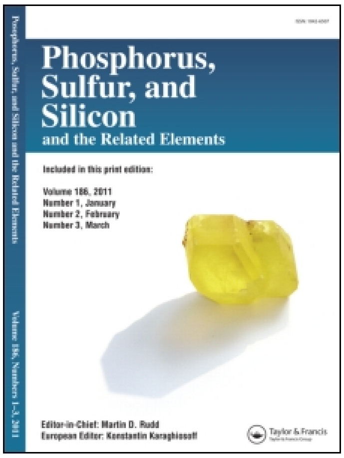

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Ring Opening Reactions of Tetrahydroimidazo[1,5- b][1,2,4]oxadiazol-2(1 H)-thiones

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To cite this Article Coşkun, Necdet and Tat, Fatma Tirli(2003) 'Synthesis and Ring Opening Reactions of Tetrahydroimidazo[1,5- b][1,2,4]oxadiazol-2(1 H)-thiones', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 4, 881 — 886

To link to this Article: DOI: 10.1080/10426500307788

URL: http://dx.doi.org/10.1080/10426500307788

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:881–886
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1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390198048

SYNTHESIS AND RING OPENING REACTIONS OF TETRAHYDROIMIDAZO-[1,5-*b*][1,2,4]OXADIAZOL-2(1*H*)-THIONES

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(Received August 12, 2002; accepted September 29, 2002)

*1,3-Dipolar cycloaddition of imidazoline 3-oxides **1** with methylisothiocyanate proceeds regio- and diastereoselectively to give tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-thiones **3** in high yields. The* cis *configuration of the adducts were proved by our double* cis *elimination test as well as by NOESY experiments. The imidazooxadiazol-2-thiones **3a–e** were treated with concentrated HCl in ethanol at 50°C to give the corresponding 4*H*-[1,2,4]oxadiazole-5-thione only in the cases where the substituent at C-6 is an aryl.*

A number of works either on cycloadditions or incorporating cycloadditions have appeared in recent years.[1] 1,3-Dipolar cycloadditions of nitrones with variety of dipolarophiles take an important place among the methods for the synthesis of five membered heterocyclic compounds.[1–4] Aryl and alkylisothiocyanates also act as dipolarophiles with respect to C=N bond but in some cases the cycloaddition may occur at C=S in the reaction with different nitrones.[4] Nitrones undergo cycloaddition to the C=N double bond of phenylisothiocyanates to give corresponding oxadiazole-5-thiones, but in reactions with substituted phenylisothiocyanates and benzoylisothiocyanate the addition to the C=S double bond predominates.[5,6] The cycloaddition reactions with alkylisothiocyanates are analogous to the reaction with arylisothiocyanates.[6] The reaction of acyclic nitrones with isothiocyanates was shown to give mainly oxadiazolidin-5-thiones.[7] We have shown the 1,3-dipolar

Uludağ University Research Fund is gratefully acknowledged for the financial support (Project No. 200I-2).

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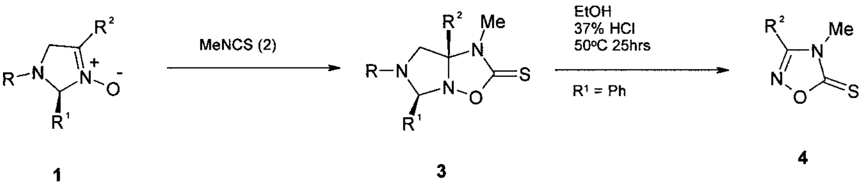
cycloaddition reactions of cyclic nitrones **1** with dipolarophiles as arylisocyanates,[8,9] styrene,[10] DMAD,[11,12] and β-pinene[13] to proceed regio and in the case of chiral nitrones diastereoselectively. An interesting feature of the adducts from isocyanate[14] and DMAD[11,12] and chiral nitrones **1** was their different behavior in the presence of secondary and tertiary amines. A quite reliable chemical way, double *cis* elimination, for determination of the relative configuration of the carbons **3a** and **6** in the tetrahydroimidazooxadiazol-2-ones, and tetrahydroimidazoisoxazolines was developed.[11,12,14]

Here we report on the reaction of cyclic nitrones **1** with twenty-fold excess of the dipolarophile without solvent, to give a new class of tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazole-2(1*H*)-thiones **3**. Methylisothiocyanate was shown to react regio and diastereoselectively with nitrones **1d–e**, the configuration of their adducts **3d–e** was confirmed by our double *cis* elimination test[11,12,14] to be *cis* as well as by NOESY experiment. An interesting rearrangement of C-6 substituted adducts **3** in the presence of HCl to give 4*H*-[1,2,4]oxadiazole-5-thione was observed.

