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A NEW ROUTE TO THE 4H-1,2-OXAZETE RING SYSTEM BY THE STEREOSPECIFIC OXIDATION OF (Z)-3,3-DIMETHYL-1,1-BIS(METHYLTHIO)-2-BUTANONE OXIME

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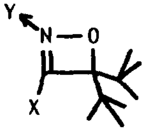
SUMMARY: A new synthesis of a functionalized 4H-1,2-oxazete by oxidation of α,α-bis-(alkylthio) oxime is described.

Berndt and Weiser recently reported the first synthesis of several stable 4H-1,2-oxazete heterocyclics (1).[1,2] Prior to their report, this particular ring system had been observed only as a reactive intermediate in the thermal and photochemical reactions of α,β-unsaturated nitro compounds.[3-6] We would like to report a synthesis of an unusually stable 4H-1,2-oxazete derivative that involves a new stereospecific reaction of α-alkylthio oximes.

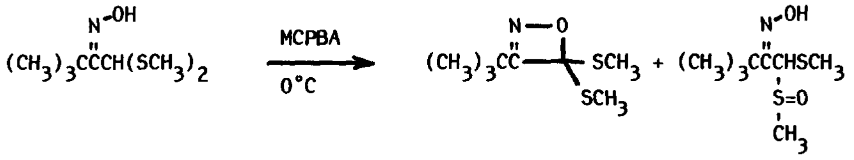


Where Y = O or electron pair

and X = H or Me

1

Oxidation of (Z)-3,3-dimethyl-1,1-di(methylthio)-2-butanone oxime (2),[7] 0.05 mol, with one equivalent of m-chloroperbenzoic acid in CH_2Cl_2 (50 mL) at 0°C gave after 16 hours a 90% yield of 3-tert-butyl-4,4-bis-(methylthio)-4H-1,2-oxazete (3), and a 7% yield of (Z)-3,3-dimethyl-1-(methylsulfinyl)-1-(methylthio)-2-butanone oxime 4, eq. 1.

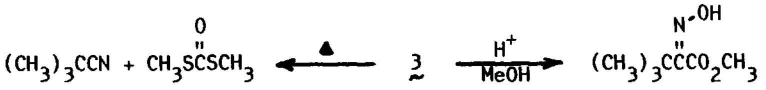


(1)

2 3 4

The methylene chloride reaction mixture was washed with $NaHCO_3$, dried (Na_2SO_4), and concentrated to a pale yellow semi-solid. Slurrying in hexane and filtration resulted in the isolation of diastereomerically pure (Z) sulfoxide **4**. Recrystallization from acetone gave **4** as a white crystalline solid, mp 132-135°C; ^1H NMR δ (acetone-DMSO-d_6): 1.20 (9H, s, t-butyl); 2.29 (3H, s, SCH_3); 3.73 (3H, s, $SOCH_3$); 4.20 (1H, s, CH); 10.9 (1H, s, OH); IR cm^{-1} (KBr): 3160, OH; 3050, 2975, 2875, CH; 1645, C=N; 1017, SO; MS 70 eV; m/e (Rel %): M^+ 223 (.05); 205 (1); 190 (1); 160 (153); 144 (11); 57 (100). Anal. Calcd for $C_8H_{17}NO_2S_2$: C, 43.0; H, 7.7; N, 6.3. Found: C, 42.9; H, 7.9; N, 6.3. Concentration of the filtrate gave an oil. Dry column chromatography (silica gel/100 x 5 cm/hexane-CH_2Cl_2-ether, 40:80:1), gave a solid which when recrystallized (hexane, -25°C) gave **3** as a white powder, m p 33-35°C; ^1H NMR δ ($CDCl_3$): 1.30 (9H, s, tert-butyl), 2.30 (6H, s, SCH_3); ^{13}C NMR δ ($CDCl_3$): 13.5 (SCH_3), 26.1 ($(CH_3)_3$), 34.2 (Cq); 107.7 (Cq); 183.5 (C=N); IR (neat): 2960, 2920, CH; 1585, C=N; 1472; 1455; 1423; 1390; 1360; 1308; 1215; 1195; 1160; and 1135 cm^{-1}; MS 70 eV, m/e (rel %): 205 (36); 190 (81); 175 (2); 158 (6); 132 (24); 127 (24); 122 (24); 91 (20); 79 (17); 75 (100); 68 (32); 57 (100); 47 (71); 45 (56); 42 (60); and 41 (82); M_r (vapor phase osmometry): 211 ± 5%, theory 205; Anal. Calcd for $C_8H_{15}NOS_2$; C, 46.5; H, 7.7; N, 6.8. Found: C, 46.8; H, 7.4; N, 6.8. The action of $KMnO_4$ on **2** in acetone was also effective in producing **3** (100% yield).

