Reactions of Nitrobenzothiazoles with Grignard Reagents. Orientation of Alkylation with Respect to the Nitro-group Position

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Nitrobenzothiazoles react with Grignard reagents giving alkyl-nitroso-compounds, except the 4-nitro-isomer which affords alkyl-nitro-derivatives. The observed highly regiospecific alkylation can be interpreted in terms of the stability of a cyclohexadiene-type intermediate. Detailed mass spectra of the products are reported.

NITROARENES are reported [1-4] to react with Grignard reagents giving *N*-alkylamines or *N*-alkylhydroxylamines by reductive alkylation. The only reported exception [5,6] is a polyaddition to the aromatic nucleus in polynitrobenzenes. We have reported [7] that alkylmagnesium halides react with 6-nitrobenzothiazole (1) to give an intermediate which is decomposed to a 7-alkyl-6-nitroso-derivative by aqueous hydrochloric acid (see Scheme). This represents the first example of reductive alkylation of a nitroarene leading to the corresponding nitroso-derivative which has undergone alkylation in the aromatic ring. In the present work we wished to ascertain whether this unusual reactivity was ascribable to the particular influence of the nitro-group in position 6 of benzothiazole, and to rationalize the high positional selectivity of alkylation, which cannot be accounted for by the different electronic effects of the S and C=N moieties on the reactivity of C-5 and C-7. We report the reactions of 4-, 5-, and 7-nitrobenzothiazoles [(12), (4), and (7)] with some Grignard reagents.

RESULTS AND DISCUSSION

The previously reported procedure [7] was modified. Reaction times were reduced to a few minutes. Moreover boron trifluoride–diethyl ether complex, instead of aqueous hydrochloric acid, was used to decompose the intermediate (see Scheme). Comparative experiments showed these changes to increase yields from 50—60 to 70—80%, at least in the reaction of 6-nitrobenzothiazole (1) with phenethylmagnesium halides.

The results in Table 1 show that 5- and 7-nitrobenzothiazoles behave similarly to the 6-nitro-isomer. However, whereas the 5-nitro-isomer (4) affords only 4-alkyl-5-nitroso-derivatives (6a and b), the 7-nitro-isomer (7) gives two nitroso-derivatives, *i.e.* 6-alkyl-7-nitroso- (9a and b) and 4-alkyl-7-nitroso-benzothiazole (11a and b), in comparable yields.

All the nitroso-compounds were obtained in the monomeric form; they were stable, both in the solid state and in solution in the usual aprotic solvents (benzene, n-hexane, chloroform, *etc.*) in the dark. The only exception was (9a), which decomposed rapidly in solution; † thus, the low yields in this case can be attributed to decomposition during work-up.

The reactivity of 4-nitrobenzothiazole (12) is anomalous: under the same experimental conditions it affords 4-nitro-7-alkyl derivatives (14a and b) in moderate yields. Traces of 4-butyl-7-nitrobenzothiazole (15a) were also isolated when compound (7) reacted with n-butylmagnesium bromide (see Table 1). At present the experimental data are not sufficient to explain these anomalies, but oxidation either of the intermediate (13) or of the

† The product was tentatively identified as the corresponding azoxy-derivative on the basis of mass spectral data.

[1] K. Nutsel in Houben-Weyl, 'Methoden der Organischen Chemie,' ed. E. Muller, 4th edn., Vol. XIII/2a, Thieme Verlag, Stuttgart, 1973, p. 47.

[2] P. Buck, *Angew. Chem.*, 1969, **81**, 136; *Angew. Chem. Internat. Edn.*, 1969, **8**, 120.

[3] M. S. Kharasch and O. Reinmuth, 'Grignard Reactions of Non-metallic Substances,' Prentice-Hall, New York, 1954.

[4] M. Gilman and R. McCracken, *J. Amer. Chem. Soc.*, 1953, **75**, 6041.

