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Stereo- and Spinselectivity of Primary (Singlet) and Secondary (Triplet) Norrish Type II Reactions[1]

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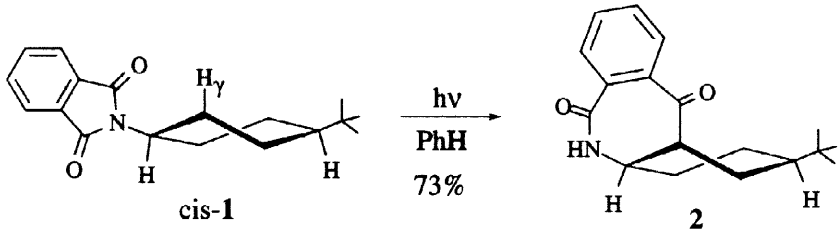
ABSTRACT : The influence of reactive conformation and substitution pattern on the Norrish Type II reactivity and selectivity of singlet-excited phthalimides was investigated. Only the cis-diasteroisomer of the 4-tert.-butyl cyclohexylamine derivatives **1** underwent Yang cyclization. The phthaloyl leucine esters **3a** and **3b** both gave primarily Yang cyclization with subsequent ring expansion. As a secondary photoreaction, **3a** gave Norrish II cleavage solely, wheras photolysis of the tert.-butyl ester **3b** resulted in a 1:1 mixture of Norrish II cleavage and Yang cyclization product **4** and **5**.

The reactivity and selectivity of electronically excited carbonyl compounds in CH-activation reactions have been studied in detail in the last decades.[2] One important influencing factor is the multiplicity of the substrate, i.e. the lifetime and the conformational flexibility are dictating the primary event of the reaction. After Norrish II abstraction of a hydrogen atom from the γ-CH-position, the competition of cleavage and Yang cyclization[3] are controlled by the geometry of the 1,4-biradical either during ISC (for triplets) or directly after CH-homolysis (for singlets).[4] Phthalimides are highly useful chromophors in order to study the behaviour of singlets because only the corresponding short-lived phthalimide singlets are capable of direct homolytic CH-activation (triplets are reactive in PET reactions).[5] Thus, the conformational situation at the ground state level can be correlated with its photochemical behaviour. We have studied this concept using the *cis*- and *trans*-1-tert.-butyl-4-phthalimido cyclohexanes **cis-1** and **trans-1**, respectively.



cis-**1** **2**

Scheme 1. Yang cyclization of cis-**1**

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In **trans-1** the phthalimido group is located in an equatorial position, for **cis-1** a twist geometry has been reported as the conformational ground state.[6] Wereas **cis-1** gave the tricyclic benzoazepine-1,5-dione **2**[7] in good yields upon irradiation, **trans-2** was not reactive. Molecular mechanics (MM2) and semiempirical (PM3) calculations indicated, that the most important factor for the reactivity of N-alkyl phthalimide singlets is the angle Δ (C-H··O=C) which (basis of calculation: 12 substrates) is 100±5° for reactive substrates and 82±5° for unreactive substrates.[8] The dihedral angle ω (C_α-C=O··H) can approach optimal values of 0° to maximum 35° for all substrates. The PM3-calculated Δ values of *cis*-**1** and *trans*-**1** are 101° and 88°, respectively. This correlation has also been found for the competition between (slow, but thermodynamically favourable) β- versus (rapid) γ- or δ-CH-abstraction in the photochemistry of N-phthaloyl α-amino acids.[9]

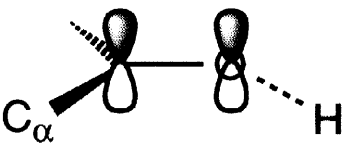
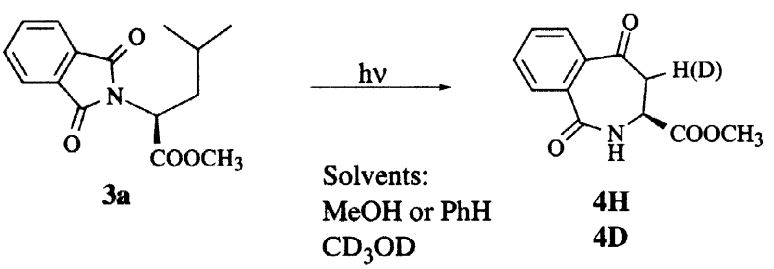


