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A novel 2:1 cycloadduct of dimethyl acetylenedicarboxylate with 3,5-diphenyl-4-methoximino-4*H*-pyrazole 1,2-dioxide

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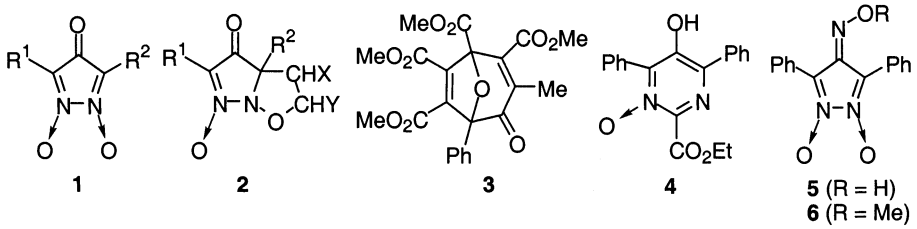
Abstract—Two equivalents of dimethyl acetylenedicarboxylate react with 3,5-diphenyl-4-methoximino-4*H*-pyrazole 1,2-dioxide in acetonitrile under reflux. The major product was shown by X-ray analysis to be a 5,8-epoxyisoxazolo[2,3-*d*]-[1,4]-diazepine derivative.

Nitrosation of α,β-unsaturated ketoximes under an oxygen atmosphere has been used to prepare a number of 4-oxo-4*H*-pyrazole 1,2-dioxides **1**.[1–4] In cycloaddition reactions with a variety of alkenes, XCH=CHY, the compounds **1** behave as nitrone dipoles, participating in dipolar cycloaddition to form 1:1 adducts of type **2**.[5,6] It is notable that the remaining nitrone moiety in **2** has never been reported to undergo cycloaddition with a second molecule of the dipolarophile.

Two examples of reactions of compounds **1** with alkyne dipolarophiles have also been reported. The pyrazolone **1** ($R^1=Ph$; $R^2=Me$) combines with dimethyl acetylenedicarboxylate (DMAD) (2 equiv.), accompanied by loss of N_2O, to produce **3**.[5] Reaction of **1** ($R^1=R^2=Ph$) with ethyl propiolate gives a product analogous to **3**, as well as the pyrimidine **4**.[7]

The 4-oximino-4*H*-pyrazole 1,2-dioxides are also formed during the nitrosation of α,β-unsaturated ketoximes and are often the major products when nitrosation is performed under an inert atmosphere. For example, nitrosation of 1,3-diphenyl-2-propen-1-one oxime under a nitrogen atmosphere gives 3,5-diphenyl-4-oximino-4*H*-pyrazole 1,2-dioxide **5**. Other 3,5-disubstituted analogs of **5** can be prepared in similar fashion.[2,3] The oximes, **5** and analogs, have attracted only limited attention when compared with that which has been afforded to the pyrazolones **1**. We have now undertaken a program directed toward an investigation of the behavior of **5** and related compounds. Since **5** exhibits limited solubility in many common solvents, we found it convenient to convert the oxime into its *O*-methyloxime derivative **6**. The methylation occurred readily upon treatment of **5** with iodomethane and sodium carbonate at room temperature in *N*,*N*-dimethylformamide. The methoxime **6** is a red–brown, crystalline solid, mp 185–87°C, with solubility properties similar to those of **1** ($R^1=R^2=Ph$).

When **6** was reacted under reflux for 3 h in acetonitrile with excess DMAD, a mixture was obtained consisting of two products in a 3:1 ratio. The major product was a crystalline, nearly colorless solid **7**, mp 200–202°C. Both ^1H and ^{13}C NMR spectra of **7** were consistent with the incorporation of 2 equiv. of DMAD and one equivalent of **6**.[8] Initial speculation that **7** had a struc-



Keywords: pyrazoles; *N*-oxides; alkynes; cycloadditions; isoxazolines; rearrangements.

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ture analogous to that of **3** was not supported by elemental analysis. The molecular formula of **7** suggested by analysis for C, H, and N was $C_{28}H_{25}N_3O_{11}$.[8] Thus, unlike the reaction of **1** (R^1 = Ph, R^2 = Me) with DMAD, no loss of N_2O had occurred.

