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Synthesis of 1,5-Dimethyl-1,4-Dihydropyrrolo[3,4-b]-pyrrol-6(5*H*)-one by Intramolecular Diels-Alder Reaction to the Imidazole Nucleus.

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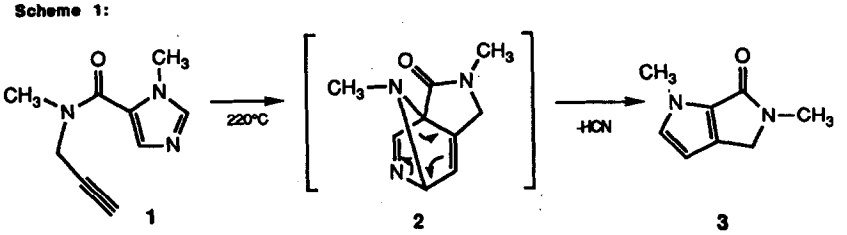
Abstract: *N*-Methyl-*N*-propargylimidazole-5-carboxamide undergoes thermal intramolecular Diels-Alder reaction to give the title compound. A related reaction of the corresponding sydnone system is also described.

Relatively few, if any, examples exist where the imidazole nucleus serves as the diene component of a Diels-Alder type cycloaddition. A recent report by Yamazaki *et al.*[1] describes the [4+2]-cycloaddition of dimethyl acetylenedicarboxylate across the diene of 1-alkylidene- and 1-arylmethyleneamino-4-aryl-2-mercaptoimidazole derivatives to give pyrroledicarboxylates after *retro*-Diels Alder transformation of the initial adducts. The formal cycloaddition was found to be unique to this specific substitution pattern on the imidazole ring Furthermore, the reaction did not occur with electron-rich dienophiles. Lipshutz and Morey[2] had previously demonstrated 1,4-dicarbonyl insertion into the azadiene system of 1,2,4-trisubstituted imidazoles *via* a Diels-Alder-like cycloaddition of singlet oxygen followed by ring opening to give diamides and dipeptides. However, recent evidence suggests that these photooxidations proceed in two steps through a hydroperoxide intermediate rather than by a concerted process to the endoperoxide.[3] One additional report describes the addition of anethole to dimethyl isoimidazole-4,5-dicarboxylate.[4]

We would now like to report the successful intramolecular cycloaddition of an unactivated alkyne to the azadiene system of imidazole. In analogy to our recently reported intramolecular additions to isoquinoline,[5] we chose to investigate derivatives of 1-methylimidazole-5-carboxylic acid. The acid, prepared as described by Rapoport,[6] was condensed with *N*-methylpropargylamine in the presence of 1,1'-carbonyldiimidazole to give the corresponding *N*-methyl-*N*-propargyl amide **1**.[7] In refluxing 1,3,5-triisopropylbenzene, Diels-Alder reaction of imidazolecarboxamide **1** occurred as in the isoquinoline system, namely *via* expulsion of a molecule of HCN from the presumed adduct **2** through a well-documented retrograde Diels-Alder reaction[8] to give the novel dihydropyrrolopyrrolone **3**. (Scheme 1). This product was obtained in 70% yield as a low melting solid[9] after silica gel chromatography.

Scheme 1:

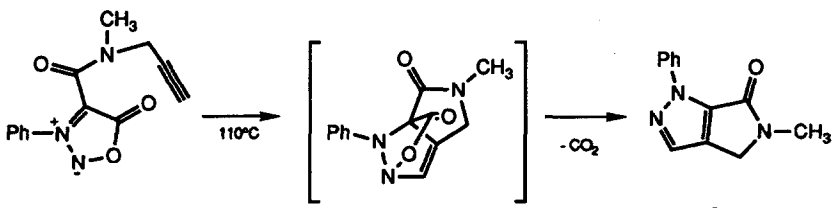


1 2 3

Whereas in the isoquinoline system a stable Diels-Alder adduct could be obtained by cyclization of *N*-methyl-*N*-allylisoquinoline-1-carboxamide, in the imidazole case no cyclization of the allyl analog was achieved at temperatures up to 250°C.

The 2-aza-1-phenyl analog of **3** was also prepared from sydnone carboxamide **4** which underwent facile 1,3-dipolar cycloaddition in refluxing toluene to give, after loss of carbon dioxide from the intermediate adduct **5**, the product **6** in 52% yield.[10] (Scheme 2) Meier *et al.* have also reported intramolecular 1,3-dipolar cycloadditions to the sydnone system.[11]

Scheme 2:



4 **5** **6**

In conclusion, the above sequences outline simple syntheses of two novel ring systems. We have also demonstrated that imidazole is a suitable diene for inverse electron demand intramolecular Diels-Alder cycloaddition reactions.

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References and Notes:

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7. **1**: NMR (300MHz, $CDCl_3$) δ 2.36 (1H,s) 3.24 (3H,s) 3.83 (3H,s) 4.33 (2H,d) 7.45 (1H, s) 7.50 (1H,s). High Field Mass spectrum: Found: 177.0890. Calcd. for $C_9H_{11}N_3O$: 177.0901.
8. Frissen, A. E.; Marcelis, A. T. M.; Plas, H. C. v. d. *Tetrahedron Lett.* **1987**, *28*, 1589-1592.
9. **3**: mp 54-56°C NMR (300MHz, $CDCl_3$) δ 3.09 (3H,s) 3.83 (3H,s) 4.09 (2H,s) 6.03 (1H,d) 6.73 (1H,d). Anal.: Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.87; H, 6.74; N, 18.30.
10. **6**: IR (neat) 3160, 1700, 1600, 1550, 1520, 1480, 760, 690 cm^{-1}. NMR ($CDCl_3$) δ 3.07 (3H,s) 4.13 (2H,s) 7.1-7.6 (4H,m) 8.15-8.35 (2H,m). Mass spectrum (FD) m/e 213.
11. (a) Meier, H.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1977**, *60*, 1087-1090. (b) Meier, H.; Heimgartner, H. *ibid.* **1986**, *69*, 927-940.

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