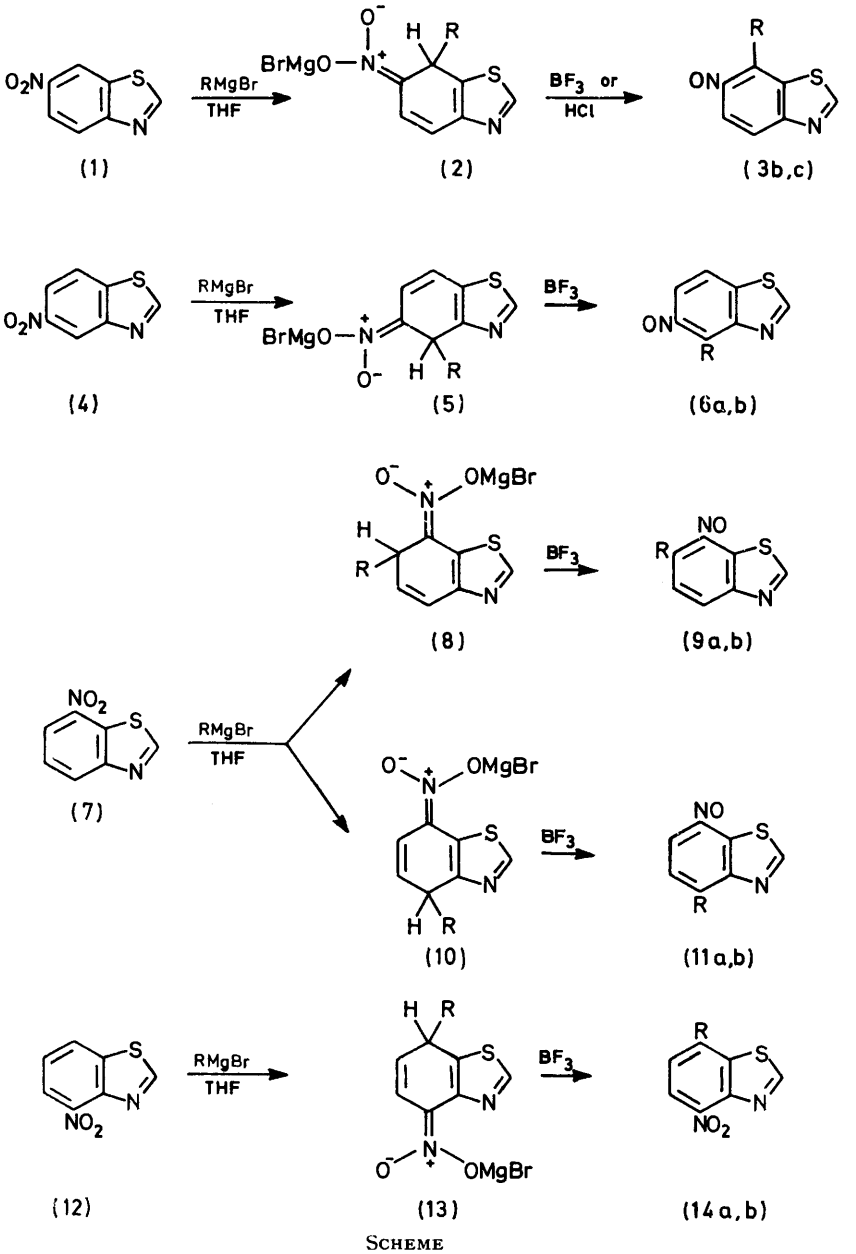
[5] T. Severin and M. Adam, *Chem. Ber.*, 1964, **97**, 186.

[6] T. Severin and M. Adam, *Chem. Ber.*, 1963, **96**, 448.

[7] G. Bartoli and G. Rosini, *Synthesis*, 1976, **4**, 270.

corresponding nitroso-derivative during the addition of boron trifluoride and water could account for our findings.

Orientation of the Entering Alkyl Group.—In every case a high positional selectivity of alkylation is observed (see Scheme). In view of the well known mode of reaction of Grignard reagents and the nature of the products, we suggest that the first step of the reaction is an addition of RMgX to give the adducts (2), (5), (8), (10), and (13). In the case of 5- and 6-nitrobenzothiazoles two *ortho*-positions (4 and 6, and 5 and 7, respectively) are available for nucleophilic attack by the alkyl group, but only attack at the 4- and 7-positions, respectively, leads to an adduct in which the aromatic character of the thiazole ring is preserved [(2) or (5)]. The possibility that the orientation is affected by the relative stabilities of the intermediate adducts is strengthened by the fact that substitution at the *ortho*- and *para*-positions is competitive in 7-nitrobenzothiazole. The 4-nitro-isomer suffers only *para*-substitution.



SCHEME

Characterization of Products.—The products were identified as nitro- or nitroso-derivatives [8] by the usual methods of analysis (see Table 2); their exact structures were deduced from ^{1}H n.m.r. and mass spectra.

Structures (3b and c) and (6a and b) were assigned on the basis of ^{1}H n.m.r. coupling constants (7.5—8.5 Hz),

[8] J. H. Boyer, 'The Chemistry of Nitroso and Nitro Groups,' Part 1, ed. H. Feuer, Interscience, New York, 1969.