It was apparent from the spectral data and elemental analysis results that the structure of **7** was quite different from those of products previously reported from the reaction of pyrazolone derivatives **1** with alkynes. X-Ray analysis was applied in order to identify this compound. Compound **7** was identified as tetramethyl 5,8-epoxy-4-(*E*)-methoximino-3a,5-diphenyl-3a,4,5,8-tetrahydro-*endo*-isoxazolo[2,3-*d*]-[1,4]-diazepine-2,3,7,8-tetracarboxylate (Fig. 1).[9] We suggest a possible route by which **7** could be formed in Scheme 1.

In Scheme 1 the initial cycloaddition of **6** with DMAD occurs selectively at the less sterically-encumbered nitrone group, which is *anti* to the methoxy group. This produces the 2,3-dihydroisoxazole ring incorporated in structure **8**. The rearrangement of 2,3-dihydroisoxazoles to 2,3-dihydrooxazoles is a well-known reaction.[10–12] In fact, Freeman has suggested that a rearrangement similar to that suggested for the conversion of **8** to **9** may be involved in the formation of **4**.[11]

We speculate that an intermediate **10** may be formed from **9** by a 1–3 shift of nitrogen, resulting in a new bond between the nitrogen and carbon atoms shown in bold. Whether such a rearrangement would occur by a concerted or a stepwise process is not obvious. Subsequent addition of a second molecule of DMAD to the nitrone moiety of **10** from the side of the bicyclic system which is *endo* with respect to the bridging oxygen atom would then give **7**.

In Scheme 1, a rearrangement step precedes the addition of a second molecule of DMAD. One might consider an alternative sequence in which a second molecule of DMAD is added to **9** to give a 2:1 adduct **11**. In structure **11** the orientation of the newly-formed dihydroisoxazole ring is *anti* with respect to the dihydrooxazole. Subsequent rearrangement involving a 1–3 shift of the nitrogen would then lead to **7**.

We consider this alternative sequence less attractive than that shown in Scheme 1. Our main concern in this case is based upon an analogy with the behavior of the compounds **1** in cycloaddition reactions. As noted previously,[5,6] cycloaddition to one of the nitrone functions in **1** produces the 1:1 adduct **2**, which resists further cycloaddition at the surviving nitrone. Although we are not prepared to rule out the conversion of **9** to **11** by a second cycloaddition, we do not feel that this is likely.

The minor product, mp 167–169°C is not yet fully characterized. However, spectral evidence and elemental analysis indicate that it is isomeric with **7**.[13] The possibility that this minor product might be formed from **7** by a 2,3-dihydroisoxazole rearrangement to a 2,3-dihydrooxazole was considered. However, when a sample of **7** was heated under reflux in acetonitrile none

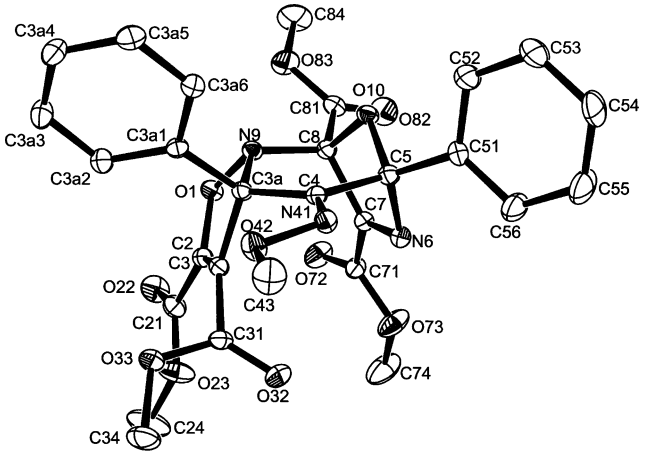
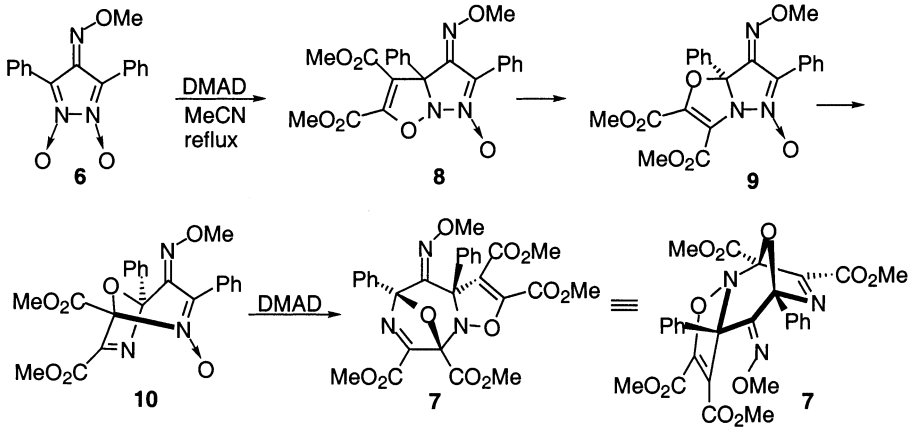
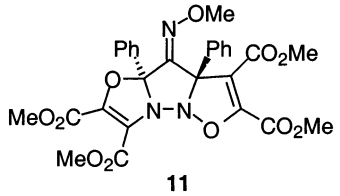


Figure 1. Perspective ORTEP view of **7** showing the atom labeling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms have been omitted for clarity.



