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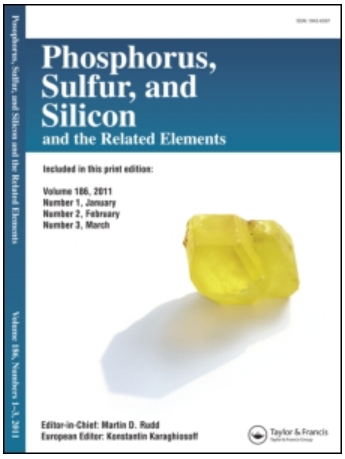

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A Convenient Synthesis of 3,4-Disubstituted-1,2,4-Thiadiazole-5(4H)-Thiones

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A CONVENIENT SYNTHESIS OF 3,4-DISUBSTITUTED-1,2,4-THIADIAZOLE-5(4H)-THIONES

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3,4-Disubstituted-1,2,4-oxadiazole-5(4H)-ones were obtained from the reaction of substituted amide oximes with ethylchloroformate. These compounds were treated with P_2S_5 to give corresponding 1,2,4-oxadiazole-5-thiones. Rearrangement of 1,2,4-oxadiazole-5-thiones, catalysed by metallic copper, yielded 1,2,4-thiadiazole-5-ones. The reaction of 1,2,4-thiadiazole-5-ones with P_2S_5 gave 1,2,4-thiadiazole-5-thiones.

Keywords: 1,2,4-Oxadiazole-5-thione; 1,2,4-thiadiazole-5-one; 1,2,4-thiadiazole-5-thione

Reaction of amide oximes with CS_2 gives 3-substituted-1,2,4-thiadiazole-5(4H)-thiones. However, the reaction of N-substituted amide oximes with CS_2 fails to obtain 3,4-disubstituted-1,2,4-thiadiazole-5(4H)-thiones[1] which are of interest from the pharmacological point of view.[2]

In our preliminary communication,[1] we have shown that 3-phenyl-4-methyl(or p-tolyl)-1,2,4-thiadiazole-5(4H)-thiones could be obtained from the thionation of corresponding 1,2,4-thiadiazole-5(4H)-ones which were prepared from the rearrangement of 3-phenyl-4-methyl(or p-tolyl)-1,2,4-oxadiazole-5(4H)-thrones.[3,4] However, this method did not work to obtain 3-pyridyl-4-alkyl(or aryl)-1,2,4-thiadiazole-5(4H)-thiones from the thionation of corresponding 1,2,4-thiadiazole-5-ones. During the thionation, somehow, all pyridyl substituted 1,2,4-thiadiazole-5-ones were decomposed. Therefore, we decided to prepare some of 3,4-disubstituted 1,2,4-thiadiazole-5(4H)-thiones as an extension of our preliminary communication. For the synthesis of 1,2,4-thiadiazole-5-thiones, the first reaction was the preparation of

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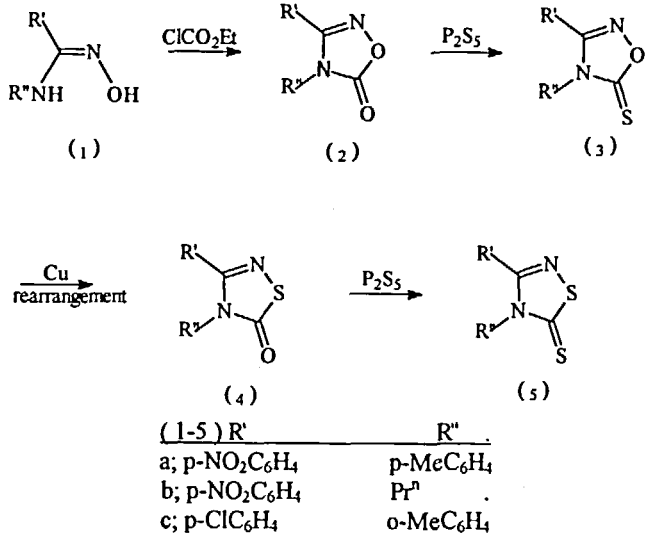
3,4-disubstituted-1,2,4-oxadiazole-5(4H)-thiones from the reaction of N-substituted amide oximes with highly toxic thiophosgene. The alternative preparation of these compounds are the thionation of 3,4-disubstituted-1,2,4-oxadiazole-5(4H)-ones which can be easily prepared[5] from the reaction of N-substituted amide oximes with ethyl chloroformate. Therefore, we first caused N-substituted amide oximes (1a-c) to react with ethyl chloroformate to give 3,4-disubstituted-1,2,4-oxadiazole-5(4H)-ones (2a-c) (Scheme 1).



