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STEREOSPECIFIC SYNTHESIS OF FUNCTIONALIZED CYCLOPENTANES.[1]

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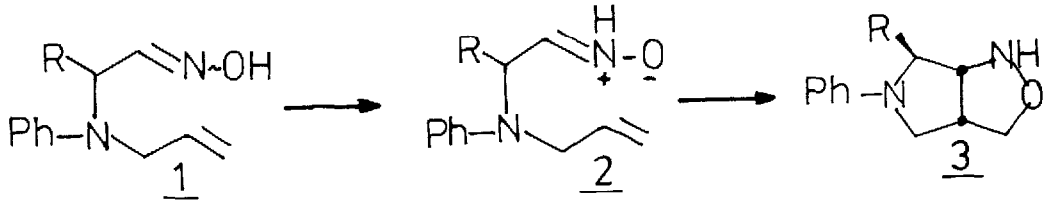
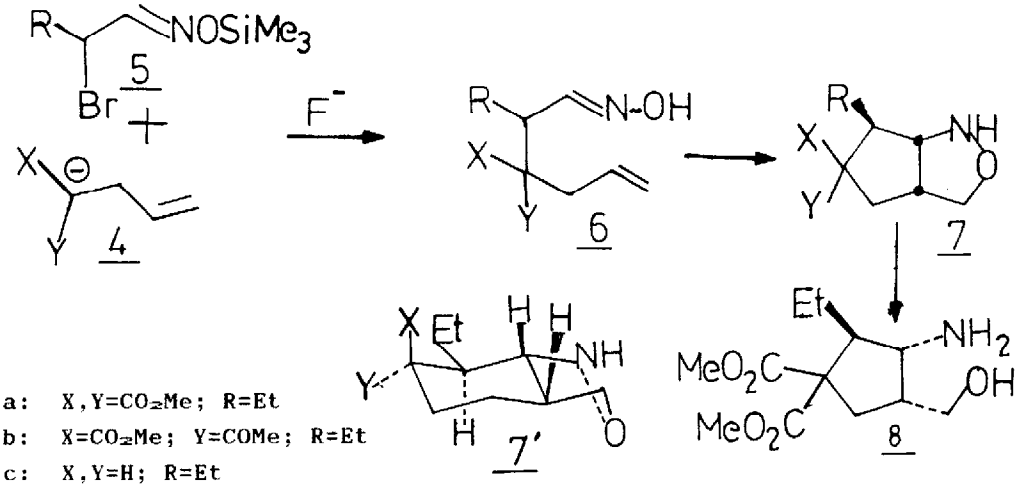
Summary: Thermal intramolecular oxime olefin cycloadditions (IOOC) lead stereoselectively to 5-or 6-membered carbocycles fused to an isoxazolidine ring. This provides a useful entry in particular to stereospecifically functionalized cyclopentanes.

Carbocyclic ring formation with simultaneous stereospecific introduction of two functional groups is of key interest in synthetic organic manipulations. Among such reactions intramolecular dipolar cycloadditions, for instance nitrile oxide-olefin[2] or nitrone-olefin cycloadditions,[3] occupy a prominent place. Recently Grigg and coworkers[4] as well as Padwa et al[5] demonstrated that under proper conditions, e.g. by employing electron deficient olefins as Michael acceptors, even oximes can undergo cycloadditions to multiple bonds. Hassner et al[6] have successfully shown that unsaturated oximes **1**, possessing an amine function, undergo intramolecular oxime-olefin cycloadditions (IOOC) to produce **3** with high stereoselectivity under thermal conditions, without the aid of an external reagent. A related ring closure was also accomplished by Heathcock et al.[7] It is still not clear whether the presence of an amine nitrogen exercises an assisting effect in the proton transfer from O to N (see intermediate **2**) in these reactions, . Hence, it was important to explore to what extend such oxime-olefin cycloadditions can be applied to formation of carbocyclic rings.



To this end, we investigated the generality of the cycloaddition of unsaturated oximes with formation of 5- and 6-membered carbocyclic rings and resulting stereochemical effects. A general entry into such system was desirable and we devised a simple synthesis of oxime olefins **6** by utilizing the α-bromooxime synthons **5**.[8] For instance, **4a** was shown to react with the O-silyl-α-bromoaldoxime 5 (R=Et) in the presence of fluoride ions to produce **6a** in good yield.[9] Most likely this reaction involves a nitrosoalkene intermediate[10] that is trapped by the carbanion. Though the unsaturated oxime **6a** did not cyclize under the mild conditions used for **1** (80°C) even in the presence of $ZnCl_2$, it did cyclize in a sealed tube at 190°C to provide **7a** as a single stereoisomer in 81% yield.[9] Hence, the cycloaddition had resulted in a stereospecific introduction of three stereocenters.

The structure assignment is based on ^1H and ^{13}C NMR, mass spectra and reduction (H_2 /Pd/C) to the amino alcohol **8a** in 68% yield. The ring junction protons in **7a** are as expected cis oriented and show coupling of 8 Hz (dihedral angle near 0°). The trans hydrogens (CHN and CHEt) also show an 8 Hz coupling constant indicative of a dihedral angle close to 180° and consistent with conformation **7'a**.