Scheme 1. Possible sequence for formation of **7**.



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of the minor product was formed, even after several days. Our current speculation is that the minor product is probably stereoisomeric with **7**. One possibility is that the minor product has the (*Z*) configuration around the oxime double bond, compared with the (*E*) configuration in **7**. This would require an initial cycloaddition in which DMAD reacts with the nitrone group that is *syn* with respect to the methoxy group in **6** instead of *anti*. In our opinion a more attractive alternative is that the minor product may differ from **7** in the orientation of the dihydroisoxazole ring. In Scheme 1, for example, this would require addition of DMAD to the *exo* face instead of the *endo* face of the bridged bicyclic intermediate **10**. We are pursuing further investigation of this reaction, as well as reactions of other methoximinopyrazoles with alkynes.

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8. ^{1}H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): 7.80 ppm (m, 2H), 7.56–7.29 (m, 8H), 3.91 (s, 3H), 3.86 (two overlapping singlets, 6H), 3.73 (s, 3H) 3.36 (s, 3H). ^{13}C NMR (75 MHz in $CDCl_3$, $^{13}CDCl_3$ at 77.0 ppm): 163.8 ppm, 163.5, 162.0, 160.1, 157.4, 146.2, 144.2, 141.4, 133.9, 129.5, 128.3, 128.1, 128.0, 127.7, 126.6, 116.2, 110.1, 95.7, 80.1, 62.4, 53.7, 53.4, 52.9, 52.6. Anal. calcd for $C_{28}H_{25}N_3O_{11}$: C, 58.03; H, 4.35; N, 7.25. Found: C, 57.84; H, 4.53; N, 7.16.
9. Crystal data for compound **7**: $C_{28}H_{25}N_3O_{11}$, $M=579.5$ g/mol, colorless, plate, size $=0.39\times0.32\times0.11$ mm^3, monoclinic, $P21/n$ (no. 14), $a=13.462(6)$ Å, $b=11.653(3)$ Å, $c=18.714(4)$ Å, $\beta=110.05(3)°$, $Z=4$, V 2758(2) Å^3, $\lambda=0.71073$ Å, $T=298(2)$ K, $D_{calcd}=1.396$ g cm^{-3}, $\mu=1.09$ cm^{-1}, $F(000)=1208$, reflections collected/unique/observed $I>2\sigma(I)$ 5062/4843/3001, R indices observed (all data): $R_1=0.046$ (0.104), $wR_2=0.102$ (0.125), parameters (restraints) $=379$ (0), GOF $=1.014$, shift/esd max (mean) $=0.000$ (0.000), largest difference peak and hole $=0.234$ and -0.194 e Å^{-3}. Hydrogen atoms were assigned positions based on the geometries of their attached carbons, and were given thermal parameters of 20% greater than those of the attached atoms. Only one of the two enantiomeric stereoisomers is depicted; however, the centrosymmetric crystal contains the racemic mixture, with enantiomers related to one another through a crystallographic inversion center. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 203552. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.
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12. Huisgen, R.; Giera, H.; Polborn, K. *Liebigs Ann./Recl*. **1997**, 1691–1696.
13. ^{1}H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): 7.83 ppm (m, 2H), 7.46 (m, 3H), 7.34 (m, 5H), 3.91 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (75 MHz in $CDCl_3$, $^{13}CDCl_3$ at 77.0 ppm): 162.1 ppm, 161.4, 160.5, 158.4, 158.1, 148.5, 147.4, 136.7, 133.3, 129.3, 128.6, 128.4, 128.0, 127.9, 113.9, 108.8, 97.5, 78.4, 62.6, 53.7, 53.1 (two overlapping absorptions), 51.7. Anal. calcd for $C_{28}H_{25}N_3O_{11}$: C, 58.03; H, 4.35; N, 7.25. Found: C, 57.98; H, 4.04; N, 7.13.