Nitrofuranyl Heterocycles. XIII (1). *N*-Methyl-3-methylthio-5-(5-nitro-2-furanyl)-1*H*-1,2,4-triazoles.

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A continuing search for new nitrofurans which might possess useful antimicrobial activity led to the synthesis of several 3-mercapto-5-(5-nitro-2-furanyl)-1*H*-1,2,4-triazoles and their methylated derivatives. This paper describes the preparation of these compounds together with proof of structure of the *N*-methylated products.

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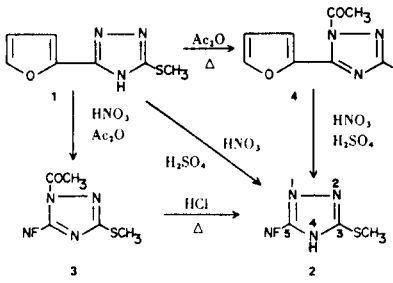
The synthesis of 3-methylthio-5-(5-nitro-2-furanyl)-4*H*-1,2,4-triazole (**2**) *via* ethyl 5-nitro-2-furancarboximidate has been reported (3). We wish to describe the synthesis of **2** from the corresponding furanyltriazole **1** by three different reaction sequences utilizing two nitration techniques (see Scheme I) and the preparation of several derivatives. In the nitration of **1**, prepared by the methylation of 5-(2-furanyl)-3-mercapto-4*H*-1,2,4-triazole (4), method A made use of a mixture of concentrated nitric and sulfuric acids (mixed acid technique) at 0° to yield **2**. When **1** was nitrated with concentrated nitric acid in acetic anhydride at 0° (method B), the *N*-acetyl compound **3** was isolated and readily hydrolyzed with concentrated hydrochloric acid to **2**. In method C, **1** was acetylated with acetic anhydride to give the *N*-acetylfuranyl compound **4**. When **4** was nitrated in mixed acid, concurrent hydrolysis occurred to yield **2**. Method A was the best procedure.

The introduction of the nitro group into the 5-position of the furan ring is readily confirmed by an inspection of the nmr spectra of **2** and **3** (see Table I). In each case, the furan protons are observed as two doublets with coupling constants of 4 cps. These values are consistent with 2,5-disubstituted furans (5). The same nmr data are observed in compounds **5**, **6**, **7**, **10**, and **12**.

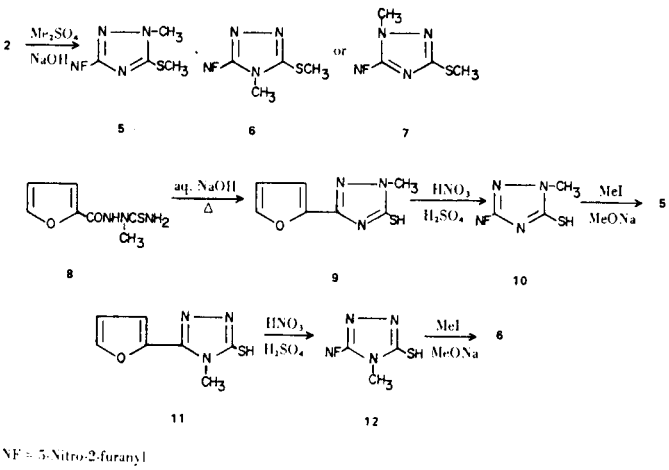
The alkylation of **2** was accomplished with dimethyl sulfate to give two methylated products separated by fractional crystallization. Since there are three possible monomethyl isomers, **5**, **6**, and **7**, it became necessary to synthesize at least two of the three possibilities by unequivocal methods (see Scheme II). The base-catalyzed cyclization of 1-furanylcarbonyl-2-methyl-3-thiosemicarbazide (**8**) gave 5-(2-furanyl)-3-mercapto-2-methyl-1*H*-1,2,4-triazole (**9**) which was nitrated in mixed acid to yield 3-mercapto-2-methyl-5-(5-nitro-2-furanyl)-1*H*-1,2,4-triazole (**10**). When **10** was methylated to give the 3-methyl-mercapto derivative, the resultant compound was found to be identical to **5**.

