Nonstereospecific 1,3-Dipolar Cycloadditions — LUMO$_{\text{Dipole}}$-HOMO$_{\text{Dipolarophile}}$ Controlled Reactions

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Dedicated to Prof. Dr. H. Offermanns on the occasion of his 60th birthday.

Abstract: FMO-theory predicts a two-step mechanism accompanied by nonstereospecificity for 1,3-dipolar cycloadditons if one HOMO-LUMO interaction dominates the other one. R. Huisgen proved this phenomenon for the combination of electron-rich thiocarbonyl ylides with electron-poor dipolarophiles. For the first time we report on nonstereospecific reactions of electron-poor 1,3-dipoles 1 and 5 with the electron-rich *trans*-enamine 2. © 1998 Elsevier Science Ltd. All rights reserved.

According to the Woodward-Hoffmann rules 1,3-dipolar cycloadditions are expected to occur in a stereospecific suprafacial manner due to the symmetry of the participating molecular orbitals.[1] Nonconcerted nonstereospecific cycloadditions are not excluded completely but until 1986 there was lack of experimental evidence (former reports of Dorn, Ozegowski and Gründemann about nonstereospecific cycloadditions of stable azomethine imines[2] had to be revised).[3, 4] The first examples experimentally proved were brought up by Huisgen, who found that the combination of electron-rich thiocarbonyl ylides with the electron-poor dipolarophiles dicyanomaleate and dicyanofumarate results in nonstereospecific 1,3-dipolar cycloadditions.[5, 6, 7] This can be explained by postulating a zwitterionic intermediate in the course of a two-step, nonconcerted 1,3-dipolar cycloaddition. FMO-theory delivers the theoretical background, since for reactants with very different orbital energies the LUMO$_{\text{dipole}}$-HOMO$_{\text{dipolarophile}}$ interaction can be neglected compared to the HOMO$_{\text{dipole}}$-LUMO$_{\text{dipolarophile}}$ interaction.

Quite recently we reported the synthesis of two new classes of colored, stable azomethine ylides 1 and 5,[8, 9, 10] electron-poor 1,3-dipoles which undergo fast additions especially to electron-rich dipolarophiles such as enolethers, enamines and ketene aminals. Kinetic investigations showed clearly that these reactions are LUMO$_{\text{dipole}}$-HOMO$_{\text{dipolarophile}}$ controlled, therefore they are the electronic counterparts to the Huisgen system. In this communication we report on nonstereospecific cycloadditions of 1 and 5 (R = *p*-tolyl) to (*E*)-1-N,N-dimethylamino-1-propene (2), a *trans*-enamine.

The reaction of the bicyclic azomethine ylide 1 with approximately one equivalent enamine 2 in acetonitrile at 20 °C results in almost quantitative formation of two diastereomeric cycloadducts 3 and 4, which can be separated by flash column chromatography.[11] It was impossible to elucidate structure and configuration of 3 and 4 by NMR-techniques alone. X-ray analysis proved the *trans*-configuration for compound 3 and the *cis*-configuration for 4, in both adducts the dimethylamino group appears in *endo*-position.[12]
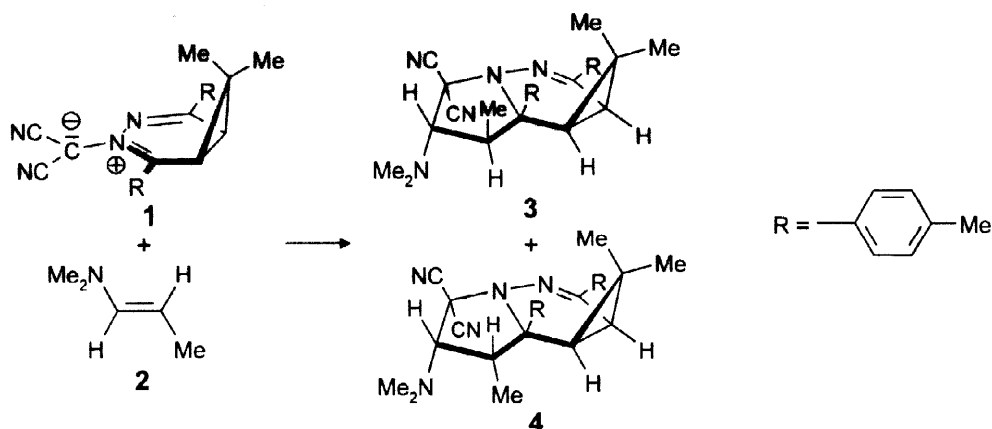
HPLC analysis showed that the formation of 3 and 4 is kinetically controlled. At 70 °C in acetonitrile both cycloadducts are still stable. Added cyclooctyne, a highly reactive dipolarophile, does not form any traces of cycloadduct therefore, no free azomethine ylide 1 can be detected in solutions of 3 or 4.

