REACTIONS OF ALDONITRONES (3-IMIDAZOLINE-3-OXIDES) WITH ISOTHIOCYANATES

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Cycloaddition of aldonitrones (derivatives of 3-imidazoline-3-oxide) to isothiocyanates depends on the N(1) substituent. Electron donating substituents facilitate cycloaddition to the C=N bond, whereas electron acceptors activate the C=S bond. Hydrolysis of adducts on the C=N bond followed by oxidation gives nitroxide radicals which are pH-sensitive spin probes.

Keywords: *aldonitrones, 3-imidazoline-3-oxide derivatives, isothiocyanates.*

Isothiocyanates undergoing 1,3-dipolar cycloaddition react at the C=S [1, 2, 3] or C=N [4, 5] bond. Aldonitrones of the pyrroline-N-oxide series attach to phenyl isothiocyanate at the C=N bond, and to its derivatives bearing accepting as well as donating substituents, mainly at the C=S bond [6]. In continuation of our work on 1,3-dipolar cycloaddition of aldonitrones of the 3-imidazoline-3-oxide series [7, 8] the influence on the direction of addition by the type of substituent on the aldonitrone was studied.

It was shown that 1-nitroso-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (**1**) under the action of isothiocyanates RNCS (R = Me, Ph) gives in good yield 1-nitroso-2,2,5,5-tetramethylimidazolidin-4-thione in every case (**2**) (Tables 1 and 2).

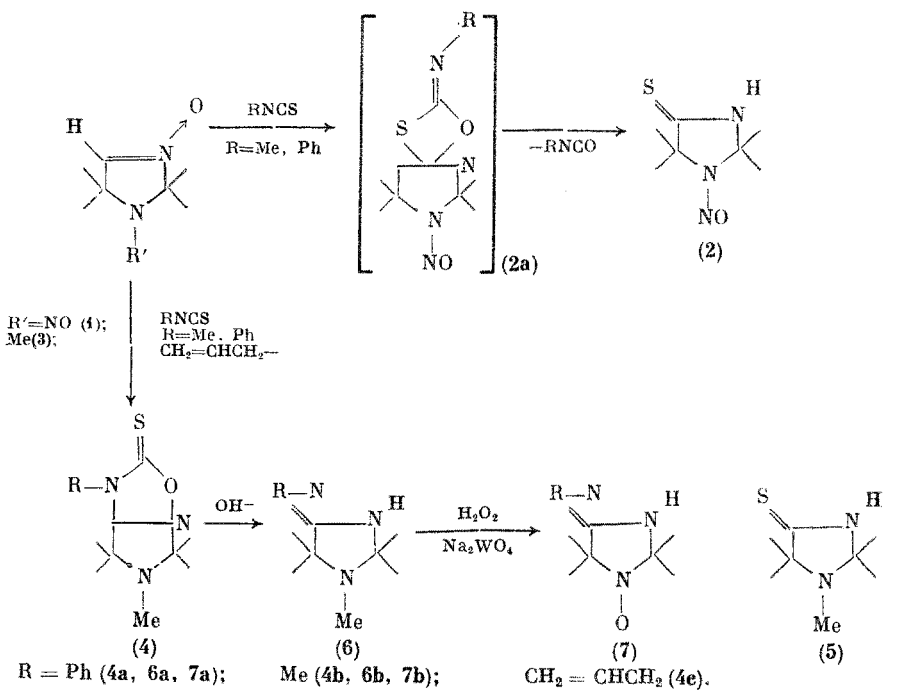

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	Mp, °C	Found/Calculated, %		
			C	H	N
2[d]	70	222–224[c]	45.57/44.92	6.99/6.95	22.87/22.46
4a[d]	85	115–117[a]	61.80/61.85	7.49/7.22	14.46/14.43
4b[d]	65	132–134[b]	52.92/52.40	8.73/8.30	18.65/18.34
4c[d]	65	78–80[a]	56.54/56.47	8.47/8.28	16.40/16.47
5[d]	98	157–159[a]	55.33/55.80	9.58/9.30	15.98/16.20
6a	98	124–125[a]	72.72/72.72	9.46/9.09	18.30/18.01
6b	60[e]	130–132[a]	63.58/63.91	10.83/11.24	24.84/24.85
7a	75	213–214[b]	66.92/67.24	7.71/7.75	18.15/18.10
7b	75	146–148[b]	55.94/56.47	9.57/9.11	24.35/24.70
8	20	68–70[a]	73.08/73.47	9.53/9.39	16.60/17.14
9	57	68–70[a]	72.99/73.47	10.08/9.39	16.55/17.14
10	25	114–116[b]	54.92/54.98	8.05/7.82	11.08/11.32
11	60	135–137[a]	68.22/68.29	8.36/8.13	16.85/17.07
12	65	103–105[a]	68.00/68.29	8.36/8.13	16.88/17.07

[a]Hexane.