Scheme I



NF = 5-Nitro-2-furanyl

Scheme II



NF = 5-Nitro-2-furanyl

Table I

Nmr Spectral Data of the Triazoles

Compound No.	SCH_3	NCH_3	Furan Protons
1	2.65	---	6.68 (m, 1H), 7.03 (d, 1H), 7.68 (m, 1H)
2	2.70	---	7.23, 7.77 (2d, 2H, J = 4)
3	2.70	2.73 ($COCH_3$)	7.45, 7.85 (2d, 2H, J = 4)
4	2.70 (s, 6H; includes the $COCH_3$ protons)	---	6.56 (m, 1H), 6.71 (d, 1H), 7.61 (m, 1H)
5	2.75	3.82	7.03, 7.36 (2d, 2H, J = 4)
6	2.69	3.77	7.38, 7.84 (2d, 2H, J = 4)
7	2.58	4.11	7.58, 7.92 (2d, 2H, J = 4)
9	----	3.54	6.40 (m, 1H), 6.86 (m, 1H), 7.56 (m, 1H)
10	----	4.00	7.30, 7.81 (2d, 2H, J = 4)
11	----	3.75	6.83 (m, 1H), 7.28 (d, 1H), 8.02 (m, 1H)
12	----	3.75	7.53, 7.97 (2d, 2H, J = 4)

The alkylation of 5-(2-furanyl)-3-mercapto-4-methyl-4*H*-1,2,4-triazole (**11**), prepared by an unequivocal method (6), followed by nitration by mixed acid yielded **6**. This compound has been prepared from **11** by nitration with mixed acid followed by alkylation (6). There appears to be no advantage of one method over the other. Compound **6** was not identical to the other product obtained by the methylation of **2**. Therefore, the structure of the other isomer must be **7**. The physical constants for all of the triazoles are given in Table II.

The position of the acetyl group in **3** and **4** has been assigned arbitrarily. It is interesting to note recent studies of the alkylation of 3-methylthio-5-(2-pyridinyl)-1,2,4-triazole by alkaline conditions and with diazomethane show that position 1 is the most favored followed by position 2 and then 4 (7).

EXPERIMENTAL (8)

5-(2-Furanyl)-3-methylthio-4*H*-1,2,4-triazole (**1**).

5-(2-Furanyl)-3-mercapto-4*H*-1,2,4-triazole (4) (117 g., 0.7 mole) was placed in a flask together with methanol (700 ml.), methyl iodide (35 ml.), and sodium methoxide (37.8 g., 0.7 mole). The mixture was refluxed for one hour and an additional amount of methyl iodide (35 ml.) added. The mixture was refluxed for 5 hours then the solvent was removed under reduced pressure. The residue was recrystallized from nitromethane to yield 57.1 g. of **1** m.p. 140-142°.

3-Methylthio-5-(5-nitro-2-furanyl)-4*H*-1,2,4-triazole (**2**).

Method A.

Into a 1000 ml., 3-necked flask fitted with a stirrer, thermometer, and addition funnel was placed concentrated sulfuric acid (450 ml.). Powdered **1** (150 g., 0.83 mole) was added at 0-15° with stirring. When most of the solid had dissolved, a solution of concentrated nitric acid (55 ml.) in concentrated sulfuric acid (220 ml.) was added dropwise at 0-15° with stirring. After the addition was completed, stirring was continued for 15 minutes at 0-10°. The solution was poured, with stirring, over 3000 ml. of cracked ice. A brown solid precipitated when the mixture was diluted to *ca.* 8000 ml. with water. The solid was collected by filtration, washed thoroughly with water, and dried at 100° to yield 140 g. of **2.**

Method B.

Crude **3** (93.8 g., 0.35 mole) was suspended in concentrated hydrochloric acid (290 ml.) and the stirred mixture was heated at reflux for 10 minutes. A solution was obtained after 2 or 3 minutes of refluxing and then the product precipitated. After cooling to room temperature in an ice bath, the mixture was diluted with water (600 ml.) and cooled for 1.5 hours. The tan solid was collected by filtration, washed with water, and dried at 100° to yield 33 g. of **2.**

Method C.