As further confirmation of the oxazete structure a methanolic solution of the 4H-1,2-oxazete (**3**) was treated with a few drops of H_2SO_4. After heating five minutes, a quantitative conversion of **3** to methyl 3,3-dimethyl-2-(hydroxyimino)butanoate (**7**) was achieved. The structure of **7** was determined from the following data: mp 65-66°C [Lit.[8]

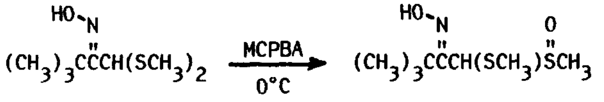


$$(CH_3)_3CCN + CH_3S\overset{O}{\overset{\|}{C}}SCH_3 \xleftarrow{\blacktriangle} \mathbf{3} \xrightarrow[MeOH]{H^+} (CH_3)_3C\overset{N\text{-}OH}{\overset{\|}{C}}CO_2CH_3$$

7

mp 69°C], ^1H NMR δ ($CDCl_3$): 1.19 (9H, s, tert-butyl); 3.87 (3H, s, OCH_3); 7.9 (1H, s, OH); IR cm^{-1} (KBr): 3265, OH; 1723, C=O; 1655, C=N; MS 70 eV, m/e (Rel %): M^+ 159 (2); 142 (55); 100 (65); 41 (100); Anal. Calcd for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.7; H, 8.7; N, 8.7. Structure **7** was configurationally pure and presumed to have the (Z) configuration. The 4H-1,2-oxazete (**3**) was also dissolved in dimethylsulfoxide (DMSO) and heated at 100°C for 18 hours to effect a quantitative conversion to pivalonitrile and S,S'-dimethyl dithiocarbonate.[9]

Reaction of the (E) isomer (5)[7] with MCPBA under identical conditions resulted in a quantitative yield of (E)-3,3-dimethyl-1-(methylsulfinyl)-1-(methylthio)-2-butanone oxime (6), as a 4:1 diastereomeric mixture, ^{1}H NMR δ (CDCl$_3$): diast. a, 1.35 (9H, s, tert-butyl); 2.19 (3H, s, SCH$_3$); 2.86 (3H, s, SOCH$_3$); 4.48 (1H, s, CH); 10.38 (1H, s, OH); diast. b, 1.35 (9H, s, tert-butyl); 2.29 (3H, s, SCH$_3$); 2.72 (3H, s, SOCH$_3$); 4.21 (1H, s, CH) 10.38 (1H, s, OH); IR cm^{-1} (neat): 3175, OH; 1620, C=N; 1010, SO; MS 70 eV, m/e (Rel %): M$^+$ 223 (0.36); 205 (.3); 160 (42); 87 (22); 57 (100).

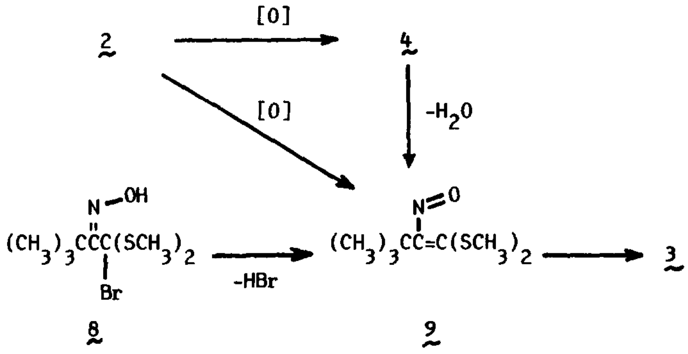


$$\mathrm{(CH_3)_3C\overset{\overset{HO\searrow N}{\|}}{C}CH(SCH_3)_2 \xrightarrow[0°C]{MCPBA} (CH_3)_3C\overset{\overset{HO\searrow N}{\|}}{C}CH(SCH_3)\overset{\overset{O}{\|}}{S}CH_3} \qquad (2)$$

5 6

The formation of 3 can be rationalized by the conversion of 2 to the α,β-unsaturated nitroso intermediate (9) that can undergo an electrocyclic ring closure to give the 4H-1,2-oxazete (3) as shown in scheme 1. Precedent for this route comes from the work of Berndt and Wieser where an α,β-unsaturated nitroso intermediate was actually isolated and found to ring close upon heating.[2] To find out if such an intermediate was involved in the present case, a methylene chloride solution of 1-bromo-3,3-dimethyl-1,1-bis(methylthio)-2-butanone oxime (8) was dehydrobrominated by refluxing in the presence of 1,5-diazabicyclo[4.3.1]nonane (DBN) according to the method of Berndt and Wieser. After 18 hours a 21% yield (isolated) of 3 was obtained. Thus, the intermediacy of 9 in the oxazete preparation appears likely. Furthermore, the isolation of

Scheme 1:



the sulfoxide **4** from the oxazete preparation and the observed stereospecificity of the reaction suggested that **9** might be formed from a Pummerer reaction of the sulfoxide **4**. Efficient ring closure processes using the Pummerer reaction have been reported.[10,11] As a test for this possibility, a methylene chloride solution of **4** was treated with an equivalent amount of *m*-chlorobenzoic acid and allowed to stand at room temperature for 16 hours. A quantitative conversion of **4** to **3** was obtained. It should be noted that the sulfoxide **4** can be converted to **3** in about 50% yield in the absence of added acid catalyst simply by heating in DMSO at 65°C for 16 hours. Thus, from these results, the Pummerer reaction of the sulfoxide **4** that was formed by oxidation with MCPBA appeared to be the precursor of **9** which goes on to the 4*H*-1,2-oxazete.

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