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TRANSFORMATION OF 1,3,4-OXADIAZOLES TO 1,3,4-THIADIAZOLES USING THIOUREA.+

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Abstract: A new and convenient procedure for the direct conversion of 1,3,4-oxadiazoles to 1,3,4-thiadiazole using thiourea as thionating agent is described.

The advent of sulphur drugs and later discovery of mesoionic compounds greatly accelerated the rate of progress in the field of thiadiazoles. The earliest use of 1,3,4-thidiazoles were in the pharmaceutical area as antibacterials with properties similar to those of the well known sulphonamide drugs. Some of the later uses are as pesticides, lubricants, antiviral, antipyretic, fungicidal, analgesic, antiinflammatory and antitumor activities.[1] The importance of the toxicities of the -N-C-S- moiety has been well established in many fungicides and the presence of thiadiazole ring is probably reasonable for their fungicidal activities. It is also important to note that these compounds find diverse applications as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complexation reagents. For instance 2-(*N*-methyl piperazinyl) and 2-(*N,N*-dialkylaminoethyl)-amino-1,3,4-thiadiazoles display antihistamine and

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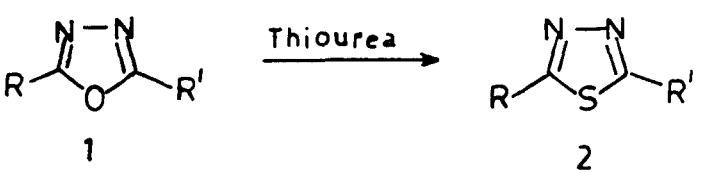
anticholenergesic activity. while 2,2-methylenediamino-bis-(1,3,4-thiadiazole) is effective against tumor in mice.[2]

The usual synthesis of 1,3,4-thiadiazoles involve dehydrative cyclization of thiosemicarbazides or compounds with the basic skeleton S-C-N-N-C-S-.[3] Dehydrative cyclization of acyl thiosemicarbazones are the standard method for preparing 1,3,4-thiadiazoles. Literature survey on the synthesis of 1,3,-thiadiazoles reveals that there is only one reference available for the direct conversion of 1,3,4-oxadiazole to 1,3,4-thiadiazole.[4] This reaction is based on the reaction of P_2S_5 with 1,3,4-oxadiazole at reflux temperature.

It was Bordwell[5] who first introduced thiourea for the direct conversion of oxirane to thiaranes by heating under reflux and later Kogabu et al[6] used this reagent for the conversion of trisoxiranes to tristhiranes. With these in facts, we thought of introducing thiourea as a new reagent for the direct conversion of 2,5-diaryl-1,3,-oxadiazole (**1**) to 2,5-diaryl-1,3,4-thiadiazole (**2**).



1 2

a) R = R' = Ph; d) R'= (NO2)C6H4-, R = $(MeO)_3C_6H_2$-.

b) R' = Ph, R = $(MeO)C_6H_4$-;

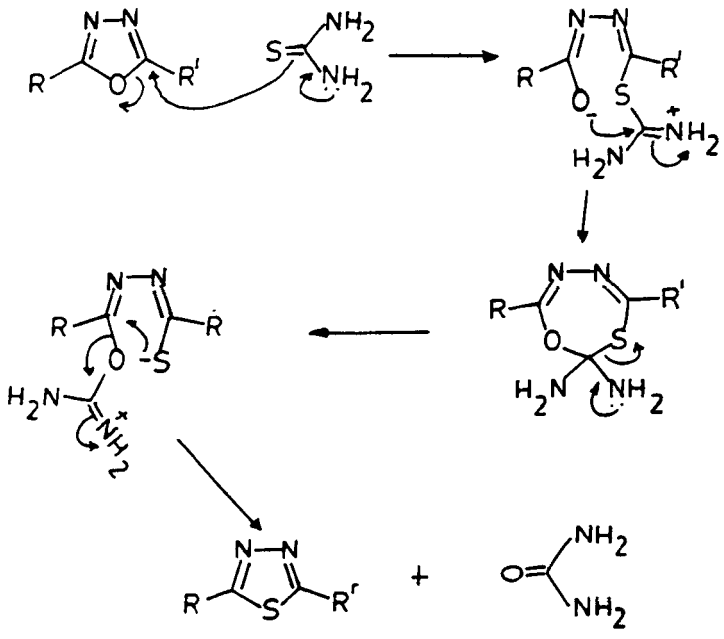
c) R' = Ph, R = $(MeO)_3C_6H_2$-;