To a stirred solution of **4** (11 g., 0.05 mole) in concentrated sulfuric acid (50 ml.) was added dropwise at 0-10° a solution of concentrated nitric acid (4 ml.) in concentrated sulfuric acid (20 ml.). When the addition was completed, the solution was poured over ice with stirring to give a brown solid. The product was collected by filtration, washed thoroughly with water, and dried at 100° to yield 5.7 g. of **2.**

1-Acetyl-3-methylthio-5-(5-nitro-2-furanyl)-1*H*-1,2,4-triazole (**3**).

Acetic anhydride (905 ml.) was placed in a 2000 ml., 3-necked flask fitted with a stirrer, addition funnel, and thermometer. Concentrated nitric acid (65 ml.) was added dropwise with stirring at 25-30°. The solution was cooled to 0° in an ice-salt bath and stirred while **1** (181 g., 1.0 mole) was added in small portions at 0-10°. Stirring was continued for 1 hour after the addition was completed during which time some solid had precipitated. The mixture was poured cautiously into a stirred solution of sodium carbonate (525 g., 5 moles) in water. Ice was added intermittently to minimize the temperature rise. A brown gum separated. The mixture was covered with ether (100 ml.) and stirring was continued while the ether was removed by a stream of air. The gum solidified as the ether evaporated. The tan solid was collected by filtration, washed with water containing a small amount of 2-propanol, and dried at 60° to yield 100 g. of **3.**

1-Acetyl-5-(2-furanyl)-3-methylthio-1*H*-1,2,4-triazole (**4**).

Acetic anhydride (350 ml.) and **1** (109 g., 0.6 mole) were

Table II

Physical Properties of the 3-Mercapto-5-(2-furanyl)-1*H*-1,2,4-triazoles

Compound No.	X	R	R_1	R_2	R_3	Yield, %	M.p. °C	Recrystallization Solvent	Formula	Analyses, Calcd./Found C	H	N
1	H	CH_3	--	--	H	45	147.5-149	Water	$C_7H_7N_3OS$	46.39/46.15	3.90/3.86	23.19/23.17
2	NO_2	CH_3	--	--	H	74 (a)	204-205	Acetic Acid	$C_7H_6N_4O_3S$	37.16/37.14	2.67/2.80	24.77/24.78
3	NO_2	CH_3	$COCH_3$	--	--	37	205-207	Acetic Acid	$C_9H_8N_4O_4S$	40.29/40.41	3.00/2.99	20.89/21.03
4	H	CH_3	$COCH_3$	--	--	93	140-141	Methanol	$C_9H_9N_3O_2S$	48.42/48.45	4.06/3.99	18.82/19.01
5	NO_2	CH_3	--	CH_3	--	63 (b)	177-178	Ethanenitrile	$C_8H_8N_4O_3S$	39.99/40.15	3.35/3.36	23.32/23.22
6	NO_2	CH_3	--	--	CH_3	50	177-178	2-Propanol	$C_8H_8N_4O_3S$	39.99/40.24	3.35/3.26	23.32/23.25
7	NO_2	CH_3	CH_3	--	--	20.8	177-178	Ethanenitrile	$C_8H_8N_4O_3S$	39.99/40.03	3.35/3.25	23.32/23.41
9	H	H	--	CH_3	--	30	234-236	Methanol	$C_7H_7N_3OS$	46.39/46.40	3.90/3.85	23.20/23.20
10	NO_2	H	--	CH_3	--	76	180-182	Aq. Acetic Acid	$C_7H_6N_4O_3S$	37.17/37.57	2.67/2.35	24.77/24.50
12	NO_2	H	--	--	CH_3	78	147-150	Acetic Acid	$C_7H_6N_4O_3S$	37.17/37.27	2.67/2.70	24.77/24.51

(a) Yield for Method A. The yield for Method B = 50% and for Method C = 42%. (b) Yield for the alkylation of **10**.

heated at reflux for 30 minutes. The solution was cooled and diluted with a mixture of ether (100 ml.) and petroleum ether (200 ml.). When the solution was cooled in an ice bath, colorless needles crystallized. The product was collected by filtration and dried to 100° to yield 125 g. of **4**.