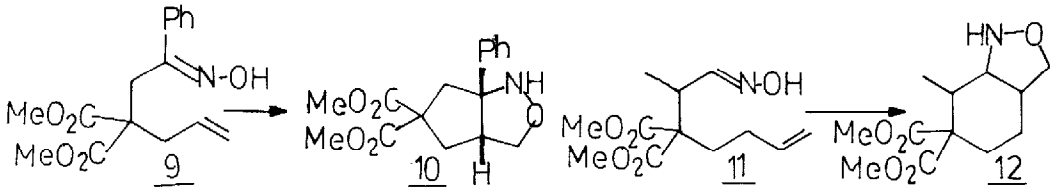


a: X,Y=CO_2Me; R=Et
b: X=CO_2Me; Y=COMe; R=Et
c: X,Y=H; R=Et
d: X,Y=H; R=Ph
e: X,Y=H; R=SO_2Ph

In a similar manner acetoacetate **4b** was converted into **6b** (81%), which on cyclization gave two diastereomers of 7b (63%). We were also successful in coupling the corresponding bromooximes 5 with an unsaturated

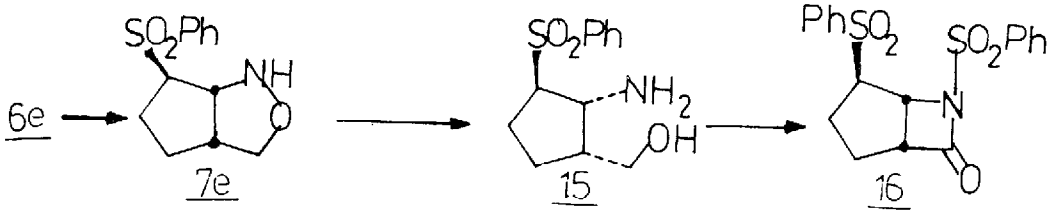
Grignard nucleophile, thus producing **6c** and **6d** respectively. These oximes likewise underwent the thermal stereospecific ring closure to **7c** and **7d** though in lower yields (55% and 61% respectively). The IOOC reactions were extended to cyclization of ketoxime **9** which provided **10** stereospecifically in 75% yield.

Cyclization with formation of cyclohexane rings was also possible. For instance, heating of **11** gave **12** in 51% yield, however the cycloaddition was not selective and a mixture of isomers resulted. On



the other hand, citronellal oxime **13** led stereospecifically and in 80% yield to the fused cyclohexane **14** when heated at 180°C for 5 h, whereas heating for 2 days at 80 °C gave **14** in only 22% yield.

Further synthetic utility of these reactions can be demonstrated by stereospecific conversion of the obtained β-amino alcohols to β-lactams. For instance, the fused isoxazolidine **7e** was transformed via the amino alcohol **15** to the fused β-lactam **16**.



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9. In a typical procedure, allyl malonate **4a** (3mmol) was stirred with NaH (3mmol) in 5 ml of dry DMF for 0.5 h under argon and cooled to 0°C. Tetrabutylammonium fluoride (1 mmol) in THF was added followed by dropwise addition of 1 mmol of O-trimethylsilyl-α-bromopropanaloxime **5**. The reaction mixture was brought to room temperature, stirred for 2 h and poured into an NH_4Cl solution. After extraction with ether, washing, drying and chromatography over silica gel (ether:petroleum ether=20:80), the unsaturated oxime **6a** was isolated as an oil in 90% yield. ^1H NMR: 7.31 (d, J=9Hz, CH=N), 5.7-5.85 (m, CH=C), 5.02-5.15 (m, CH_2=C), 3.73 (s, 2MeO), 2.77 (ddd, J=11, 9, 2.5 Hz, CH), 2.65 (dt, J=7, 1 Hz, CH_2C=C), 1.72 (ddd, J=15, 7, 2.5 Hz, 1H), 1.20-1.44 (m, 1H), 0.90 (t, J=7 Hz, Me). MS CI $C_{12}H_{19}NO_5$ 258 (100%, $(MH)^+$).

A solution of 55 mg of **6a** in 5 ml of toluene in a sealed tube was heated at 190°C for 5 h until tlc indicated complete consumption of starting material. Chromatography over silica (ether:petroleum ether=60:40) gave 45 mg of isoxazolidine **7a** (81%). ^1H NMR: 5.18 (br s, 1H), 3.72 (s, 6H), 3.67 (t, J=8Hz, 1H), 3.44 br dd, J=9, 6.5 Hz, 1H), 3.30 (dq J=9.5, 8.5, 8, 6.5 Hz), 2.59 (dd, J=13.5, 8.5 Hz, 1H), 2.27 (dd, J=10.8, 4.5 Hz, 1H) 1.85 (dqd, J=13.5, 7.5, 4.5 Hz, 1H), 1.77 dd, J=13.5, 9.5 Hz), 1.31 (1H, ddq, J=13/5, 10, 7.5), 1.03 (t, J=7.5 Hz, 3H). ^{13}C-NMR: 171.31 (s), 171.81 (s), 77.68 (t), 71.99 (d), 63.94 (s), 52.89 (d), 52.35 (q), 52.05 (q), 46.87 (d), 40.40 (t), 24.22 (t), 12.63 (q). MS CI $C_{12}H_{19}NO_5$ 226 (60%, M-HNO), 225 (100%, M-MeOH).

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