RESEARCH ON 2,1,3-THIA- AND SELENADIAZOLE

XLVII. Nitration of Benz-2,1,3-Thiadiazole and its Derivatives*

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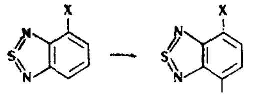
Benz-2,1,3-thiadiazole and its derivatives are readily nitrated with sodium nitrate in concentrated sulfuric acid, to primarily give high yields of mono- and dinitro derivatives. Some of these are reduced by sodium dithionite to the corresponding amino derivatives, and the same reducing agent is also used to reduce some o-nitroanilines to the corresponding o-diamines.

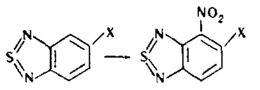
It was previously shown [2, 3] that nitration of halogen or nitro derivatives of benz-2,1,3-thiadiazole (I) by sodium nitrate and concentrated sulfuric acid, gives high yields of the corresponding dinitro derivatives. Thus it is possible to introduce a nitro group at the 5 (6) position** which is less prone to electrophilic substitution.

For preparative purposes, particularly when working with small amounts (0.01–0.001 mole), the method given is superior to nitration with fuming nitric acid. Further investigation is of interest to ascertain the possibility of preparing some o- and p- dinitro derivatives of I of importance for a number of direct syntheses.

Nitration of I with an equimolecular amount of sodium nitrate (5 minutes, 95°–100°) gives a 96% yield of the 4-nitro derivative of I, II. Under the same conditions, 4-methylbenz-2,1,3-thiadiazole (III) gives a high yield of a mixture of 4-methyl-5-nitro- (IV) and 4-methyl-7-nitrobenz-2,1,3-thiadiazole (V), in the ratios 36% and 64% respectively.


VI, VIII VII, IX

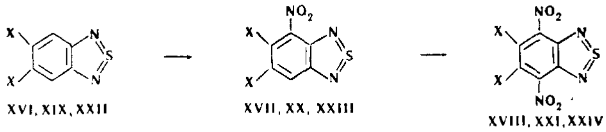
VI, VII X = Cl; VIII, IX X = Br


X, XII, XIV XI, XIII, XV

X, XI X = CH$_3$; XII, XIII X = Cl; XIV, XV X = Br

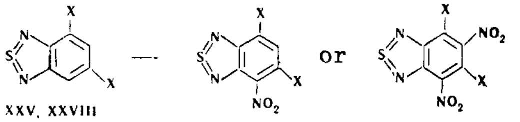
Similarly, nitration of 4-chloro-(VI), 4-bromo-(VIII), 5-methyl-(X), 5-chloro-(XII), and 5-bromobenz-2,1,3-thiadiazole (XIV) gives 98% yields of, respectively 4-chloro-7-nitro-(VII), 4-bromo-7-nitro-(IX), 5-methyl-4-nitro-(XI), 5-chloro-3-nitro-(XIII), and 5-bromo-4-nitrobenz-2,1,3-thiadiazole (XV). Equimolecular amounts of 5,6-dimethylbenz-2,1,3-thiadiazole (XVI) and sodium nitrate give a high yield of mixed nitro derivatives, from which are isolated 60% 4-nitro-(XVII) and 8% 4,7-dinitro-5,6-dimethylbenz-2,1,3-thiadiazole (XVIII); the latter is obtained in 96% yield when the reaction is run with 2.4 mole sodium nitrate.

With an equimolecular quantity of sodium nitrate, 5,6-dichloro(dibromo)benz-2,1,3-thiadiazole (XIX, XXII) gave 5,6-dichloro(dibromo)-4-nitrobenz-2,1,3-thiadiazole (XX, XXIII); while with excess sodium nitrate the corresponding dinitro derivatives XXI and XXIV are obtained.


