

INTRAMOLECULAR DIELS-ALDER CYCLOADDITION OF ISOXAZOLE DERIVATIVES
CATALYZED BY BRÖNSTED ACIDS

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Abstract-Isoxazoles 3c-e undergo intramolecular Diels-Alder cycloaddition
at 200°C only in CHCl_3 solution or in toluene with CF_3COOH catalysis.

The recently reported¹ observation that 3-methyl-5-vinylisoxazole can undergo
Diels-Alder cycloaddition to activated dienophiles, prompted us to test the possi-
bility of achieving the intramolecular cycloaddition,² as a new way for the synthe-
sis of selectively functionalized polycyclic compounds.

The substrates for the cycloaddition reaction are easily obtained, with high
yields, by a Wittig reaction of the phosphorane 1³ with unsaturated aldehydes
(Table I)⁴. Always mixtures of E and Z isomers are obtained, the ratio changing in
dependence of the base used. The isomers can be separated easily by flash chromato-
graphy, but are generally used without separation for the thermal reactions, since
the single E and Z isomers would bring to the same mixture of diastereoisomeric
cycloadducts. Only in one case (entry d) the mixture has been submitted to flash
chromatography to get an unseparable mixture of the pair of isomers with the fixed
E stereochemistry at the dienophile part of the molecule.

By heating the compound 3a in toluene in a sealed tube 20h at 200°C only the E
phenol 4⁴ is obtained quantitatively, arising from a Claisen rearrangement. The
isoxazole 3b, in refluxing mesitylene (164°C), affords the compound 5⁴ in 58%
yield, i.e. the product of a Claisen-Cope rearrangement. Heating of the isoxazoles

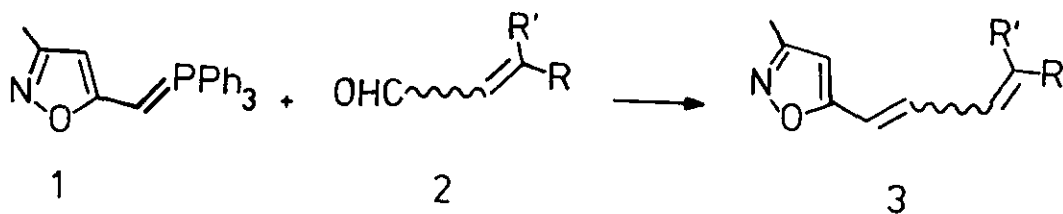
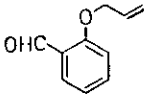
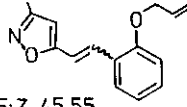
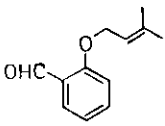
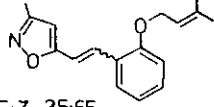
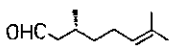
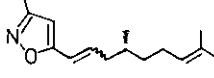
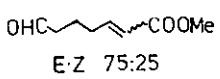
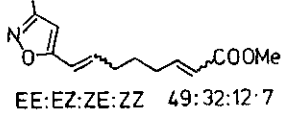
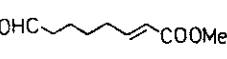
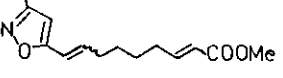
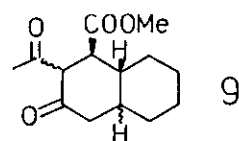
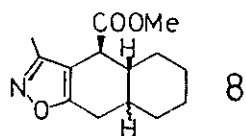
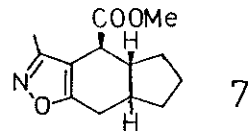
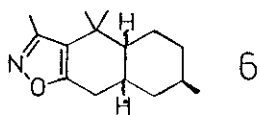
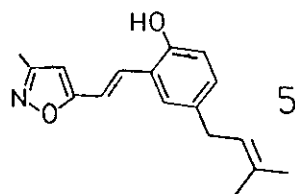
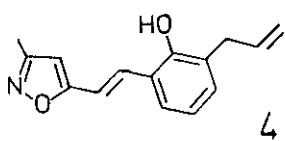


TABLE I

entry	aldehydes 2	reaction conditions	products 3	yield%
a		24h, rt tBuOK	 E:Z 45:55	83
b		4h, rt NaNH ₂	 E:Z 35:65	98
c		1h, -78° 14h, rt BuLi	 E:Z 55:45	98
d	 E:Z 75:25	1h, -78° 14h, rt BuLi	 EE:EZ:ZE:ZZ 49:32:12:7	79
e		1h, -78° 3h, rt BuLi	 E:Z 57:43	60



3c-e in the same conditions for longer periods leads to the almost complete recovery of the starting materials, together with unidentified decomposition products, particularly in the case of compounds 3d-e.