[b]Hexane:ethyl acetate = 4:1.

[c]Chloroform.

[d]S Found/Calculated: (2) 17.01/17.05; (4a) 10.67/10.99; (4b) 13.42/13.97; (4c) 12.10/12.55; (5) 18.52/18.60.

[e]Yield from thermolysis.

Formation of thioamide (2) can be explained by the initial addition of isothiocyanate to aldonitrone at the C=S bond with formation of intermediate (2a) which then splits with expulsion of an isothiocyanate molecule and 1,2-migration of H to nitrogen.

Upon treatment of 1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide (3) with phenyl isothiocyanate a crystalline compound (4a) was isolated in high yield, the IR spectrum of which shows at 1500-1700 cm^{-1} the presence of only an aromatic ring band. Addition at the C=S bond is excluded, since in this case a band at 1600 cm^{-1} should be observed, as is observed for exocyclic C=N bonds in similar compounds [10]. Compound (4a) was identified as an adduct at the C=N bond, and TLC of the reaction mixture showed not even trace amounts of thioamide (5), the possible addition product at the C=S bond [6]. Compound (5) was obtained independently by reaction of aldonitrone (3) with CS_2 by a method of [11]. Aldonitrone (3) with methyl and allyl isothiocyanates also gives cycloadducts at the C=N bond (4b and 4c) (Tables 1 and 2).

It is known that cycloadducts of nitrones with isothiocyanates are extremely unstable and upon thermolysis and hydrolysis they form N-substituted amidines [6, 12]. Accordingly, upon alkaline hydrolysis of cycloadducts (4a, b) and thermolysis of (4b) there were obtained N-substituted amidines, derivatives of 3-imidazoline (6a, b), which additionally confirms the structure of cycloadducts (4).

Paramagnetic amidines, derivatives of 3-imidazoline, are used as pH-sensitive spin probes [13, 14]; therefore it is of interest to investigate their diamagnetic analogs and their conversion to paramagnetic derivatives with the goal of creating a wide

TABLE 2. Spectral Parameters of the Synthesized Compounds

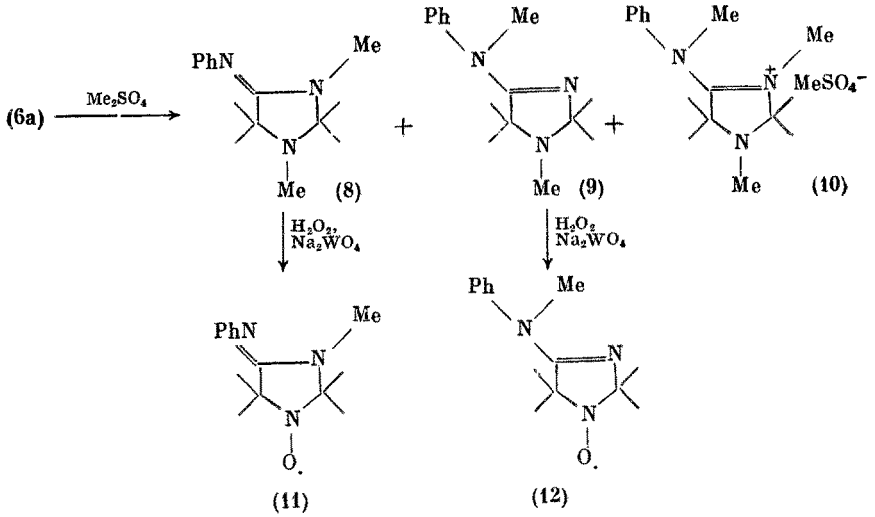
N	IR spectrum (KBr, ν, cm^{-1})	UV spectrum {λ, nm (log ε)}	PMR spectrum ($CDCl_3$, δ, ppm)		
			Me_2C	MeN	aromatic, etc.
2	1540(C=S)[a]	270(4.45)	1.69(6H) 1.89(3H) 1.92(3H)		
4a	2800(MeN)	222(4.35) 267(4.02) 281(4.00)	1.06(3H) 1.10(3H) 1.24(3H) 1.52(3H)	2.27	5.57 s (1H, CH) 7.90 m (5H)
4b	2820(MeN)	–	1.17(6H) 1.45(3H) 1.09(3H)	2.27 3.25	4.29 s (1H, CH)
4c	2800(MeN)	250(4.16)	1.04(3H) 1.12(6H) 1.45(3H)	2.23	3.70 m (1H)[f] 4.83 m (1H)[f] 5.33 m (2H)[f] 5.85 m (1H)[f] 4.91 s (1H, CH)
5	1540(C=S)[b] 3420(N–H)[b] 3150(N–H)[b]	270(4.78)	1.32(6H) 1.37(6H)	2.36	
6a	1550(N–H)[c] 2800(MeN) 1620(C=N)	258(4.17)	1.30(12H)	3.32	5.37br.(1H, NH) 7.35 m (5H)
6b	1550(N–H)[c] 1630(C=N) 2800(MeN)	–	1.14(6H) 1.27(6H)	2.29 2.87	3.11br.(1H, NH)
7a	1640(C=N) 3350(N–H)	210(4.11) 256(4.17)			
7b	1624(C=N)[c] 1555(N–H)[c] 3330(N–H) 3375(N–H)	238(3.61)			
8	2800(MeN) 1650(C=N)	238(4.09)	1.12(6H) 1.24(6H)	2.25 2.74[d]	7.00 m (5H)
9	1605(C=N) 2800(MeN)	–	0.85(6H) 1.29(6H)	2.20 3.22[e]	7.29 s (5H)
10	2820(MeN) 1625(C=N)	250(3.75)	1.40(6H) 1.64(6H)	2.39 2.64[e] 3.70[d]	7.50 s (5H) 3.77 (3H, $CH_3SO_4^-$)
11	1660(C=N)	234(4.11)			
12	1605(C=N)	240(3.81)			