When we carried out the reaction of 1,3,4-oxadiazoles with thiourea at reflux temperature for 3 to 4 days, we observed only 2 to 5% of oxadiazoles gets converted

to thiadiazoles. Thus in order to reduce the reaction time and to increase the yield, the reaction is carried out in a sealed tube at water bath temperature. In a typical experiment, solution of 2,5-diaryl-1,3,4-oxadiazoles (**1**) in tetrahydrofuran was heated in a sealed tube for 10 to 15 hr. After 15 hr, the reaction mixture showed two spots, minor one correspond to the starting material and the major one for new compound. After the workup, we obtained thiadiazole as creamy white crystalline compound in 65-72% yield. ^{1}H NMR of all the diaryl thiadiazoles (**2**) showed peaks due to aromatic protons and other substituents in the expected region. ^{13}C NMR showed singlets in the region 164.57-164.63 ppm either due to C-5 or C-2. The remaining aromatic ring carbons appear at expected region. The diary-1,3,4-thiadiazoles gave molecular ion as the base peak.

The probable mechanism for the formation of 2,5-diaryl-1,3,4-thiadiazole (**2**) involves the initial attack of sulphur atom of thiourea assisted by the lone pair of electron on the nitrogen at positions 2 or 5 of 2,5-diaryl-1,3,4-thiadiazole followed by ring opening reaction to yield the thiouronium salt. This thiouronium salts undergo rearrangement to form mesomeric oxouronium salt via the formation of oxathiadiazepine derivative. Further ring closure of oxouronium salt will lead to the formation of thiadiazole with the elimination of urea molecule (Scheme).

Further evidence for the ring opening reaction is based on the fact that the alkyl and aryl 1,3,4-oxadiazole derivatives undergo ring opening reaction with water as nucleophile.[4] The reaction with ammonia or primary amines provide a useful synthesis of 1,3,4-thiadiazole.[7] Bordwell and et al[5] proposed a similar mechanism for the conversion of oxiranes to thiranes. All these results support our proposed mechanism.



EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker MHz spectrometer in $CDCl_3$ solution. The ^1H NMR spectra were measured at 300 MHz, Me_4Si was used as an internal standard, and the chemical shifts are expressed in ppm (δ). The ^{13}C NMR spectra were measured at 75 MHz and the values are in parts per million downfield from Me_4Si. mass spectra were obtained on a Fennigan 4021 mass spectrometer. Chromatographic separations were carried out on a silica gel (70-230 mesh, Merck) coloumn using chloroform-acetone (7:1) as the eluent.

General procedure for the preparation of 2,5-diaryl-1,3,4-thiadiazole (2): ***Typical procedure for the preparation of 2,5-diphenyl-1,3,4-thiadiazole*** **(2a):** A mixture of 2,5-diphenyl-1,3,4-oxadiazole (**1a**) (1.10 g, 5 mmol), thiourea (1 g, 13.15 mmol) dissolved in tetrahydrofuran (5 ml) taken in a test tube, which was then sealed. The