The isomer ratio 3 (*trans*-adduct) : 4 (*cis*-adduct) depends only scarcely on the polarity of the solvent used (CH_3CN: 48:52, CCl_4: 52:48, acetone: 56:44, dioxane: 65:35, toluene: 54:46).

Likewise, azomethine ylide 5 combines rapidly with the *trans*-enamine 2 in a nonstereospecific way leading again to a mixture of two diastereomeric cycloadducts 6 and 7.[13] The structures of the resulting compounds could be determined by X-ray[12] and ^{1}H-NMR analysis. Both products, the *trans*-adduct 6 and the *cis*-adduct 7, are formed in this reaction showing the *endo*-position of the dimethylamino group.[14] HPLC investigations showed that also the cycloaddition of azomethine ylide 5 with *trans*-enamine 2 is kinetically controlled (yield: 98 %) at 20 °C in acetonitrile. But in acetonitrile at 50 °C the cycloadducts 6 and 7 split into the starting compounds with rate constants of $1.06 \cdot 10^{-6}$ s^{-1} and $4.21 \cdot 10^{-5}$ s^{-1}.[15]

Furthermore, HPLC showed that the *trans* (6):*cis* (7)-ratio depends only little on the solvent used but due to the reversibility of the cycloaddition the obtained ratios are not so accurate (20 °C; CH_3CN: 45:55, CH_2Cl_2: 25:75, $CH_3CO_2C_2H_5$: 23:77, dioxane: 16:84, toluene: 10:90).
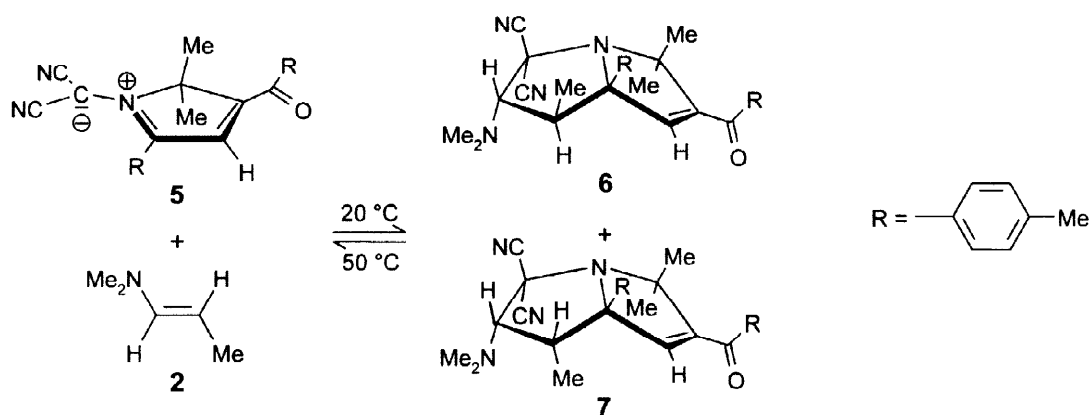
In analogy to Huisgen's results[4] we are inclined to explain the nonstereospecific cycloadditions of the electron-poor azomethine ylides 1 and 5 with *trans*-enamine 2 by a two-step reaction via zwitterionic intermediates such as 8 and 10 as shown for the reaction of 1 with 2. This mechanistic approach is also applicable for the reaction of 5 with 2. A preceding *trans-cis*-isomerism of the enamine 2 before the cycloaddition step can be excluded.[16]