XVI, XIX, XXII XVII, XX, XXIII XVIII, XXI, XXIV

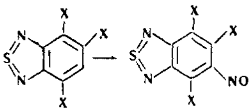
XVI, XVII, XVIII X = CH$_3$; XIX, XX, XXI X = Cl; XXII, XXIII, XXIV X = Br

Reaction of equimolecular quantities of 4,6-dichloro(dibromo)benz-2,1,3-thiadiazole (XXV, XXVIII) gives 4,6-dichloro(dibromo-7-nitrobenz-2,1,3-thiadiazole (XXVI, XXIX); with 4 molecules of sodium nitrate the latter gives 4,6-dichloro(dibromo)-5,7-dinitrobenz-2,1,3-thiadiazole (XXVII, XXX).


XXV, XXVIII XXVI, XXIX XXVII, XXX

XXV–XXVII X = Cl; XXVIII–XXX X = Br

Nitration of 4,5,7-trichloro(tribromo)benz-2,1,3-thiadiazole (XXXI, XXXIII) with 2 molecules of sodium nitrate gives 4,5,7-trichloro(tribromo)-6-nitrobenz-2,1,3-thiadiazole (XXXII, XXXIV)*.


XXXI, XXXIII XXXII, XXXIV

XXXI, XXXII X = Cl, XXXIII, XXXIV X = Br

Equimolecular amounts of 5-methyl-4-chloro(bromo)benz-2,1,3-thiadiazole (XXXV, XXXIX) and sodium nitrate give an 83% yield of 5-methyl-4-chloro(bromo)-7-nitrobenz-2,1,3-thiadiazole (XXXVI, XL). Treatment of XXXV with 4 molecules of sodium nitrate gives a 61% yield of XXXVI, and this is obviously due to the oxidizing action of the excess of nitric acid. The structures of XXXVI and XL are proved by their reduction to 5-methyl-4-chloro(bromo)-7-aminobenz-2,1,3-thiadiazole (XXXVII, XLI), and conversion of the latter by the Sandmeyer reaction to 5-methyl-4,7-di-

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*For Part XLVI see [1].

**The same thing is found in the nitration of halogeno- and methylnitrobenz-2,1,3-selenadiazoles [15–16].

*Nitration of XXXIII also gives a substance of undetermined structure, mp 216°–218° C.

Table 1

Reduction of o-Nitroanilines with Sodium Dithionite

o-Nitroaniline (g)	Solvent (amount in ml)	Na dithionate, g	Yield, g (%)	Mp, °C (solvent for crystallizing)	References
4-Methyl-2-nitroaniline (3)	Water (150)	18	1.2 (80)	90 (petrol ether)	7
4-Bromo-2-nitroaniline (2,17)	Water (30)	10	1.7 (91)	63 (water)	8
4-Chloro-2-nitroaniline (20)*	Water + EtOH + 25% aqueous NaOH solution (200+100+100)	60	14.8 (80)	69—71 (benzene + +petrol ether 1:1)	9
4, 5-Dibromo-2-nitroaniline (3)**	Water (50)	8	2.36 (80)	83 (water)	8
4, 6-Dichloro-2-nitroaniline (35)	Water + EtOH (3000 +200)	300	25.5 (85)	61 (EtOH)	10, 11

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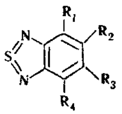
*Diluted with an equal volume of water before extracting with dichloroethane.