Methylation of **2** (Preparation of **5** and **7**).

A stirred solution of **2** (68 g., 0.3 mole) and sodium hydroxide (16 g., 0.4 mole) in water (680 ml.) was treated at room temperature with dimethyl sulfate (40 g., 0.32 mole) in one portion. Stirring was continued for 15 minutes during which time the temperature rose to 37° and a brown solid separated. The solid was collected by filtration, washed with water, 2-propanol and ether and dried at 60° to yield 56 g., m.p. 135-155°. The crude material was recrystallized from ethanenitrile to yield 15 g. of **7**. Evaporation of the filtrate left a residue which was stirred several times with DMF and filtered. The remaining solid was recrystallized from ethanenitrile to give 1.0 g. of **5**.

1-(2-Furanylcarbonyl)-2-methyl-3-thiosemicarbazide (**8**).

A 5000 ml., 3-necked flask, fitted with a stirrer, thermometer, and addition funnel was charged with 2-methylthiosemicarbazide (9) (150 g., 1.43 moles) in water (1500 ml.). The stirred solution was cooled to 0° and held $< 10°$ with an ice-salt bath while 2-furanylcarbonyl chloride (186 g., 1.45 moles) was added dropwise. After one-half of the acid chloride had been added, a solution of sodium carbonate (106 g., 0.87 mole) in water (300 ml.) was added slowly. The addition of the sodium carbonate solution was completed ahead of the addition of the acid chloride. The mixture was stirred at room temperature for 2 hours. The product was collected by filtration as colorless needles to yield 253 g. (88%) of **8**, m.p. 193-195°. An analytical sample was prepared by recrystallization from methanol, m.p. 202-204°.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.18; H, 4.48; N, 21.20.

5-(2-Furanyl)-3-mercapto-2-methyl-2*H*-1,2,4-triazole (**9**).

A 2000 ml., 3-necked flask fitted with a stirrer was charged with **8** (150 g., 0.75 mole) and sodium hydroxide (36 g., 0.9 mole) in water (600 ml.). The mixture was heated on a steam bath with stirring for 2 hours. The solution was cooled and acidified with concentrated hydrochloric acid. The crude product was collected by filtration and recrystallized to yield 41 g. of **9**.

2-Methyl-3-methylmercapto-5-(5-nitro-2-furanyl)-2*H*-1,2,4-triazole (**10**).

Compound **9** (78 g., 0.43 mole) was added at 10-20° with stirring to concentrated sulfuric acid (390 ml.). When most of the solid had dissolved, the stirred mixture was treated dropwise at 10-20° with a solution of concentrated nitric acid (30 ml.) in concentrated sulfuric acid (120 ml.). After the addition was completed, stirring was continued at 10-20° for 15 minutes. The solution was poured over ice to give a tan solid. The product was collected by filtration with difficulty, washed thoroughly with water, and dried by suction to yield 75 g. of **10**.

In a similar manner, **11** (6) was nitrated to yield **12**.

2-Methyl-3-methylthio-5-(5-nitro-2-furanyl)-2*H*-1,2,4-triazole (**5**).

A mixture of **10** (75 g., 0.33 mole), sodium methoxide (18 g., 0.33 mole) and methyl iodide (47 g., 0.33 mole) and methanol (375 ml.) was heated at reflux for 30 minutes. The mixture was cooled and filtered to yield 51 g. of **5** as a tan solid. The analytical sample was identical in all respects, *e.g.*, mixture m.p., ir, and nmr spectra, with **5** obtained from the methylation of **2**.

In a similar manner, **6** was obtained from **12**. The analytical sample of **6** was different in all respects, *e.g.*, mixture m.p., ir, and nmr spectra, from **7** obtained by the methylation of **2**, and from **5**.

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