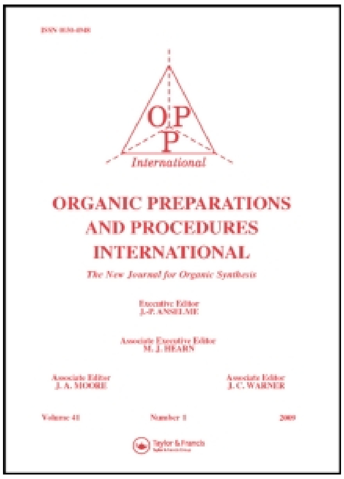

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# SYNTHESIS OF 1,3,4-THIADIAZOLYL UREAS

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# SYNTHESIS OF 1,3,4-THIADIAZOLYL UREAS

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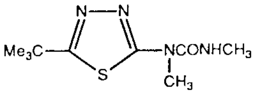
In connection with studies directed toward the synthesis of tebuthiuron, N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'dimethylurea, (1), known as Graslan$^R$, Spike$^R$, or Perflan$^R$, a broad-spectrum herbicide,[1] it became of interest to synthesize compounds 4 and 5 for structure-activity relationship. This brief note describes a facile method for the preparation of these two compounds as shown below.



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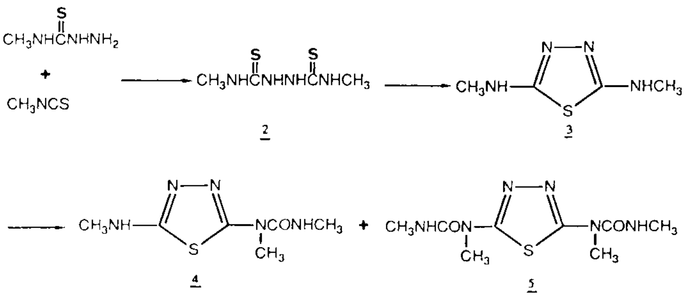

Treatment of 2, readily obtained from 4-methyl-3-thiosemicarbazide and methyl isothiocyanate in the presence of conc. sulfuric acid and polyphosphoric acid provided 3 which upon reaction with a two and one-half fold excess of methyl isocyanate, afforded 5 in good yield. A mixture of 3, 4 and 5 was isolated when 3 was treated with an equivalent amount of methyl isocyanate. Separation of the mixture was achieved by preparative HPLC to give 4.

## EXPERIMENTAL SECTION

1,6-Dimethyl-2,5-dithiobiurea (2).- To a refluxing solution of 4-methyl-3-thiosemicarbazide (10.5 g., 0.1 mole) in 100 ml of ethanol was added a toluene solution containing methyl isothiocyanate (7.3 g., 0.1 mole), and the mixture was refluxed for 5 hrs and cooled. The product was collected, washed with ethanol and dried at 50° in vacuo to afford 14.8 g (83%) of 2 as white crystals, mp.220-222°; $M^+$ 178; $H^1$NMR (DMSO/$d_6$): δ 2.86 (d, 3, N-$CH_3$), 7.98 (broad, 1, N-H), 9.25 (s, 1, N-H).

Anal. Calcd. for $C_4H_{10}N_4S_2$: C, 26.95; H, 5.65; N, 31.43; S, 35.97

Found: C, 26.92; H, 5.40; N, 31.22; S, 36.06

2,5-Bismethylamino-1,3,4-thiadiazole (3).- 1,6-Dimethyl-2,5-dithiobiurea (2, 25 g., 0.14 mole) was added to a solution containing polyphosphoric acid and conc. sulfuric acid (150 g., 3:1 by weight) while the temperature was maintained between 5-10° with an ice-water bath. The reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 6 hrs then cooled to 5°. Water (250 ml) was added and the pH of the reaction mixture was adjusted to 7.5 with conc. ammonium hydroxide. The product was collected, washed with water and recrystallized from methanol to afford 12.0 g (59%) of white crystals of 3, mp. 169-173°; $M^+$ 1.44; $H^1$NMR (DMSO/$d_6$): δ 2.72 (s, 1, N-$CH_3$), 6.72 (broad, 1, N-H).