(1) (2) (3)

(4) (5)

(1-5) R'	R''
a; p-$NO_2C_6H_4$	p-MeC_6H_4
b; p-$NO_2C_6H_4$	Pr^n
c; p-ClC_6H_4	o-MeC_6H_4

SCHEME 1

When compounds (2a-c) were refluxed in xylene with an excess of P_2S_5 for 15 h, the thiones (3a-c) were obtained. The thermal rearrangement of thiones (3a and 3b) to compounds (4a and 4b) were carried out with a catalytic amount of copper powder in diphenyl ether at 180°C for 8–9 h. Under similar conditions, the attempts of rearrangement of 3c to corresponding 4c failed. In all cases the thiones were found to be decomposed. This rearrangement was succesful with a catalytic amount of copper powder in xylene at reflux temperature and 3c was completely rearranged to 4c in 15h.The treatment of compound (4a-c) in xylene with excess of P_2S_5 gave compounds (5a-c).

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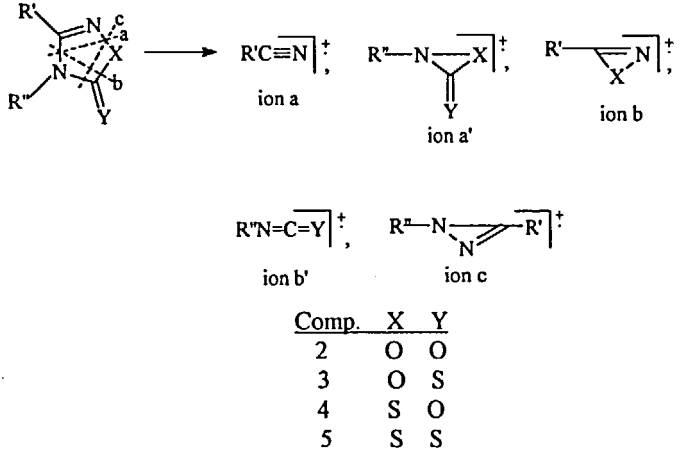
Rapid analysis of compounds (2–5) were particularly simple, since compounds (2) and (4) have a C=O frequency (i.r.) at 1675–1780 cm^{-1}, whilst compounds (3) and (5) have C=S vibrations[6] in the region of 1200–1400 cm^{-1}.

The mass spectral analysis also supported the structural assignment. Compounds (2–5) were observed to cleave under electron impact to give two fragments. One of them contains three and the other two of the atoms involved in the parent ring. The presence of a C=N double bond in the ring limits the number of fragmentation modes to three among the five possible fragmentation directions as shown in Scheme 2. This type of fragmentations were observed in five-membered[7–9] or six-membered[10,11] heterocyclic ring systems as the reverse of Diels-Alder cycloaddition reaction.



Comp.	X	Y
2	O	O
3	O	S
4	S	O
5	S	S

SCHEME 2

The Table I gives the intensity of the fragment ions.

The series of compounds (3) gave very similar mass spectra corresponding to compounds (4). Compounds (3) always had prominent R' CNS fragments. Even, at a source temperature as low as 50°C, the R' CNS fragments were observed. Therefore, we think that R' CNS must arise largely by rearrangement of the molecular ion rather than rearrangement of the molecule (Scheme 3).

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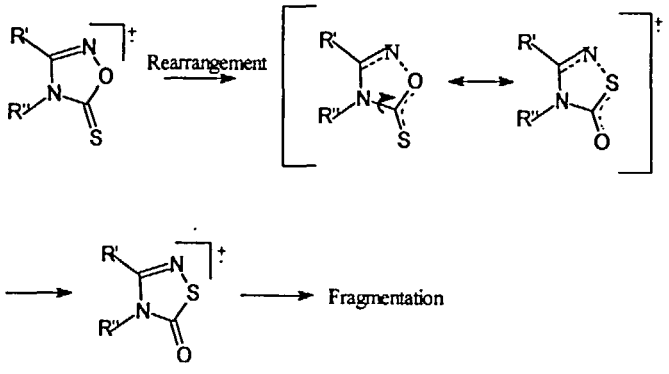

SCHEME 3

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Similar mass spectrometric rearrangements have been previously observed[12] in the rearrangement of N-alkylphtalimides, N-phenylthiono amides[13] thione-esters and thionocarbonates.

TABLE I Fragmentation data for compounds (2–5) m/z (relative abundances*, %)

Comp.	M^+	*ion a*	*ion a'*	*ion b*	*ion b'*	*ion c*
2a	297(85)	148(7)	149(47)	-	133(8)	253(100)
2b	249(62)	148(13)	-	164(62)	85(58)	205(19)
2c	286(100)	137(27)	149(39)	153(4)	133(23)	242(60)
3a**	313(100)	148(22)	-	180(50)	133(100)	253(14)
3b**	265(61)	148(12)	117(3)	180(74)	-	-
3c**	302(100)	137(64)	165(28)	169(88)	133(47)	242(16)
4a	313(100)	-	165(19)	-	133(62)	-
4b	265(53)	-	117(3)	180(73)	85(22)	-
4c	302(100)	137(22)	165(21)	169(73)	133(14)	242(3)
5a	329(100)	148(16)	181(61)	180(47)	149(31)	253(9)
5b	281(19)	148(6)	-	180(4)	-	205(3)
5c	318(100)	137(33)	181(34)	169(43)	149(51)	-

*Relative abundances of less than 3% are omitted.
**The compounds rearrange to corresponding compounds (4) before the fragmentation.