TABLE 1

Reactions of nitrobenzothiazoles with RMgX

Substrate	R	Products	M.p. (°C) †	Yield (%)	Column eluant ‡
(1)	$PhCH_2{\cdot}CH_2$	(3b)	80—82	70—80	CH–EA (4 : 1 v/v)
(4)	Bu^n	(6a)	90—92	65—75	CH–EA (4 : 1 v/v)
	$PhCH_2{\cdot}CH_2$	(6b)	*ca.* 80 §	70—80	Benzene
(7)	Bu^n	(9a)	*ca.* 45 §	10—15	CH–EA (4 : 1 v/v)
		(11a)	*ca.* 50 §	30—35	
		(15a)	68—69	Trace	
	$PhCH_2{\cdot}CH_2$	(9b)	87—88	35—40	CH–EA (9 : 1 v/v)
		(11b)	84—86	35—40	
(12)	Bu^n	(14a)	40—41	40—50	CH–EA (9 : 1 v/v)
	$PhCH_2{\cdot}CH_2$	(14b)	144—146	65—70	CH–EA (7 : 3 v/v)

† From n-hexane. ‡ CH = cyclohexane, EA = ethyl acetate. § Decomp.

TABLE 2

Analytical and spectroscopic data of nitroso- and nitro-alkylbenzothiazoles

Compound	Analysis (%) * C; H; N	$\nu_{max.}$(KBr)/cm^{-1} NO	$\nu_{max.}$(KBr)/cm^{-1} NO_2	$\lambda_{max.}$($CHCl_3$)/nm (ε)	τ ($CDCl_3$)
(6a)	60.0; 5.5; 12.7 59.55; 5.45; 12.8	1 450		760 (44)	0.9 (1 H, s, H-2), 2.45 (1 H, d, $J_{6,7}$ Hz, H-6), 3.7 (1 H, d, H-7), 5.4—5.8 and 7.7—9.3 (2 H and 7 H, m, Bu)
(6b)	67.15; 4.5; 10.45 68.85; 4.3; 10.75	1 450		760 (43)	1.1 (1 H, s, H-2), 2.60 (1 H, d, $J_{6,7}$ 8.5 Hz, H-6), 3.0 (s H, m, CPh), 3.8 (1 H, d, H-7), 5.2—5.5 and 6.6—6.9 (2 H and 2 H, m, $CH_2{\cdot}CH_2$)
(9a)	60.0; 5.5; 12.7 59.75; 5.15; 12.95	1 460		725	1.31 (1 H, s, H-2), 2.0 (1 H, d, $J_{4,5}$ 8.5 Hz, H-4), 2.65 (1 H, d, H-5), 5.9—6.3 and 7.9—9.3 (2 H and 7 H, m, Bu)
(9b)	67.15; 4.5; 10.45 67.3; 4.65; 10.5	1 420		750 (39)	0.95 (1 H, s, H-2), 1.65 (1 H, $J_{4,5}$ 8.5 Hz, H-4), 2.40 (1 H, d, H-5), 2.85 (5 H, m, Ph), 5.4—5.8 and 6.4—6.8 (2 H and 2 H, m, $CH_2{\cdot}CH_2$)
(11a)	60.0; 5.5; 12.7 59.8; 5.35; 12.85	1 460		700 (45)	0.8 (1 H, d, $J_{5,6}$ Hz, H-6), 1.20 (1 H, s, H-2), 2.4 (1 H, d, H-5), 6.6—7.0 and 7.9—9.2 (2 H and 7 H, m, Bu)
(11b)	67.15; 4.5; 10.45 66.9; 4.65; 10.65	1 400		715 (43)	0.65 (1 H, d, $J_{5,6}$ 8.0 Hz, H-6), 0.9 (1 H, s, H-2), 2.35 (1 H, d, H-5), 2.8 (5 H, m, Ph), 6.2—6.5 and 6.7—7.0 (2 H and 2 H, m, $CH_2{\cdot}CH_2$)
(14a)	55.9; 5.1; 11.85 56.2; 4.9; 12.0		1 510 1 340		0.85 (1 H, s, H-2), 1.9 (1 H, d, $J_{5,6}$ 8.0 Hz, H-5), 2.75 (1 H, d, H-6), 6.8—7.2 and 7.9—9.2 (2 H and 7 H, m, Bu)
(14b)	63.35; 4.25; 9.85 63.55; 4.1; 10.1		1 510 1 340		0.7 (1 H, s, H-2), 1.8 (1 H, d, $J_{5,6}$ 8.5 Hz, H-5), 2.5—3.0 (5 H, m, Ph), 2.7 (1 H, d, H-6), 6.4—7.1 (4 H, m, $CH_2{\cdot}CH_2$)
(15a)	63.35; 4.25; 9.85 66.6; 4.3; 10.1		1 470 1 330		

* Upper line required; lower line found.