**The solid which came down after cooling was filtered off and washed with water.

Table 2



Compound	R_1	R_2	R_3	R_4	Mp, ° C (solvent for crystallizing)*	Formula	Found, %			Calculated, %			Yield, %
							Cl or Br	N	S	Cl or Br	N	S	
XX	NO_2	Cl	Cl	H	95—97 (et)	$C_6HCl_2N_3O_2S$	28.40	16.83	12.56	28.40	16.80	12.80	86.5
XXI	NO_2	Cl	Cl	NO_2	200 (70% et)	$C_6Cl_2N_4O_4S$	24.04	19.08	10.60	24.07	18.98	10.85	77.4
XXIII	NO_2	Br	Br	H	130—132 (et)	$C_6HBr_2N_3O_2S$			9.38			9.41	85.0
XXIV	NO_2	Br	Br	NO_2	233—235 (et)	$C_6Br_2N_4O_4S$	42.03	15.05	8.37	41.67	14.58	8.33	77.0
XXVI	NO_2	Cl	H	Cl	127—128 (et)								72.0
XXVII	NO_2	Cl	NO_2	Cl	128—129 (et)	$C_6Cl_2N_4O_4S$	23.93	19.80	10.81	24.07	18.98	10.85	59.3
XXIX	NO_2	Br	H	Br	155—156 (mc: w, 1:1)								90.0
XXX	NO_2	Br	NO_2	Br	141—143 (et)	$C_6Br_2N_4O_4S$			8.13			8.33	83.3
XXXII	Cl	Cl	NO_2	Cl	129—130 (mc: w, 1:1)	$C_6Cl_3N_3O_2S$	38.45	15.12	11.31	37.43	14.76	11.25	70.0
XXXIV	Br	Br	NO_2	Br	153—155 (mc: w, 4:1)**	$C_6Br_3N_3O_2S$	57.60	10.52	7.63	57.41	10.05	7.66	50.0
XXXVI	Cl	CH_3	H	NO_2	175—176 (mc)	$C_7H_4ClN_3O_2S$	15.23	18.82	13.73	15.47	18.30	13.94	82.6
XL	Br	CH_3	H	NO_2	188—190 (d)	$C_7H_4BrN_3O_2S$	29.52	15.80	11.29	29.19	15.33	11.68	80.0
XLV	CH_3	NO_2	NO_2	Cl	163—165 (et)	$C_7H_3ClN_4O_4S$	13.10	20.89	11.51	12.90	20.40	11.66	30.0
XLVI	CH_3	NO_2	NO_2	Br	183—185 (et)	$C_7H_3BrN_4O_4S$	25.82	17.65	9.98	25.08	17.56	10.03	32.0

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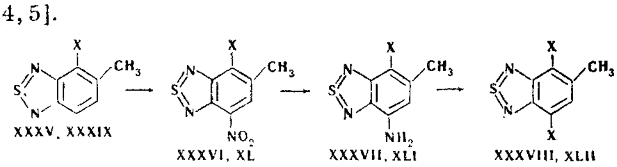
*et = EtOH; mc = methylcellosolve; w = water; d = dioxane.

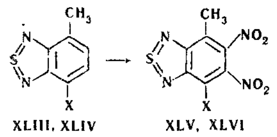
**Recrystallization of the nitration product from methylcellosolve, and then from dioxane, gave yellow crystals of undetermined structure mp 216°–218° C, which did not give a color with ethanolic alkali. Found: N 7.40; 7.50; S 7.19; 7.26%. XXXIV was precipitated on diluting the filtrate after crystallizing.

chloro(dibromo)benz-2, 1, 3-thiadiazole (**XXXVIII, XLII**) [4, 5].



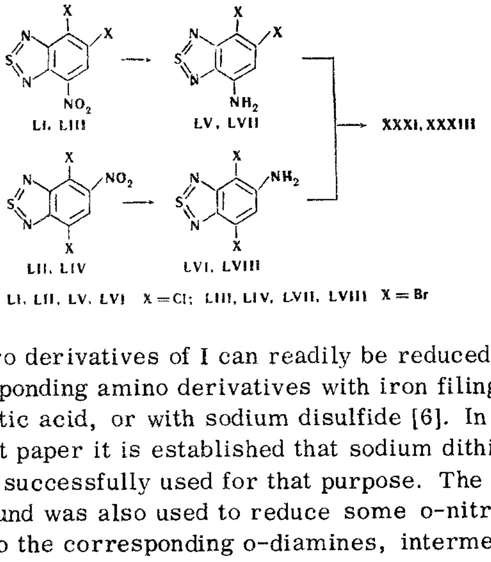
XXXV–XXXVIII X Cl; XXXIX–XLII X = Br

Treatment of 4-methyl-7-chloro-(**XLIII**) or 4-methyl-7-bromobenz-2, 1, 3-thiadiazole (**XLIV**) with 4 molecules of sodium nitrate gives a 30% yield of 4-methyl-7-chloro-(**XLV**) or 4-methyl-7-bromo-5,6-dinitrobenz-2, 1, 3-thiadiazole (XLVI) respectively.