EXPERIMENTAL

IR spectra were recorded on a Simadzu FTIR-821PC Fourier Transform IR spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC 200-L(200 MHz). Mass spectra were run at 70 eV on VCZAP SpEC instrument. Silica Gel HF_{254} was used for preparative thin layer chromatography. Melting points were determined on a Büchi apparatus and are uncorrected. N-Substituted-benzamide oximes were prepared from the reaction of hydroxamic acid chloride with primary amines as described in the literature.[5]

3-(p-Nitrophenyl)-4-((p-tolyl)-1,2,4-oxadiazole-5(4H)-one, 2a; General Procedure

Ethyl chloroformate (11 mmol, 1,2g) in 15ml of xylene was added dropwise to a solution of n-(p-tolyl)-p-nitrobenzamide oxime (1a) (22 mmol, 6g) in 30ml of xylene. The reaction mixture was refluxed for 9 h. After cooling, the precipitate was filtered off and the solvent was evaporated under reduced pressure. The remaining solid was recrystallized from ethanol to give compound (2a) (4.1g, 63 %); mp 182–184°C;

IR(KBr): 1514(C=N), 1772cm^{-1} (C=O);

^{1}H NMR($CDCl_3$): δ 2.42(s, 3H, CH_3), 7.13(d, 2 aromatic H), 7.27(d, 2 aromatic H), 7.61(d, 2aromatic H), 8.21(d, 2 aromatic H);

MS (EI, 70 eV): m/z 297(M^+).

3-(*p*-Nitrophenyl)-4-(n-propyl)-1,2,4-oxadiazole-5(4H)-one, 2b

The compound was recrytallized from ethanol; yield 68%; mp 108–110°C;

IR(KBr): 1529(C=N), 1770cm^{-1}(C=O);

^{1}H NMR($CDCl_3$) : δ 0.87(t, 3H, CH_3), 1.65(m, 2H, CH_2), 3.67(t, 2H, CH_2), 7.83(d, 2 aromatic H), 8.44(d, 2 aromatic H);

MS (EI, 70 eV): m/z 249(M^+).

3-(p-Chlorophenyl)-4-(o-tolyl)-1,2,4-oxadiazole-5-(4H)-one, 2c

The compound was recrystallized from ethanol; yield 83%; mp 152–154°C;

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IR(KBr): 1602(C=N), 1774cm^{-1}(C=O);

^{1}H NMR($CDCl_3$): δ 2.29(s, 3H, CH_3), 7.27(d, 2 aromatic H), 7.40(m, 6 aromatic H);

MS (EI, 70 eV): m/z 286(M^+)

3-(p-Nitrophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione, 3a; General Procedure

3-(p-Nitrophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-one (2a) (12 mmol, 3.6g) and P_2S_5 (6 mmol, 1.34g) were refluxed in xylene for 15 h. Hot solution was filtered and xylene was evaporated under reduced pressure. The remaining solid was recrystallized from ethanol to give compound (3a) (1.7 g, 45%); mp 120–122°C;

IR(KBr): 1346(C=S), 1512cm^{-1}(C=N) ;

^{1}H NMR($CDCl_3$): δ 2.50(s, 3H, CH_3), 7.25(d, 2 aromatic H), 7.40(d, 2 aromatic H), 7.62(d, 2 aromatic H), 8.28(d, 2 aromatic H);

MS (EI, 70 eV): m/z 313(M^+).

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3-(p-Nitrophenyl)-4-(n-propyl)-1,2,4-oxadiazole-5(4H)-thione, 3b

The compound was recrystallized from ethanol; yield 59%, mp 113–115°C;

IR(KBr): 1309(C=S), 1527cm^{-1} (C=N);

^{1}H NMR($CDCl_3$): δ 0.90(t, 3H, CH_3), 1.71(m, 2H, CH_2), 3.92(t, 2H, CH_2), 7.84(d, 2 aromatic H), 8.45(d, 2 aromatic H);

MS (EI, 70 eV): m/z 265(M^+).