Anal. Calcd. for $C_4H_8N_4S$: C, 33.32; H, 5.59; N, 38.85; S, 22.24

Found: C, 33.53; H, 5.86; N, 38.61; S, 22.34

1,1'-(1,3,4-Thiadiazole-2,5-diyl)-bis-(1,3-dimethylurea) (5).- 2,5-Bismethylamino-1,3,4-thiadiazole (3, 1.0 g., 0.007 mole) was suspended in 45 ml of toluene, and the mixture was heated to 60°. A solution containing 5 ml of toluene and methylisocyanate (2.0 g., 0.35 mole) was added to the above suspension and the temperature was maintained at 60° for 5 hrs. The mixture was cooled to 5°, and the product was collected, washed with toluene and recrystallized from methanol-ether to give 1.3 g (72%) of white crystals of 5, (differential thermoanalysis shows endotherms at 215°, 226°, and 242°, all of which indicates steps of decomposition); $M^+$. 258 (FD and EI); $H^1$NMR (DMSO/$d_6$): δ 2.72 (d, 3, J = 6Hz, NH-$CH_3$), 3.44 (s, 3, N-$CH_3$), 7.40 (q, 1, J = 6Hz, CONH).

Anal. Calcd. for $C_8H_{14}N_6O_2S$: C, 37.20; H, 5.46; N, 32.54; S, 12.41

Found: C, 37.38; H, 5.25; N, 32.27; S, 12.29

1,3-Dimethyl-1-[5-(methylamino)-1,3,4-thiadiazole-2-yl]urea (4).- 2,5-Bismethylamino-1,3,4-thiadiazole (3, 1.0 g., 0.007 mole) was suspended in 45 ml of toluene, and the mixture was heated to 60°. A solution containing 5 ml of toluene and methylisocyanate (0.4 g, 0.007 mole) was added to the above suspension, and the temperature was maintained at 60° for 4 hrs. The reaction mixture was cooled to 5°, and the product was collected, washed with toluene and a mixture (by HPLC analysis) of 3, 4 and 5 was isolated. Separation of the mixture was achieved by preparative HPLC with a micro porasil column and 67% THF:33% $CH_3CN$ as the mobile phase to provide 0.44 g of solid which was recrystallized from methanol-ether to give 0.4 g (28%) of 4 as white crystals, mp. 202°; $M^+$ 201 (FD and EI); $H^1$NMR (DMSO/$d_6$): δ 2.70 (d, 3, J = 6Hz, CONH$CH_3$), 2.80 (d, 3, J = 6Hz, NH$CH_3$), 3.40 (s, 3, N-$CH_3$), 7.0 (q, 1, J = 6Hz, NH$CH_3$), 7.30 (q, 1, J = 7Hz, CONH$CH_3$).

Anal. Calcd. for $C_6H_{11}N_5OS$: C, 35.81; H, 5.51; N, 34.80; S, 15.93

Found: C, 36.04; H, 5.54; N, 34.62; S, 16.00

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## 1-METHYL-4-NITRO-5-IMIDAZOLYL SULFONES

Submitted by (01/31/86) Ned D. Heindel*[†], C. Jeffrey Lacey*, Belle A. Mease* and David V. Woo[†]

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4-Nitroimidazoles substituted in the 5-position with sulfur-containing groups such as sulfide, sulfonamide, sulfone, and sulfonate have been reported as radiation sensitizers in Chinese hamster cells.[1] The sulfones, of which only a few are known, have been prepared by oxidation of the sulfides (2) or by nucleophilic displacement of halogen by a sodium arylsulfinate on 1-methyl-4-nitro-5-chloroimidazole.[2] We now report the synthesis of six new sulfones by the controlled oxidation of imidazole