XLIII, XLV X = Cl; XLIV, XLVI X = Br

Previously [2] it was postulated that nitration of 4, 5-dichloro-(**XLVII**), 4, 7-dichloro-(**XLVIII**), 4, 5-dibromo-(**XLIX**), and 4, 7-dibromobenz-2, 1, 3-thiadiazole (L) gives, respectively 4, 5-dichloro-7-nitro-(**LII**), 4,5-dibromo-7-nitro-(**LIII**), and 4,7-dibromo-5-nitrobenz-2, 1, 3-thiadiazole (LIV). In the present paper the structures of nitro derivatives **LI–LIV** are proved by reducing them to amines LV–LVIII respectively, and conversion by the Sandmeyer reaction, LV and LVI to 4, 5, 7-trichlorobenz-2, 1, 3-thiadiazole (XXXIII).



LI, LII, LV, LVI X = Cl; LIII, LIV, LVII, LVIII X = Br

Nitro derivatives of I can readily be reduced to the corresponding amino derivatives with iron filings and 2% acetic acid, or with sodium disulfide [6]. In the present paper it is established that sodium dithionite can be successfully used for that purpose. The same compound was also used to reduce some o-nitroanilines to the corresponding o-diamines, intermediates for syntheses of the starting benz-2, 1, 3-thiadiazoles.

EXPERIMENTAL

Synthesis of the starting o-diamines. Portions of the sodium dithionite were added to a stirred aqueous solution (or solution in another solvent) of the o-nitroaniline, the mixture heated to boiling, cooled, and extracted with dichloroethane. Removal of the solvent by distillation gave the diamines, which were purified by recrystallizing from the appropriate solvents (Table 1).

4, 5-Dichloro- and 4, 5-dibromo-1, 2-diaminobenzenes. These were prepared from o-dichloro(dibromo)benzene by nitrating and then reducing with Sn in conc HCl, the 4, 5-dichloro(dibromo)-1, 2-dinitrobenzenes formed [12].

5, 6-Dibromobenz-2, 1, 3-thiadiazole (XXII). 5 ml $SOCl_2$ was added gradually to a solution of 1.0 g (4 mM) 4, 5-dibromo-1, 2-diaminobenzene in 5 ml pyridine, at such a rate that the temperature did not exceed 75°–80° C. When addition was complete, the mixture was heated for 2–3 min on a steam bath, cooled, diluted with an equal volume of water, the solid filtered off, dried, and purified by running a toluene solution through activated alumina. Evaporation of the eluate to dryness gave a colorless powder mp 130°–132° C. Found: N 9.68; 9.77; S 10.38; 10.49%, calculated for $C_6H_2Br_2N_2S$: N 9.52; S 10.88%.

Benz-2, 1, 3-thiadiazoles I, **X**, **XII**, **XIV**, **XIX**, **XXV**, **XXVIII** were obtained similarly, yields 85–95%.

Nitration with sodium nitrate-concentrated sulfuric acid. The sodium nitrate* was added in portions to a stirred solution of the substituted benz-2, 1, 3-thiadiazole in 5–10 times the amount of sulfuric acid, at 95°–100° C. After heating for 5 min at 100° C, the products were cooled, poured onto ice, the solid filtered off, washed with water, dried, and recrystallized from the appropriate solvent. The nitro derivative formed crystals, which were slightly soluble in water and gave a color, mainly red or violet, with ethanolic alkali.

Table 2 gives properties of compounds prepared for the first time. The mps of the known compounds correspond to those given in the literature [2–4, 6, 14].

