INTRAMOLECULAR [3 + 2] CYCLOADDITIONS OF MESOIONIC CARBONYL YLIDES

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Summary: Intramolecular cycloadditions of isomünchnones, formed by rhodium acetate catalyzed decomposition of N-(diazoacetoacetyl)-alkenylamides, afford highly functionalized cycloadducts with regio- and stereochemical specificity.

The intramolecular reaction of carbenes with carbonyl groups results in the formation of cyclic carbonyl ylides. The requisite carbenes may be generated by photochemical or transition metal catalyzed decomposition of diazo compounds¹). This approach, pioneered largely by lbata and coworkers, allows a convenient generation of various five- or six-membered carbonyl ylides, which can be trapped with alkenes, alkines and hetero multiple bonds²). So far, however, only few examples are known, where such cyclic carbonyl ylides subsequently react with internal dipolarophiles^{3,4}). Surprisingly, the major class of cyclic carbonyl ylides, the isomünchnones⁵), has never been used in an intramolecular cycloaddition reaction, despite the obvious implications for natural product synthesis. Thus, depending on the internal dipolarophile (alkene or alkine), compounds containing annelated piperidines or furans should be easily accessible.



In this communication we report the realization of intramolecular isomunchnone cycloadditions with non-activated alkenes. The required acyclic diazo compounds were readily prepared by a two step sequence from the corresponding unsaturated benzylamides. According to the method of Doyle⁶), the benzylamides were treated with butyllithium at -78° C in tetrahydrofuran followed by the addition of diketene to afford the N-acetoacetyl compounds in about 50 % yield (80 % based upon recovered amide). The diazo group was then introduced with tosylazide/triethylamine in the usual way⁷). For the "tandem cyclization-cycloaddition reaction" a solution of the diazo compound in toluene (0.3 M) was added dropwise to a refluxing mixture of rhodium acetate (1-2 mol %) in the same amount of toluene. Rapid gas evolution occured, indicating the formation of the intermediate isomunchnone. After complete addition, the solvent was removed and the products were purified by flash chromatography (Table 1). Entries 1-6 in Table 1 demonstrate that the cycloadditions proceed in high yield⁸). Most notable is the fact that only one isomer is formed⁹). The ¹³C-NMR spectra clearly indicate the presence of cycloadducts by two characteristic signals between 92 and 107 ppm, which can be assigned to the O*C*(COCH₃)CON- and the hemiamidal-carbon¹⁰). The relative stereochemistry of cycloadduct **6** was established by an X-ray analysis, which



Table 1. Intramolecular Cycloadditions of Isomünchnones

showed that the addition of the olefin took place endo with regard to the 1,3-dipole and anti to the methyl group in the side chain¹¹). An X-ray structure for 6 is shown in Figure 1. Included, as well, are important bond lenghts and angles.

Figure 1.



On the basis of this X-ray analysis the stereochemistry of the remaining adducts was tentatively assigned as shown.

Furthermore, the effect of the electron withdrawing acyl group on the rate and stereochemical outcome of the cycloaddition was examined. Deacylation of the N-diazoacetoacetyl compounds 1 and 3 could be accomplished with

pyrrolidine (1.4 eq, CH₃CN, -20°C, 2 h) in high yield¹²⁾. The crude diazoacetyl compounds 13a,b were purified by flash chromatography and used directly for the cycloaddition reaction.



Under the same reaction conditions as above the yield for the cycloadducts **14a,b** decreases and compounds **15a,b** become byproducts. This could result from the addition of water to the intermediate isomunchnone. Other minor products, which are not cycloadducts were also found. Thus, without the acyl group, the reactivity of the **1,3-dipole** decreases and alternative pathways become competitive. The structure assignment of **14a,b** follows from the ¹H-NMR-data of proton H_a. In compound **14a** H_a appears as a dublett (δ = 4.76 ppm, J = 5.1 Hz), which is in agreement with vicinal angles to the neighboring protons of 30 and 90°, respectively. The same coupling constant is found for **14b** (δ = 4.59 ppm, J = 5.1 Hz). Such values are only possible, if the adducts result from an endo approach of the olefin to the carbonyl ylide.

Selective modification of the cycloadducts is exemplified by the reductive opening of the epoxy bridge in compound 4. Thus, treatment of 4 with four equivalents of triethylsilane and two equivalents of boron trifluoride etherate (CH₂Cl₂, -20°C \rightarrow RT, 6 h) afforded the annelated piperidine 16 in 68 % yield.



The relative stereochemistry of 16 was established on the basis of the coupling constants of H_d (δ = 3.67 ppm), which showed two trans-diaxial couplings of J = 9.5 Hz and one axial-equatorial coupling of J = 6.8 Hz.

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- All cycloadducts gave satisfactory elemental analysis and were fully characterized by spectroscopic means. Data for compound 6: m.p. 121-122°C (MeOAc-hexanes); IR υ_{max} (KBr) 2950, 1730, 1700, 1400, 1360, 1235, 1070, 935, 700 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.84 (d, 3H, J = 6.8 Hz, Me), 1.13 (d, 3H, J = 7.1 Hz, Me), 1.36-1.45 (m, 1H), 1.61-1.72 (m, 2H), 1.86-2.06 (m, 2H), 2.18-2.28 (m, 1H), 2.20 (dq, 1H, J = 3.4, 7.1 Hz) 2.39 (s, 3H, CH₃CO), 4.32, 4.50 (2d, 1H each, J = 15 Hz, PhCH₂), 7.28-7.33 (m, 5H_{arom}); ¹3C-NMR (100 MHz, CDCl₃) δ 201.59 (MeCO), 170.77 (amide-CO), 136.95, 128.64, 128.34, 127.85 (benzyl-C), 106.20 (hemiamidal-C), 94.29, 54.94, 46.41, 43.56, 32.49, 32.14, 27.56, 15.40, 12.56; MS *m/e* (%) 314 (2), 313 (M+, 8), 271 (5), 258 (5), 180 (80), 109 (13), 91 (100).
- 9. All cycloadducts are racemic; only one enantiomer is depicted.
- The chemical shift values (CDCl3, ppm) for these carbons are as follows: 2 (93.23, 106.42); 4 (95.41, 105.64); 6 (94.29, 106.20); 8 (93.18,95.65); 10 (92.48, 97.96); 12 (97.4, 104.43).
- Crystals were grown from dichloromethane-hexanes; further details of the structure determination are deposited at the Fachinformationszentrum Energie, Physik, Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (West-Germany). These data are available with quotation of the registry number CSD-52852, the authors, and the reference to this publication.
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