TABLE 3

Mass spectra of *ortho*-nitroso-alkyl and *para*-nitroso- or -nitro-alkylbenzothiazoles; relative intensities of major peaks

Compound:	(3c)	(6a)	(6b)	(9a)	(9b)	(16b)	(16c)	(11a)	(11b)	(14a)	(14b)	(15a)
Mol. wt.:	254	220	268	220	268	282	268	220	268	236	284	236
Ion												
M	30	31	4.5	47	8	14	67	15	55	100	29	22
M − H	33		5.5				65	59				
M − O								13	1.5	3.5		100
M − OH	100	100	100	81	100	100	100					
M − NO								18	5			33
M − C_3H_7		95		100				100		13		
M − NO_2										7	5	
M − C_4H_9		66		43								38
M − C_6H_5	18						23					
M − C_7H_7	10		29		8	6	10					
C_7H_7	7.5	7	74	7	46	29	8		100	5	100	26
C_6H_5	12	16	9	22	7	5	15	7	4.5	9	3.5	62
C_5H_5	6	7	21	6.5	14	10	6	3.5	11	4	12	23

which were characteristic of aromatic *ortho*-protons. These assignments were confirmed by the mass spectra; the base peak is consistent with loss of OH from the molecular ion, showing the same '*ortho*-effect' as in *o*-alkylnitrobenzenes,[9] *o*-alkyl-diaryl sulphines,[10] and *o*-alkylaryl arylsulphonyl sulphines.[11]

Mass spectrometry was very useful in determining the structures of the alkyl-nitroso-compounds arising from the reaction of the 7-nitro-compound (7); indeed ^1H

[9] S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, 1966, **88**, 4974.

[10] A. Tangerman, L. Thijs, A. P. Anker, and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 458.

[11] A. Tangerman and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 461.

n.m.r. spectra of the products (9) and (11) showed the coupling constants of the two aromatic protons for the structures to be distinguished. However the mass spectrum of (9) shows the same '*ortho*-effect' as all *o*-alkyl-nitroso-compounds; in contrast, loss of NO is observed with the isomer (11), as expected for a *meta*- or *para*-derivative (see Table 3). On the basis of similar spectroscopic behaviour, structures (14a and b) were also assigned. Mass spectroscopy coupled with ^{1}H n.m.r. analysis thus appears to represent a useful tool for distinguishing an *o*-alkyl-nitroso-derivative from its positional isomers.

EXPERIMENTAL

I.r., u.v., ^{1}H n.m.r. and mass spectra were recorded with a Perkin-Elmer 402, a Perkin-Elmer 257, a JEOL 60 MHz (tetramethylsilane as internal standard), and a JEOL MS-D 100 instrument, respectively.

Nitrobenzothiazoles were prepared by nitration of benzothiazole.[12]

Tetrahydrofuran (thf) was purified by distillation over lithium aluminum hydride and then stored over sodium wire under nitrogen. n-Butyl bromide, phenylethyl bromide, and boron trifluoride–diethyl ether complex are commercial products (Schuchardt).

Synthesis of Alkyl-nitroso- or Alkyl-nitro-benzothiazoles. General Procedure.—A solution of alkylmagnesium halide (0.02 mol) in thf (50 ml) was added dropwise at room temperature under nitrogen to the nitrobenzothiazole derivative (0.01 mol) dissolved in thf (20—50 ml). A red colour immediately appeared. The mixture was stirred for a few min and then boron trifluoride in thf was added until the resulting solution appeared yellow (in some cases a pale yellow precipitate was obtained). After addition of water, the mixture was extracted with methylene chloride; the organic layer was washed several times with water, dried ($MgSO_4$), and evaporated at reduced pressure. The crude product was chromatographed on a silica gel column.

In the reaction of the 7-nitro-compound (7) with n-butylmagnesium bromide all the operations were performed in the dark so as to avoid decomposition of the product (9a).

Reactions, products, and physical data are reported in Table 1. Elemental analyses and i.r., u.v., and ^{1}H n.m.r. data of new alkyl-nitroso- and alkyl-nitro-benzothiazoles are collected in Table 2; the ^{1}H n.m.r. spectrum of 4-butyl-7-nitrobenzothiazole (15a) could not be recorded owing to lack of material. The ε value for compound (9a) is not reported because of its fast decomposition in solution. Mass spectra of compounds (6a and b), (9a and b), (11a and b), (14a and b), and (15a) are collected in Table 3 with those of 7-benzyl-6-nitrosobenzothiazole (3c), 2-methyl-6-nitroso-7-phenethyl- and 7-benzyl-2-methyl-6-nitroso-benzothiazole (16b and c), prepared as reported previously.[7]

[6/1518 *Received*, 3*rd August*, 1976]

[12] E. R. Ward and W. H. Poesche, *J. Chem. Soc.*, 1961, 2825.