[4+2] CYCLOADDITIONS OF 3-METHYL-5-VINYLISOXAZOLE

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Abstract – 3-Methyl-5-vinylisoxazole is reported to undergo Diels-Alder cycloadditions with activated dienophiles

Use of isoxazole derivatives in organic synthesis has received a wide interest by organic chemists, but little has been done on the utilization of such compounds as part of a diene system capable to undergo [4+2] cycloadditions. Several diene systems present in heterocyclic or vinyl-heterocyclic compounds have been reported to undergo Diels-Alder cycloadditions,[1-4] but 2,1-benzisoxazole represents the sole known example involving isoxazole derivatives.[5] Therefore, the cycloaddition of 3-methyl-5-vinylisoxazole (**4**) to activated dienophiles, here described, appears to be unprecedented. In view of the easy isoxazole ring-opening,[6] this reaction represents a valuable step to functionalized cyclic compounds.

The 5-vinylisoxazole **4** has been reported as a minor product of the acetonitrile oxide cycloaddition to vinylacetylene,[7] the addition to the double bond being predominant. Thus, the depicted two-step procedure has to be preferred for the higher overall yield (50%) and easier product isolation.

4 + **RHC=CHR'** → **6** → **7**

5
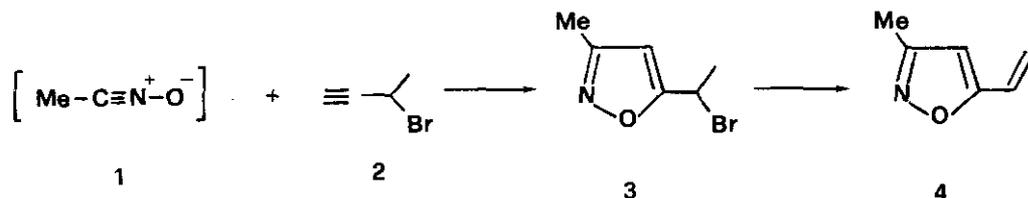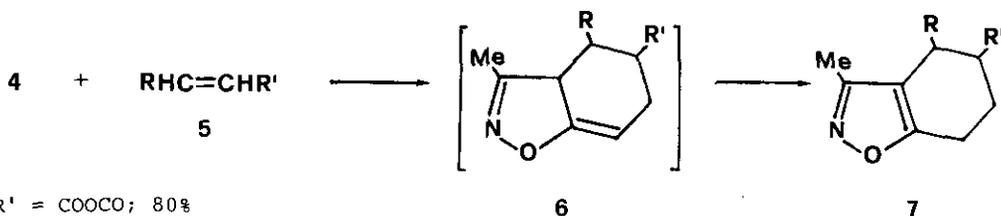
a : R-R' = COOCO; 80%
b : R = COMe, R' = H; 25%
c : R = COOMe, R' = H; 6%

Cycloaddition reactions of **4** were performed in a sealed tube in benzene solution at 120°C for 3 days. Hydroquinone was added to the reaction mixtures of the dienophiles **5b** and **5c** in order to reduce, but not to avoid, polymerization and copolymerization of the vinyl derivatives: these reactions are mainly responsible for the low yields observed in these cases. Aromatization of the isoxazole ring, *via* a 1,3-proton shift, occurs readily in the reaction conditions allowing the direct isolation of compounds **7** ; only the intermediate **6b** has been detected in the mass spectrum of the raw reaction material. The G.C. report on the crude reaction mixture from **5b** shows two peaks at RT 9.84 and RT 11.74 with the same molecular ion (see experimental section): the first compound has been assigned the structure **6b** on the basis of the preferred *retro* Diels-Alder fragmentation. This compound rearranges completely, during flash column chromatography of the reaction mixture, to the second product (RT 11.74) **7b** .

The regiochemistry of products **7b** and **7c** has been established on the basis of spectroscopic data. The proton NMR spectra show three sets of signals with ratios 1:2:4 for the protons of the six-membered ring, in agreement with the proposed regiochemistry. Furthermore, in a double resonance experiment on the compound **7b**, irradiation in the range of shielded methylene protons (2.20-1.70 δ) caused the multiplet resonances at δ 3.55 (1H) and 2.68 (2H) to collapse in two broad singlets.

The observed regioselectivity to the "ortho" substituted tetrahydrobenzisoxazoles **7b,c** is consistent with considerations on the Frontier Orbital interactions[8] and is in agreement with the regiochemistry observed with other vinyl heterocycles.[1,3,4]

A comparison between the reactivities of the vinylisoxazole **4** and of other vinyl derivatives of five-membered heterocycles draws some considerations. A vinylisoxazole would be expected to react as a diene better than vinyl derivatives of other five-membered heterocycles, due to the lower aromaticity and the higher 4-5 bond order.[9] The isoxazole ring has been described in fact as "an imine, the effect of oxygen being mainly to hold the imine chain in a fixed configuration".[10] Nevertheless, the actual behaviour suggests that the electron-deficiency experienced by the diene system in **4** is responsible for its lower reactivity and the Frontier Orbital interactions are predominant over any consideration on aromaticity and bond fixation.