Cyclic nitrones **1** were refluxed in acetonitrile in the presence of phenylisothiocyanate for 48 h but no conversion to the corresponding imidazooxadiazol-2-thiones was observed; the nitrones were recovered unchanged. This was in contrast with the reaction of the same nitrones with arylisocyanates where the reaction proceeds in high yields to give the corresponding imidazooxadiazole-2-ones.[14] However, nitrones **1** convert in high yields to the corresponding **4** using the dipolarophile as a solvent, (see Table I).



SCHEME 1

The structure of compounds **3** was established on the basis of their IR, ^{1}H, and ^{13}C NMR spectra and elemental analysis. The absence of an absorption in the 1510–1650 cm^{-1} region of the IR spectra of compounds **3** was indicative for the regioisomer arising from the addition to C=N double bond. Alternative addition to C=S bond should give an exocyclic imine having C=N stretching vibration in the mentioned region.[6] Characteristic pattern of adducts **3a–c** are the two proton AB systems

TABLE I Tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazole-2(1*H*)-thiones **3** and Oxadiazolones **4**

	Yields of **3**	R	R^1	R^2	m.p. of **3** (°C)	Yields of **4**
a	65	4-MeC_6H_4	H	Ph	116.6	0
b	70	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	155–155.6	—
c	70	4-$MeOC_6H_4$	H	Ph	98	0
d	90	4-$MeOC_6H_4$	Ph	Ph	149.8	56
e	95	4-MeC_6H_4	Ph	Ph	146.3–147	60

at 3.73 ($J_{AB} = 10.80$ Hz) and 4.72 ppm ($J_{AB} = 10.76$ Hz) assigned to C-4 and C-6 methylenes. The AB system for C-4 protons of **3d–e** appears at nearly 4.20 ppm and the singlet for C-6 proton have δ 5.92 and 6.02 for **3d** and **3e** respectively. These chemical shifts are in good agreement with the chemical shifts for the same protons in the adducts obtained from the same imidazoline 3-oxides and phenylisocyanate where the *cis* relation of the phenyls at C-**3a** and C-6 was deduced from NOESY and the double *cis* elimination amine test experiments. The thiocarbonyl carbon's shifts in the ^{13}C NMR spectra of compounds **3** are at δ approximately 183 ppm.

We assume that due to the sterical hindrance the dipolarophile should attack the nitrones **1d–e** from the opposite side of the phenyl at C-2. This will result in *cis* 3a,6-diphenylimidazooxadiazole-2-thiones **3d–e**. This was the case in all of the tetrahydroimidazo adducts reported.[8–13]

The reaction of **3d** with aniline (1:2 molar ratio) in ethanol at reflux for 24 h gave the corresponding nitrone **1** and N-methyl-N-phenylthiourea. This was in agreement with the reaction of arylisocyanate adducts with aniline where the products were also nitrone **1** and the corresponding N,N-diarylurea.

Thermal treatment of adducts **3** in the condensed phase under vacuum led to the formation of corresponding imidazoles in high yields. The same reaction with the adducts of nitrones **1** with arylisocyanates led to the formation of corresponding nitrones.[8,9]

Adducts **3a–c** convert to the corresponding imidazole within 30–40 min in the presence of diethyl- or triethylamine in refluxing acetonitrile. Adducts **3d–e** were refluxed for 4 h with excess of diethylamine expecting a double *cis* elimination as in the cases of DMAD and isocyanate[14] adducts and this was the case; the corresponding imidazole was the only product formed. However the same adducts remained unchanged when triethylamine was used at the same conditions. A similar behavior of the *cis* DMAD adducts have been reported recently.[11,12] *cis* Arylisocyanate adducts also did not give elimination but undergo

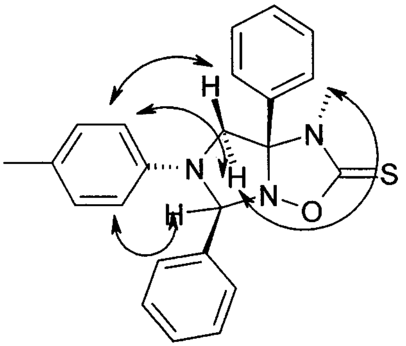
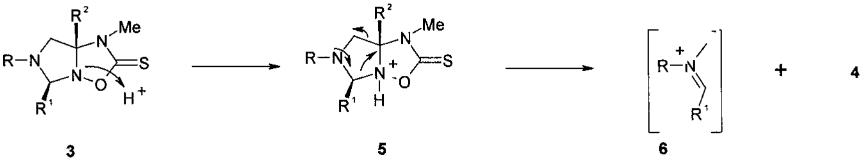


FIGURE 1 Selected NOESY correlations for **3e**.

retro cycloaddition when treated with triethylamine for a long time.[14]

Some selected NOESY correlations for **3e** are given in Figure 1 below. Methyl groop's protons are in relation with the part of the AB system at C-4 as shown in the Figure 1. This proton in turn gives cross peak with the protons of the *p*-tolyl ring. The proton at C-6 gives also cross peak with the protons of the aryl at N-5. All these give a quite reliable base for the assignment of *cis* configuration for compounds **3d–e**.