Attempts to obtain the cycloaddition reaction by the catalysis of Lewis acids like AlCl_3 ⁵ or EtAlCl_2 ⁶, Bentonite- Fe^{3+} ⁷ or radical cations like Bentonite- Fe^{2+}/t -Butylphenol⁸ with the substrates 3c or 3e failed.

To our surprise, running the thermal reaction of the substrates 3c-e in CHCl_3 solution⁹ in a sealed tube over 150°C, the cycloadducts were observed by GC-MS monitoring. The isoxazole 3c, after 48h at 200°C, showed only a 10% conversion to a mixture of cycloadducts 6 (broad peak by GC-MS). The more activated substrates 3d and 3e, however, after 36h¹⁰ gave the respective cycloadducts 7 and 8 as mixtures of their cis and trans stereoisomers (related to the carbocycle rings fusion) in 3:1 and 1.2:1 ratio respectively.¹¹ The aromatized product is the only one detected by GC-MS, in accord to previous observations.¹ The ring-fusion position adjacent to the carbomethoxy group with the hydrogen cis to the ester function relies on the E stereochemistry of the dienophile part of the starting material. The complexity of the spin system associated with the bridged protons doesn't allow the assignment of the cis/trans stereochemistry to the isomers.

The absence of any cycloaddition product when O,N-bistrimethylsilylacetamide (BSA)¹² is added to the reaction mixture, indicates that the cycloaddition reaction is catalysed by the acidity arising from thermolysis of CHCl_3 . However, no trace of the cycloadducts is observed by leaving the substrate 3d in CHCl_3 solution for one month. The Brønsted acid catalysis at high temperature is also demonstrated by the obtainment of the cycloadducts 7 by heating the substrate 3d in toluene in a sealed tube at 180°C with addition of 0.5 equiv. of CF_3COOH . The same reaction mixture doesn't give any trace of the cycloadducts at room temperature.

To our knowledge this is the first example where the CHCl_3 is able to behave as an acid catalyst in a Diels-Alder reaction. Since P. Laszlo¹³ reports that "the acids of Brønsted type are, practically, inefficient" for the Diels-Alder reaction, the activation process observed by us needs a deeper investigation.

The synthetic application of the vinylisoxazole route to functionalized polycyclic compounds, shown by the obtainment of decalone 9^{4,14} by Ni/Raney cleavage of the isoxazole ring, will be the object of further studies in our group.

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9. CHCl₃ used (RPE Carlo Erba supply) was washed three times with water, dried over Na₂SO₄ and distilled. However, no appreciable differences are observed using the solvent without any purification, apart from evidence of partial transesterification.
10. The reactions were run in a sealed tube at 200°C with 0.15 M solution of the substrates, added of 10 mol% of hydroquinone.
11. The dark brown reaction mixtures were passed through a short pad of silica gel to give light brown oils (92% and 78% for 3d and 3e respectively) gaschromatographically pure (GC-MS: Hewlett-Packard 5790A/5970A, capillary column Heliflex coated with RSL-150 30m x 0.25mm, Helium flow 1 ml/min, 2 min at 150° then 10°/min rate). The NMR spectra however show traces of starting materials hardly removed even by repetitive flash chromatography or preparative TLC.

7 RT 8.10 (major), 8.28 (minor); MS m/e(%): 235 (6, M⁺), 177 (20), 176 (100, M⁺-COOMe); ¹H-NMR: δ 3.74 (s, 3H, major isomer), 3.70 (s, 3H minor), 3.45-2.80 (m, 3H), 2.60-1.10 (m, 8H), 2.18 (s, 3H, minor), 2.08 (s, 3H, major); ¹³C-NMR (major isomer): δ 173.3, 169.5, 157.3, 111.7, 51.8, 47.2, 43.9, 42.7, 30.1, 28.5, 28.4, 23.2, 9.9.

8 RT 9.86 (major), 9.92 (minor); MS m/e(%): 249 (6, M⁺), 191 (25), 190 (100, M⁺-COOMe); ¹H-NMR: δ 3.77 (s, 3H, major isomer), 3.72 (s, 3H, minor), 3.40-3.00 (m, 1H), 2.80-2.60 (m, 2H), 2.50-1.10 (m, 10H), 2.20 (s, 3H, minor), 2.10 (s, 3H, major); ¹³C-NMR (major isomer): δ 173.6, 167.2, 156.9, 109.8, 51.8, 45.5, 42.2, 38.1, 33.7, 29.4, 25.4 (2C), 23.6, 9.7.
12. For the ability of BSA to act as an acid scavenger see B.M. Trost, M. Lautens and B. Peterson, Tetrahedron Lett., 1983, 24, 4525.
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14. 9 MS m/e(%): 252 (6, M⁺), 193 (100), 151 (17), 150 (3), 43 (37); ¹H-NMR: δ 3.70 (s, 3H), 3.25 (m, 1H), 2.50-2.00 (m, 3H), 2.05 (s, 3H), 1.85-1.10 (m, 10H).

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