The wider application and the synthetic utilization of this new diene system will be the object of further studies in our group.

EXPERIMENTAL

Melting points were determined on a microscope RCH Kofler apparatus, and are uncor-
rected. IR spectra were measured on a Perkin-Elmer 283 spectrophotometer; ^{1}H-NMR
spectra on Perkin-Elmer R 32 (90 MHz) and Varian XL-200 (200 MHz) spectrometers;
^{13}C-NMR on a Varian FT-80A (20 MHz) spectrometer. Gas chromatograms and Mass spec-
tra were carried out on a Hewlett-Packard 5790A gas-chromatograph (capillary column
OV 1, 25 m, 0.2 mm I.D.) connected with a Hewlett-Packard 5970A mass selective de-
tector. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh)
and short column chromatography on Merck silica gel 60 (70-230 mesh). All solvents
and reagents were dried and distilled before use.

5-(1-*Bromoethyl*)-3-*methylisoxazole* (**3**).
Phenyl isocyanate (40 mmoles = 4.76 g) was added to a solution of 3-bromobut-1-yne
(**2**, 20 mmoles = 2.66 g) in 20 ml of dry benzene, stirred at r.t. under positive ni-
trogen pressure, followed by a slow addition of a mixture of nitroethane (22 mmoles
= 1.651 g) and triethylamine (0.2 ml) in benzene (5 ml). The reaction mixture imme-
diately got coloured, then crystals of diphenylurea slowly precipitated, under spon-
taneous reflux of the solvent. After 4h stirring, an equal volume of dry diethyl e-
ther was added and the solid filtered off and thoroughly washed with ether. The oil
obtained after concentration, distilled by Kugelrohr (80°C, 0.06 torr), gave 3.043 g
of **3** as a pale yellow oil (yield 80%).
^{1}H-NMR (CDCl$_3$): δ 6.12 (s, 1H), 5.14 (q, J=7 Hz, 1H), 2.27 (s; 3H), 2.15 (d, J=7 Hz,
3H). ^{13}C-NMR (CDCl$_3$): δ 171.2, 159.4, 101.8, 34.5, 23.4, 10.9. IR (CCl$_4$): 2980, 2930,
2870, 1605, 1440, 1415, 1375, 1335, 1265, 1225, 1175, 1130 cm^{-1}. MS: m/z (%) 191 and
189 (4, M$^+$), 134 and 132 (60), 110 (45), 79 (19), 55 (39), 53 (76), 42 (100). (Found:
C, 38.88; H, 4.34; N, 7.76%. Calc for C$_6$H$_8$BrNO: C, 38.73; H, 4.33; N, 7.53%).

3-*Methyl*-5-*vinylisoxazole* (**4**).
The substituted isoxazole **3** (5 mmoles = 0.95 g) was added to a suspension of potas-
sium *tert*-butoxide (10 mmoles = 1.12 g) and dibenzo-18-C-6 (0.25 mmoles = 90 mg) in
dry benzene (20 ml) stirred under nitrogen and cooled in ice. The solution became
coloured and monitoring by TLC (light petroleum + AcOEt 20%) showed the reaction to
be complete after 1h. The reaction mixture was diluted with light petroleum (bp 30-
50°C) and washed with ammonium chloride sat. aq. sol. (2 x 25 ml), then with water.
The organic solution dried and concentrated gave an oil which was subjected to Ku-
gelrohr distillation (60°C, 5 torr) to give 345 mg (yield 60%) of **4** as a colourless
volatile oil.
By using 1.5 eq of butoxide and 2 mol % of 18-C-6 in the same conditions a 50% yield
was obtained.

^{1}H-NMR (CDCl$_3$): δ 6.60 (dd, J=20,12 Hz, 1H), 6.04 (s, 1H), 5.95 (dd, J=20,1.6 Hz, 1H), 5.53 (dd, J=12,1.6 Hz, 1H), 2.26 (s, 3H). ^{13}C-NMR (CDCl$_3$): δ 167.8, 159.8, 122.3, 119.9, 102.0, 11.2. IR (CCl$_4$): 2970, 2930, 2860, 1605, 1570, 1450, 1415, 1375, 1285, 1275, 1180 cm^{-1}. MS: m/z (%) 109 (100, M$^+$), 82 (75), 80 (11), 55 (66), 54 (40), 39 (33). GLC (carrier gas He, 1.5 Kg/cm^2; 2 min at 50°C, then 5 deg/min ramp): RT 3.48 (99%).

4,5,6,7-*Tetrahydro-3-methyl-1,2-benzisoxazole-4,5-cis-dicarboxylic Anhydride* (**7a**).