mixture was then kept for 24 to 30 hrs at 120-50°C in an oil bath. After the reaction, it was extracted into dichloromethane followed by thorough washing with water, brine solution and finally dried over anhydrous Na_2SO_4. The starting material was removed by coloumn chromatography using chloroform:acetone (7:1, v/v) as eluent. Crystallization of the solid from methanol gave 65% (0.70 g) of **2a** as creamy white crystalline compound, m.p. = 127-29°C. ^1H NMR ($CDCl_3$): δ 7.54 (bs, 3H, 3',4',5'-H) and 8.14 (s, 2H, 2', 6'-H); ^{13}C NMR ($CDCl_3$): δ 124.03 (C-1',1"), 126.97 (C-2',6'), 129.08 (C-3',5'), 131.71 (C-4',4"), 164.63 (C-2,5); Mass spectrum: m/z (relative intensity) for $C_{14}H_{10}N_2S$ 238(M^+, 100), 210 (43), 7(8). Anal. calcd. C 70.56, H 4.23, N 11.76, S 13.45; found C 70.43, H 4.12, N 11.44, S 12.24.

2-(4'-Methoxyphenyl)-5-phenyl-1,3,4-thiadiazole (2b): Obtained from **1b** (1.26 g 5 mmol) and thiourea (1 g, 13.15 mmol) as pale yellow crystalline compound in 60% (0.77 g) yield, m.p. = 133-35°C. ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 7.03 (bs, 2H, ArH), 7.55 (bm, 3H, Ar-H), 8.08 (d, 2H, ArH) and 8.12 (d, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 55.51 (OCH_3), 114.54 (C-3",5"), 116.56 (C-1"), 124.01 (C-1'), 126.97 (C-2',6'), 128.68 (C-2",6"), 129.09 (C-3',5'), 162.37 (C-4"), 164.25 (C-5), 164.53 (C-2); Mass spectrum: m/z (relative intensity) for $C_{15}H_{12}N_2OS$ 268(M^+, 100), 240(36), 165(12), 135(8), 107(4), 103(10), 77(6). Anal. calcd. C 67.15, H 4.51, N 10.45, S 11.93; found C 67.02, H 4.32, N 10.34, S 11.72.

2-(3',4',5'-Trimethoxyphenyl)-5-phenyl-1,3,4-thiadiazole (2c): Obtained from **1c** (1.56 g 5 mmol) and thiourea (1 g, 13.15 mmol) as creamy white crystalline compound in 69% (1.09 g) yield, m.p. = 193-95°C. 1H NMR ($CDCl_3$): δ 3.94 (s, 3H, OCH_3), 3.98 (s, 6H, OCH_3), 7.36 (bs, 2H, Ar-H), 7.55 (m, 3H, ArH) and 8.14 (s, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 56.49 and 61.04 (OCH_3), 104.45 (C-2",6"), 119.07 (C-1"), 124.00 (C-1'), 126.97 (C-2',6'), 129.09 (C-3',5'), 131.71 (C-4',4"), 141.42 (C-4"),

153.80 (C-3",5"), 164.57 (C-2,5); Mass spectrum: m/z (relative intensity) for $C_{17}H_{16}N_2O_3S$ 328(M^+, 100), 300(40), 225(18), 193(20), 167(8), 135(8), 103(10), 77(4). Anal. calcd. C 54.69, H 4.05, N 11.25, S 8.59; found C 54.52, H 3.95, N 11.09, S 8.42.

2-(3',4',5'-Trimethoxyphenyl)-5-(p-nitrophenyl)-1,3,4-thiadiazole (2d): Obtained from **1d** (1.8 g 5 mmol) and thiourea (1 g, 13.15 mmol) as pale yellow crystalline compound in 55% (1.05 g) yield, m.p. = 216-217°C. 1H NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 3.95 (s, 6H, OCH_3), 7.36 (s, 2H, ArH), 8.32 (d, 2H, ArH) and 8.40 (s, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 56.50 and 61.10 (OCH_3), 104.70 (C-2',6'), 118.32 (C-1'), 124.40 (C-3",5"), 127.86 (C-2",6"), 129.50 (C-1"), 141.45 (C-4'), 149.65 (C-4"), 153.84 (C-3',5'), 162.84 (C-5) and 164.58 (C-2); Mass spectrum: m/z (relative intensity) for $C_{17}H_{15}N_3O_5S$ 373(M^+, 100), 345 (35), 167(12), 122(4).

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