Compounds **3** with $R^1 = H$ converts slowly to the corresponding imidazoles when heated gently on a water bath in ethanol in the presence of 37% HCl or remain unchanged. However at the same reaction conditions adducts **3d** having $R^1 = Ar$ was shown to convert to 4*H*-[1,2,4]oxadiazole-5-thione **4**. The probable mechanism of the reaction is outlined in Scheme 2. Protonation of adduct **3** at the bridgehead nitrogen led to the formation of an ammonium species **5** which undergoes retro 1,3-dipolar cycloaddition to give the corresponding azomethine ylide **6** and oxadiazol-5-thione **4**. To our knowledge this is the first example of acid induced rearrangement of tetrahydroimidazooxadiazole-5-thiones.



SCHEME 2

The azomethine ylide formation was deduced from its hydrolysis products, namely the aldehyde and corresponding amine. Thus the method described serves as an alternative cycloaddition way to the oxadiazol-5-thiones accessible by the reaction of N-substituted amide oximes with ethyl chloroformate and thiophosgene.[18,19]

EXPERIMENTAL

Melting points were taken on an Electrothermal Digital melting point apparatus. IR spectra were recorded on a Mattson 1000 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in deuteriochloroform with a little DMSO-d$_6$. Freshly prepared imidazoline 3-oxides[15–17] were used after recrystallization from either ethanol or acetone.

*Tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-thiones 3a-e: General Procedure*

The mixture of imidazoline 3-oxide **1** (2 mmol) and methylisothiocyanate (20 mmol) was heated for 2 h at 80°C. The excess of isothiocyanate was removed under vacuum and the residue dissolved in ethanol at heating and left to crystallize at room temperature. The formed white crystals were separated by filtration and dried under vacuum.

*3-Methyl-3a-phenyl-5-*p*-tolyl-tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-thione* ***(3a)***. IR (KBr) No absorption corresponding to $\nu_{C=N}$; ^{1}H NMR (CDCl$_3$ and DMSO-d$_6$) δ ppm 2.27 (3H, s), 3.0 (3H, s), 3.46 (1H, d, $J = 10.71$), 4.2 (1H, d, $J = 10.78$), 4.36 (1H, d, $J = 10.67$), 5.07 (1H, d, $J = 10.78$), 6.68 (2H, d, $J = 7.7$), 7.05 (2H, d, $J = 7.6$), 7.43–7.54 (5H, m). ^{13}C NMR (CDCl$_3$ and DMSO-d$_6$) δ ppm 20.11; 31.04; 53.94; 75.46; 93.46; 115.02; 126.44; 128.64; 129.16; 129.46; 129.49; 135.51; 142.68; 182.42. Calcd for $C_{18}H_{19}N_3OS$ C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found C, 66.84; H, 6.31; N, 12.67; S, 9.47.

3-Methyl-3a,6-diphenyl-5-(4-methoxyphenyl)-tetrahydroimidazo-[1,5 b*][1,2,4]oksadiazol-2(1*H*)-thione* ***(3d)***. No absorption corresponding to $\nu_{C=N}$; ^{1}H NMR (CDCl$_3$) δ ppm 3.0 (3H, s), 3.7 (3H, s), 4.18 (1H, d, $J = 11$), 4.23 (1H, d, $J = 11$), 5.92 (1H, s), 6.63 (2H, d, $J = 8.46$), 6.73 (2H, d, $J = 8.46$), 7.2–7.24 (3H, m), 7.31–7.42 (7H, m). ^{13}C NMR (CDCl$_3$) δ ppm 31.94; 55.72; 87.23; 55.87; 92.61; 115.24; 116.88; 126.94; 127.86; 128.86; 128.99; 129.38; 130.02; 136.19; 136.97; 139.55; 154.11; 183.63. Calcd for $C_{24}H_{23}N_3O_2S$ C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found C, 69.70; H, 5.42; N, 9.27; S, 6.83.

The reaction of ***3d–e*** *with HCl.* To a suspension of adduct **3** (0.15 mmol) in ethanol HCl (0.13 mL, 37%) was added and the mixture heated at 50°C on a water bath for 25 h. The solvent was removed and the residue extracted with dichloromethane (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under vacuum. The products isolated by recrystallization or column chromatography were the corresponding 4-Methyl-3-phenyl-4*H*-[1,2,4]oxadiazole-5-thione, yield 56%. m.p. 117–118°C; lit[19] m.p. 119–120.

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