4, 5, 7-Trichlorobenz-2, 1, 3-thiadiazole (XXXI). 40 ml Hot water was gradually added to a stirred mixture of 2 g (0.008 mole) 4, 5-dichloro-7-nitrobenz-2, 1, 3-thiadiazole (**LI**) and 5 g (0.029 mole) Na dithionite in 10 ml boiling EtOH, the whole cooled, the yellow precipitate filtered off, washed with water, and dried. Yield 1.23 g (70%) 4, 5-dichloro-7-aminobenz-2, 1, 3-thiadiazole (**LV**), mp 126° C (ex water).

0.5 g (2.3 mM) LV was dissolved in 1.5 ml conc H_2SO_4, the solution stirred, and a solution of 0.15 g (2.2 mole) $NaNO_2$ in 1.5 ml conc H_2SO_4 added. After stirring for 10 min, the mixture was poured into a mixture of 6 g ice and 5 ml conc HCl, and a solution of 2.5 g CuCl in 12.5 ml conc HCl added. The whole was brought to a boil and steam distilled, to give 0.11 g (20%) colorless crystals, mp 122°–124° C, undepressed mixed mp with known **XXXI** [5, 13]. The latter was prepared similarly to 4, 7-dichloro-5-nitrobenz-2, 1, 3-thiadiazole (**LII**), via 4, 7-dichloro-5-aminobenz-2, 1, 3-thiadiazole (LVI).

4, 5, 7-Tribromobenz-2, 1, 3-thiadiazole (XXXIII). Similarly to the above, 0.8g (3 mM) 4, 5-dibromo-7-nitrobenz-2, 1, 3-thiadiazole (**LIII**), 2.5 g (15 mM) Na dithionite, 2.5 ml EtOH, and 20 ml water gave 0.45 g (55%) 4, 5-dibromo-7-aminobenz-2, 1, 3-thiadiazole (**LVII**); dark crystals mp 138°–143° C (ex water). Also similarly to the above, 0.2 g (1.4 mM) $NaNO_2$ in 0.7 ml conc H_2SO_4, a mixture of 3 g ice and 2.5 ml hydrobromic acid, 1 g CuBr in 5 ml hydrobromic acid gave 0.05 g (21%) **XXXIII**, colorless crystals, mp 152°–154° C, undepressed mixed mp with the authentic compound prepared as described in [13]. **XXXIII**, was prepared similarly from 4, 7-dibromo-5-nitrobenz-2, 1, 3-thiadiazole (**LIV**) via 4, 7-dibromo-5-aminobenz-2, 1, 3-thiadiazole (**LVIII**).

4-Chloro-5-methyl-7-aminobenz-2, 1, 3-thiadiazole (XXXVII). A solution of 0.1 g (1.4 mM) $NaNO_2$ in 1 ml conc H_2SO_4 was added with stirring to a solution of 0.2 g (1 mM) **XXXVII** in 1 ml conc H_2SO_4. The whole was stirred for 10 min, then poured into a cold solution of 1 g CuCl in 5 ml conc HCl, the mixture heated to boiling, and the reaction product steam distilled off, giving colorless crystals mp 139°–140° C, undepressed mixed mp with known compound prepared as described in [4, 5].

4, 7-Dibromo-5-methylbenz-2, 1, 3-thiadiazole (XLII). Similarly to the above, 0.8 g (3 mM) 4-bromo-5-methyl-7-nitrobenz-2, 1, 3-thiadiazole (**XL**), 2.5 g (15 mM) Na dithionite, 2.5 ml EtOH, and 20 ml water gave 0.4 g 4-bromo-5-methyl-7-aminobenz-2, 1, 3-thiadiazole (**XLI**). Also similarly to the above, 0.15 g (0.6 mM) **XLI** in 0.7 ml conc H_2SO_4, 0.1 g (1.4 mM) $NaNO_2$ in 0.7 ml conc H_2SO_4, a mixture of 3 g ice and 2.5 ml hydrobromic acid, 1 g CuBr in 5 ml hydrobromic acid, gave 0.03 g **XLII**; colorless crystals, mp 145°–146° C,

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*For the mole ratios of the reactants, see the general part.

undepressed mixed mp with the same compound prepared as described in [4, 5].

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