3-(p-Chlorophenyl)-4-(o-tolyl)-1,2,4-oxadiazole-5(4H)-thione, 3c

The compound was recrystallized from ethanol; yield 64%; mp 144–146°C;

IR(KBr): 1336(C=S), 1602cm^{-1}(C=N);

^{1}H NMR($CDCl_3$): δ 2.29(s, 3H, CH_3), 7.37(d, 2 aromatic H), 7.46(m, 6 aromatic H);

MS (EI, 70 eV): m/z 302(M^+).

3-(p-Nitrophenyl)-4-(p-tolyl)-1,2,4-thiadiazole-5(4H)-one, 4a; General Procedure

3-(p-Nitrophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione (3a) (3.84 mmol, 1.2g) was heated in diphenyl ether (0.8 ml) in a tube for 8 h at 180°C in the presence of a catalytic amount of copper powder. The reaction mixture was extracted with ether and filtered. The solvent was evaporated under reduced pressure, and the remaining solid was recrytallized from ethanol to give compound (4a) (0.5g, 41%); mp 138–140°C;

IR(KBr): 1529(C=N), 1692cm^{-1}(C=O);

^{1}H NRM($CDCl_3$): δ 2.20(s, 3H, CH_3), 6.87(d, 2 aromatic H), 7.07(d, 2 aromatic H), 7.34(d, 2 aromatic H), 7.90(d, 2 aromatic H);

MS (EI, 70 eV): m/z 313(M^+).

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3-(p-Nitrophenyl)-4-(n-propyl)-1,2,4-thiadiazole-5(4H)-one, 4b

The compound was recrystallized from ethanol; yield 46%; mp 84–86°C;

IR(KBr): 1523(C=N), 1683cm^{-1}(C=O);

^{1}H NMR($CDCl_3$): δ 0.81(t, 3H, CH_3), 1.56(m, 2H, CH_2), 3.75(t, 2H, CH_2), 7.74(d, 2 aromatic H), 8.36(d, 2 aromatic H);

MS (EI, 70 eV): m/z 265(M^+).

3-(p-Chlorophenyl)-4-(o-tolyl)-1,2,4-thiadiazole-5(4H)-one, 4c

The compound was recrystallized from ethanol; yield 72%; mp 122–124°C;

IR(KBr): 1595(C=N), 1681cm^{-1}(C=O);

^{1}H NMR($CDCl_3$): δ 2.14(s, 3H, CH_3), 7.13(d, 2 aromatic H), 7.25(m, 6 aromatic H);

MS (EI, 70 eV): m/z 302(M^+).

3-(p-Nitrophenyl)4-(p-tolyl)-1,2,4-thiadiazole-5(4H)-thione, 5a; General Procedure

3-(p-Nitrophenyl)-4-(p-tolyl)-1,2,4-thiadiazole-(4H)-one (4a) (0.8 mmol, 0.25g) was heated with an excess of P_2S_5 (0.4 mmol, 0.08g) in xylene for 15 h. The hot reaction mixture was filtered and xylene was evaporated under reduced pressure. The remaining crude product was chromato-

graphed on Silica Gel Hf_{254} layer with ethyl acetate : light petroleum (40-60) (1:3) (Rf: 0.55) to give oily compound (5a) (0.095g, 36%).

IR(KBr): 1348(C=S), 1521cm^{-1}(C=N);

^{1}H NMR($CDCl_3$): δ 2.42(s, 3H, CH_3), 7.16(d, 2 aromatic H), 7.35(d, 2 aromatic H), 7.70(d, 2 aromatic H), 815(d, 2 aromatic H);

MS (EI, 70 eV): m/z 329(M^+).

3-(p-Nitrophenyl)-4-(n-propyl)-1,2,4-thiadiazole-5(4H)-thione, 5b

The compound was chromatographed on Silica Gel HF_{254} layer with ethyl acetate : light petroleum (40-60) (1:3) (Rf: 0.62) to give oily compound (5b) (0.13 g, 42%).

IR(KBr): 1217(C=S), 1517cm^{-1}(C=N);

^{1}H NMR($CDCl_3$): δ 0.83(t, 3H, CH_3), 1.68(m, 2H, CH_2), 4.10(t, 2H, CH_2), 7.78(d, 2 aromatic H), 8.41(d, 2 aromatic H);

MS (EI, 70 eV): m/z 281(M^+).

3-(p-Chlorophenyl)-4-(o-tolyl)-1,2,4-thiadiazole-5(4H)-thione, 5c

The compound was chromatographed on Silica Gel HF_{254} layer with ethyl acetate : light petroleum (40-60) (1:4) (Rf: 0.66) to give oily compound (5c) (0.9g, 57%).

IR(KBr): 1224(C=S), 1485cm^{-1}(C=N);

^{1}H NMR($CDCl_3$): δ 2.10(s, 3H, CH_3), 7.15(d, 2 aromatic H), 7.35(m, 6 aromatic H);

MS (EI, 70 eV): m/z 318(M^+).

Acknowledgements

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