[a]See [9].
[b]In CCl_4.
[c]Bending.
[d]*Endo*.
[e]*Exo*.
[f]CH_2=CH–CH_2–.

set of spin probes which differ in lipophilicity and alkalinity constants p*K*. Oxidation of amidines (**6a, b**) in H_2O_2 in the presence of sodium tungstate gives nitroxyl radicals (**7a, b**)* and alkylation of amidine (**6a**) with dimethyl sulfate results in two compounds with very similar R_f's, which were identified as alkylation products at the endocyclic (**8**) and exocyclic (**9**) nitrogen atoms. Compound (**8**) has a UV spectrum characteristic of N-phenylimines (Table 2) and (**9**) adsorbs weakly in the UV region. Upon increase of reaction time the single alkylation product is salt (**10**) (see scheme on top of following page).

Oxidation of compounds (**8**) and (**9**) gives radicals (**11**) and (**12**), whose EPR spectra are also sensitive to change of pH. Alkylated amidines have better lipophilicity and higher p*K*'s (see Experimental) in comparison with nonalkylated precursors. It should be noted that radicals (**11, 12**) could not be obtained by direct alkylation of amidine (**7a**).

*This oxidative dimethylation of sterically hindered tertiary amines was realized first in [15].



Thus, the data shown indicate that the direction of cycloaddition of isothiocyanates to aldonitrones of the 3-imidazoline-3-oxide series depends on the type of substituent in position 1 of the imidazoline ring: donating substituents promote cycloaddition of the C=N bond and accepting ones at the C=S bond. Adducts of isothiocyanate with 1-methylaldonitrone can serve as synthons for obtaining new pH-sensitive spin probes.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr pellets and solutions in CCl_4, UV spectra on a Specord UV-VIS instrument in EtOH, and PMR spectra on Varian A56/60A and Bruker AC-200 instruments. Alkalinity constants (p*K*) for amidine radicals were determined* by a method of [14]. Aldonitrones (**1**) and (**3**) were synthesized by a method of [16].

Reactions of Aldonitrones with Isothiocyanates (General Method). To a solution of 10 mmoles of aldonitrone in 15 ml of $CHCl_3$ 15 mmoles of isothiocyanate was added and the mixture was left for 2 days with periodic checking of the reaction course by TLC. After disappearance of the starting aldonitrone the mixture was evaporated and chromatographed on silica gel with ether–hexane (1:1) as eluent.

1,2,2,5,5-Pentamethylimidazolidin-4-thione (5). A solution of 1 g (6.4 mmoles) of compound (**3**) in 2 ml of CH_2Cl_2 and 6 ml of CS_2 was boiled in a water bath until disappearance, according to TLC, of the starting aldonitrone (~20 h). The solution was evaporated until dry and the solid residue was recrystallized from hexane.

1,2,2,5,5-Pentamethyl-4-(N-phenylamino)-3-imidazoline (6a). A 2.3-mmole portion of cycloadduct (**4a**) was added to 20 ml of a 10% water–alcohol solution of NaOH and the mixture was left to stand, monitoring periodically by TLC. After disappearance of the starting (**4a**) the mixture was evaporated to minimum volume, then 5 ml of H_2O was added and extracted with $CHCl_3$. The chloroform solution was extracted with 1% H_2SO_4 solution, the acidic extract neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was dried with $MgSO_4$ and evaporated. Hydrolysis of the cycloadduct (**4b**) was carried out the same way.