Further investigations are under way to prove all reaction steps experimentally. In principle also a system of competing concerted and two - step cycloadditions has to be discussed.
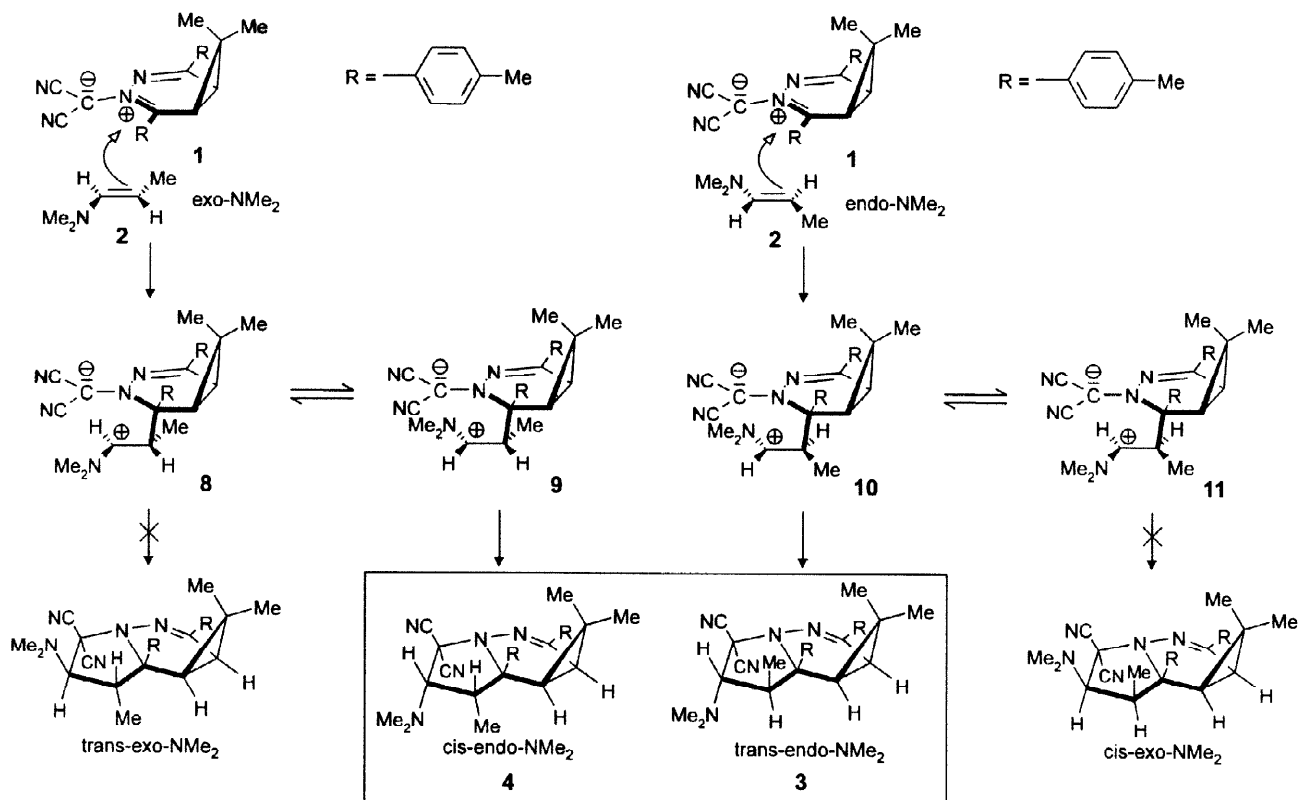
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11. To a solution of **1** (105 mg, 0.287 mmol) in acetonitrile (25 ml) protected by an atmosphere of nitrogen was added **2** (29.7 mg , 0.349 mmol) at ambient temperature. After 3 hours the solvent was removed and the residue separated by flash column chromatography (CH_2Cl_2, SiO_2). The adducts **3** and **4** were obtained after recrystallization from CH_2Cl_2/hexane. **3**: (51.3 mg, 40 %), colorless crystals. M.p. 208-209 °C. ^{1}H- NMR (250 MHz, $CDCl_3$, 24 °C, TMS): δ = 0.08 (s, 3H, CH_3), 0.96 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.73 (d, ^3J = 8.3 Hz, 1H, cyclopropyl-H), 1.78 (d, ^3J = 8.3 Hz, 1H, cyclopropyl-H), 2.34 (s, 3H, tolyl-CH_3), 2.36 (s, 3H, tolyl-CH_3), 2.65 (dq, ^3J = 12.4 Hz, ^3J = 6.6 Hz, 1H, $H_3CC\underline{H}$), 2.69 (s, 6H, NMe_2), 3.54 (d, ^3J = 12.4 Hz, 1H, $Me_2NC\underline{H}$), 7.09-7.24 (m, 4H, ArH), 7.27-7.31 (m, 2H, ArH), 7.67-7.70 (m, 2H, ArH). MS (EI-70 eV): 452 (3) [M$^+$], 366 (100) [ylide$^+$], 85 (25) [$C_3H_5NMe_2{}^+$]. Calcd.for $C_{29}H_{33}N_5$ (451.6): C,77.13; H, 7.37; N, 15.51. Found: C, 76.89; H, 7.41; N, 15.41. **4**: (59.4 mg, 46 %), colorless crystals. M.p. 215-216 °C. ^{1}H-NMR (250 MHz, $CDCl_3$, 24 °C, TMS): δ = 0.32 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.20 (d, ^3J = 7.0 Hz, 3H, CH_3), 1.70 (d, ^3J = 8.2 Hz, 1H, cyclopropyl-H), 1.78 (d, ^3J = 8.2 Hz, 1H, cyclopropyl-H), 2.32 (s, 6H, NMe_2), 2.36 (s, 3H, tolyl-CH_3), 2.36 (s, 3H, tolyl-CH_3), 2.76 (dq, ^3J = 7.0 Hz, ^3J = 4.7 Hz, 1H, $H_3CC\underline{H}$), 2.94 (d, ^3J = 4.7 Hz, 1H, $Me_2NC\underline{H}$), 7.11-7.36 (m, 5H, ArH), 7.57-7.60 (m, 1H, ArH), 7.69-7.72 (m, 2H, ArH). MS (EI-70 eV): 452 (3) [M$^+$], 366 (100) [ylide$^+$], 85 (24) [$C_3H_5NMe_2{}^+$]. Calcd. for $C_{29}H_{33}N_5$ (451.6): C, 77.13; H, 7.37; N, 15.51. Found: C, 76.92; H, 7.49; N, 15.34.

