addition to the 0.617g further 0.033g=4% was obtained by preparative layer chromatography of the mother liquor residues on two plates (mobile solvent: toluene/methanol 85:15vol%); the substance was extracted from silica gel with 150ml of methanol, the solvent evaporated and the residue recrystallized from 0.3ml of ethyl acetate.

From benzaldehyde-N,N-dicyclohexylhydrazone 2e[11] 8e[12] was formed. 8e did not always crystallize from the reaction mixture, therefore CCl_4 was removed at 20°C and the residue dissolved in 2ml of ethyl acetate; 8e crystallized overnight at +6°C and was washed with 0.3ml of ice-cold ethyl acetate. The combined mother liquors were evaporated to dryness, the residue was dissolved in 0.5ml of ethyl acetate, crystallized at +6°C, and the separated product recrystallized from 1ml of ethanol. Thus from 0.569g 2e 0.672g=70% resp. 0.756g=79% 8e resulted.

From 4-nitrobenzaldehyde-N,N-(ß,ß'-oxy-diethylene)hydrazone 3a[11]—9a[12] was formed. After a six-month reaction time of 0.470g 3a and 0.985g tosNCO in 4ml of CH_2Cl_2 (because of too low solubility of 3a in CCl_4), 0.1ml of water was added and the mixture was evaporated to dryness. When methanol was added to the residue 0.030g 9a remained undissolved. The ir spectrum of the residue of the evaporated methanolic solution did not show the C=O bands in the range between 1730 cm^{-1} and 1770 cm^{-1} which are characteristic of the structures 4-6.

From 4-nitrobenzaldehyde-N,N-pentamethylene hydrazone 3b[11] a mixture was formed which was separated in the components 9b[12] and 12b[12] according to the procedure described in [1]. Five tests yielded from 0.467g 3b: 0.468g=54.4% 9b and 0.455g= 34.5% 12b resp. 0.394g=45.7% 9b and 0.538g=40.8% 12b resp. 0.408g=47.4% 9b and 0.390g=29.6% 12b resp. 0.477g=55.4% 9b and 0.305g=23.1% 12b resp. 0.381g=44.2% 9b and 0.412g=31.2% 12b (12b is crystallizing with one mol methanol; MG=659.7).

From 0.386g 4-nitrobenzaldehyde-N,N-dimethylhydrazone 3c[11] 0.63g=81% resp. 0.69g=88% (4-nitrophenyl)glyoxylic acid(4-methylphenyl-sulfonamide)N,N-dimethylhydrazone 9c[11] were formed.

From 0.438g 4-nitrobenzaldehyde-N,N-tetramethylene hydrazone 3d[11] 0.73g=88% resp. 0.77g=92% (4-nitrophenyl)glyoxylic acid(4-methylphenyl-sulfonamide)N,N-tetramethylene hydrazone 9d[11] were formed.

From 0.659g 4-nitrobenzaldehyde-N,N-dicyclohexylhydrazone 3e[11] 1.04g=99% resp. 1.05g=100% 9e[12] were formed.

L I T E R A T U R E

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