Thermolysis of Cycloadduct (4b). A solution of cycloadduct (**4b**) in $CHCl_3$ was heated for 15 min at 60°C, then evaporated to dryness, the residue boiled a few minutes with hexane, and the hot solution was filtered. Amidine (**6b**) precipitated from hexane as colorless crystals.

2,2,5,5-Tetramethyl-4-(N-phenylamino)-3-imidazolin-1-oxyl (7a). To a solution of 0.13 g of amidine (**6a**) in 5 ml of MeOH there was added 0.14 g of Triton B, 0.14 g of sodium tangstate, and 5 ml of 30% H_2O_2. The mixture was heated for 5 h at 50°C, then extracted with $CHCl_3$, dried with $MgSO_4$, evaporated, and chromatographed on silica gel ($CHCl_3$ as eluent). Oxidation of amidine (**6b**) was carried out analogously. For (**7a**) pK = 5.0 ± 0.1, for (**7b**) pK = 6.2 ± 0.1.

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1,2,2,3,5,5-Hexamethyl-4-(N-phenylimino)-imidazolidine (8) and 1,2,2,5,5-Pentamethyl-4-(N-phenyl-N-methylamino)-3-imidazoline (9). To a solution of 1 mmole of amidine (**6a**) in 5 ml of $CHCl_3$ there was added 18 mmoles of freshly distilled Me_2SO_4 and 0.2 g of Na_2CO_3. The mixture was left for 3 days and evaporated; then 5 ml of 5% Na_2CO_3 solution was added to the mixture. The mixture was extracted with $CHCl_3$, the extract evaporated, and the residue chromatographed on a preparative plate of neutral Al_2O_3, ether–hexane (1:1) as eluent. Compound (**8**) has an R_f of 0.7 and compound (**9**) of 0.5 {DC Alufolien, ether–hexane (1:1) as eluent}. Compounds (**8**) and (**9**) were oxidized similarly to (**6a**). For (**10**) pK = 5.5 ± 0.1; for (**11**) pK = 6.1 ± 0.1.

REFERENCES

1. D. Martin and W. Mucke, *Liebigs Ann.*, **682**, 90 (1965).
2. R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).
3. J. W. Lown, G. Dallas, and J. W. Maloney, *Can. J. Chem.*, **47**, 3557 (1969); J. W. Lown, *Rec. Chem. Prog.*, **32**, 51 (1971).
4. R. Huisgen, *Angew. Chem. Int. Edn.*, **2**, 565 (1963).
5. H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
6. D. St. C. Black and K. G. Watson, *Austr. J. Chem.*, **26**, 2473 (1973).
7. V. V. Martin, L. B. Volodarskii, M. A. Voinov, T. A. Berezina, and T. F. Lelyukh, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 8, 1875 (1988).
8. T. A. Berezina, V. V. Martin, L. B. Volodarskii, V. V. Khramtsov, and L. M. Vainer, *Bioorg. Khim.*, **16**, No. 2, 262 (1990).
9. W. Wolten and W. Woss, *The Chemistry of Amines*, J. Zabicky (ed.), Interscience, London–New York (1970), p. 383.
10. R. Huisgen, R. Grashey, M. Seidl, H. Knupfer, and R. Schmidt, *Liebigs Ann.*, **658**, 169 (1962).
11. N. R. Vanifatova, M. V. Evstiferov, V. V. Martin, O. M. Petrukhin, L. B. Volodarskii, and Yu. A. Zolotov, *Zh. Anal. Khim.*, **43**, No. 3, 435 (1988).
12. J. Goerdeler and R. Schimpf, *Chem. Ber.*, **102**, 1496 (1973).
13. V. V. Khramtsov and L. M. Vainer, *Usp. Khim.*, **40**, No. 9, 1440 (1988).
14. V. V. Khramtsov, L. M. Vainer, I. A. Grigor'ev, V. A. Reznikov, G. I. Shchukin, and L. B. Volodarkii, *Zh. Khim. Fiz.*, **4**, No. 5, 637 (1985).
15. V. D. Sholle, L. A. Krinitskaya, and É. G. Rozantsev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 1, 149 (1969).
16. I. A. Grigor'ev, G. I. Shchukin, V. V. Martin, and V. I. Mamtyuk, *Khim. Geterotsikl. Soedin.*, No. 2, 247 (1985).