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13. A solution of **5** (305 mg, 0.829 mmol) in acetonitrile (10 ml) protected by an atmosphere of nitrogen was treated with **2** (150 mg, 1.76 mmol). After 4.5 hours at ambient temperature the diastereomers were separated by flash column chromatography (ethyl acetate/hexane 1:2, SiO_2) and recrystallized from ethyl acetate/hexane. **6**: (143 mg, 38 %), colorless crystals. M.p. 152-153 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 21 °C, TMS): δ = 0.59 (d, ^3J = 6.7 Hz, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.32 (s, 3H, tolyl-CH_3), 2.44 (s, 3H, tolyl-CH_3), 2.77 (s, 6H, NMe_2), 2.90 (dq, ^3J = 6.7 Hz, ^3J = 12.3 Hz, 1H, $H_3CC\underline{H}$), 3.69 (d, ^3J = 12.3 Hz, 1H, $Me_2NC\underline{H}$), 6.80 (s, 1H, olefinic-H), 6.80-7.26 (m, 4H, ArH), 7.27-7.33 (m, 2H, ArH), 7.76-7.84 (m, 2H, ArH). MS (EI-70 eV): 452 (2) [M$^+$], 367 (36) [ylide$^+$], 85 (100) [$C_3H_5NMe_2{}^+$]. Calcd. for $C_{29}H_{32}N_4O$ (452.6): C, 76.96; H, 7.13; N, 12.38. Found: C, 76.96; H, 7.21; N, 12.32. **7**: (158 mg, 42 %), colorless crystals. M.p. 142-143 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 21 °C, TMS): δ = 1.39 (d, ^3J = 7.3 Hz, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.33 (s, 3H, tolyl-CH_3), 2.39 (s, 6H, NMe_2), 2.43 (s, 3H, tolyl-CH_3), 2.57 (dq, ^3J = 5.4 Hz, ^3J = 7.3 Hz, 1H, $H_3CC\underline{H}$), 3.27 (d, ^3J = 5.4 Hz, 1H, $Me_2NC\underline{H}$), 6.62 (s, 1H, olefinic-H), 7.14-7.16 (m, 2H, ArH), 7.21-7.30 (m, 4H, ArH), 7.59-7.66 (m, 2H, ArH). MS (FD): 452 (100) [M$^+$]. Calcd. for $C_{29}H_{32}N_4O$ (452.6): C, 76.96; H, 7.13; N, 12.38. Found: C, 76.92; H, 7.25; N, 12.32.

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15. In order to measure the reaction rate solutions of **6** and **7** were treated with a large excess of cyclooctyne, a highly reactive 2π-compound, which rapidly traps the dipole **5** irreversibly.

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