A suspension of the vinylisoxazole **4** (1 mmole = 109 mg) with maleic anhydride (**5a**, 3 mmoles = 294 mg) in dry benzene (0.5 ml) was placed in a sealed tube. After 3 days at 120°C the solution was concentrated *in vacuo* to remove all volatiles (solvent and excess of maleic anhydride). The residue was passed through a short pad of silica gel (eluant diethyl ether), the solvent concentrated to give a white crystalline solid, mp 156-157°C (166 mg, 80%) corresponding to **7a**.

^{1}H-NMR (CDCl$_3$): δ 4.15 (dt, J=9,1 Hz, 1H), 3.61 (dt, J=9,4 Hz, 1H), 2.92-1.90 (m, 4 H), 2.41 (s, 3H). ^{13}C-NMR (CDCl$_3$): δ 171.2, 169.0, 167.8, 158.1, 104.8, 40.2, 38.3, 20.9, 19.4, 10.1. IR (CDCl$_3$): 2940, 1870, 1800, 1785, 1640, 1460, 1440, 1425, 1285, 1240, 1205, 1070, 1055 cm^{-1}. MS: m/z (%) 207 (30, M$^+$), 135 (100), 134 (28), 120 (10), 106 (23), 93 (43), 66 (60), 51 (15). (Found: C, 57.96; H, 4.57; N, 6.73%. Calc for C$_{10}$H$_9$NO$_4$: C, 57.97; H, 4.38; N, 6.76%).

4-*Acetyl-4,5,6,7-tetrahydro-3-methyl-1,2-benzisoxazole* (**7b**).

A solution of the vinylisoxazole **4** (1 mmole = 109 mg), methyl vinyl ketone (**5b**, 5 mmoles = 350 mg) and hydroquinone (0.05 mmoles = 5 mg) in dry benzene (0.5 ml) was placed in a sealed tube and heated 3 days at 120°C. GC-MS monitoring (carrier gas He, 1.35 Kg/cm^2; 2 min at 60°C, then 10 deg/min ramp) showed two peaks with RT 9.84 (**6b**) [m/z 179 (28%, M$^+$), 136 (50), 110 (13), 109 (100), 82 (47), 55 (28), 43 (34)] and RT 11.74 (**7b**, see below). The mixture was then passed through a short pad of silica gel to remove polymeric materials. Purification by flash chromatography (petroleum ether + AcOEt, 1:1) afforded 44 mg of an oil corresponding to the sole product **7b** (yield 25%).

^{1}H-NMR (CDCl$_3$): δ 3.55 (m, 1H, collapses in a broad singlet on irradiating at 2.20-1.70), 2.68 (t, J=4 Hz, 2H, collapses in a broad singlet on irradiating at 2.20-1.70), 2.20 (s, 3H), 2.20-1.70 (m, 4H), 2.13 (s, 3H). ^{13}C-NMR (CDCl$_3$): δ 207.8, 168.4, 157.9, 110.2, 45.3, 27.7, 26.0, 22.2, 20.3, 10.2. IR (CCl$_4$): 2980, 2950, 2860, 1725, 1645, 1460, 1445, 1430, 1360, 1170, 1115 cm^{-1}. MS: m/z (%) 179 (3, M$^+$), 136 (100), 108 (11), 95 (5), 94 (6), 82 (14), 67 (13), 55 (16), 43 (27). (Found: C, 67.03; H, 7.41; N, 7.83%. Calc for C$_{10}$H$_{13}$NO$_2$: C, 67.02; H, 7.31; N, 7.82%).

4-Carbomethoxy-4,5,6,7-tetrahydro-3-methyl-1,2-benzisoxazole (**7c**).

A mixture of the vinylisoxazole **4** (1 mmole = 109 mg), methyl acrylate (**5c**, 5 mmoles = 430 mg) and hydroquinone (0.5 mmoles = 55 mg) in dry benzene (0.5 ml) was heated 3 days in a sealed tube at 120°C. Flash chromatography (petroleum ether + AcOEt, 2:1) afforded 12 mg of a waxy solid (**7c**, 6%).

^{1}H-NMR (CDCl$_3$): δ 3.70 (s, 3H), 3.50 (m, 1H), 2.67 (m, 2H), 2.20 (s, 3H), 2.20-1.70 (m, 4H). ^{13}C-NMR (CDCl$_3$): δ 178.0, 173.2, 168.3, 109.9, 51.9, 36.7, 26.0, 22.2, 19.8, 10.1. IR (CCl$_4$): 2955, 2870, 1745, 1645, 1510, 1460, 1435, 1425, 1355, 1340, 1220, 1190, 1170, 1060 cm^{-1}. MS: m/z (%) 195 (8, M$^+$), 136 (100), 108 (5), 95 (3), 94 (3), 82 (9), 67 (9), 55 (11). (Found: C, 61.52; H, 6.47; N, 7.56%. Calc for C$_{10}$H$_{13}$NO$_3$: C, 61.53; H, 6.71; N, 7.17%).

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