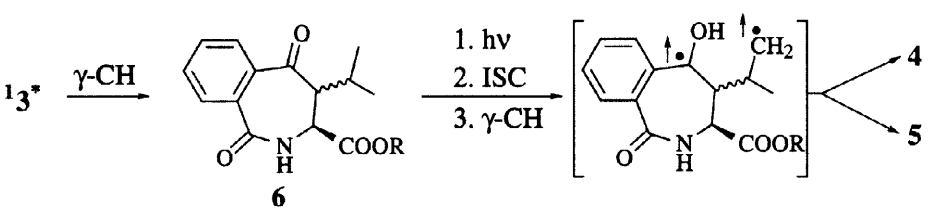
Fig.1 . Optimal approach for CH-abstraction

As conformationally more flexible model substrates, the leucine derivatives **3a** and **3b** were investigated.[10] The one-photon transformation reported for the isoleucine case was not observed for **3**, i.e. deuterium was incorporated at the α-position of product **4D** when the reaction was performed in deuterated methanol. Thus, a sequence of a primary (singlet) Yang cyclization and a secondary (triplet) Norrish II cleavage leads to the formation of the benzoazepine-1,5-diones **4**.



Scheme 2. Yang cyclization followed by Norrish II cleavage of **3a**

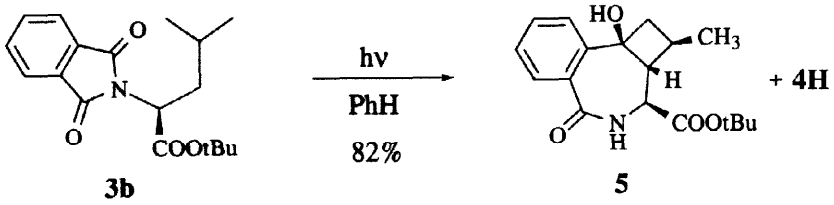
We were not able to detect (by NMR or GC) the intermediary isopropyl-substituted intermediate **6**. Thus, the secondary Norrish reaction must be much more efficient, at least by a factor of 50. This assumption is reasonable, because quantum yields for Norrish II cleavage reactions with triplet acetophenone analogs are in the order of 0.7 to 1.0,[11] whereas the corresponding reactions with singlet phthalimides are in the order of 0.02 to 0.05.[12]



Scheme 3. Mechanism of the photochemical transformations of leucine derivatives

A remarkable effect was observed with the N-phthaloyl leucin *tert.*-butyl ester **3b**: beside 50% of the regular Yang cyclization / Norrish II cleavage product **4H**, another 50% of a cyclobutanol **5** was observed. The tricyclic "double Yang product" showed only one set of resonance lines in proton and

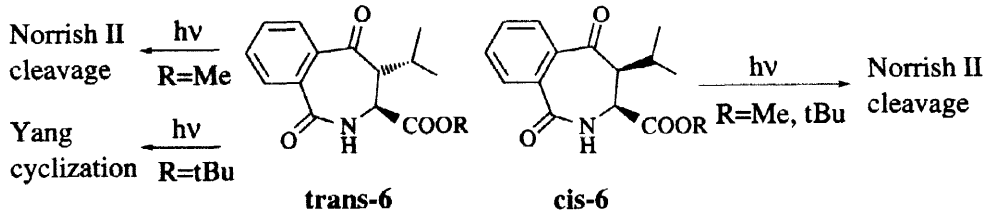
carbon NMR, indicating that only one out of 8 possible diastereo-isomers was formed. The X-ray structure analysis of 5[13] showed that the cyclobutane ring is *trans*-fused with respect to the ester group. Thus, the isoproyl group in the corresponding precursor molecule **X** also must be located *trans*.



3b **5**

Scheme 4. Two subsequent Yang cyclizations of **3b**

From molecular mechanics calculations we concluded the following mechanistic scenario: the methyl and the tert.-butyl ester **3a** and **3b** do not strongly differ with respect to their ground-state conformational distribution, i.e. *cis* and *trans*-**6** can be formed in both cases. Whereas for *cis*-**6** the Yang II cleavage process dominates irrespectively of the ester group, the diastereoisomeric intermediate *trans*-**6** prefers Yang cyclization in case of the tert.-butyl ester.



trans-6 **cis-6**

We are currently working on independent syntheses of compounds **6** in order to corroborate this unusual chemoselectivity which is correlated with the reactive conformations of the Norrish II biradical intermediates

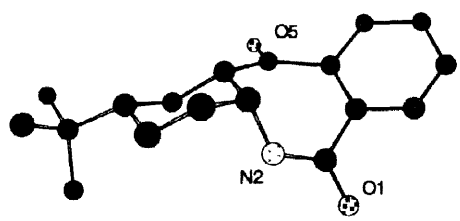


Fig. 2. Crystal structure of compound **2**

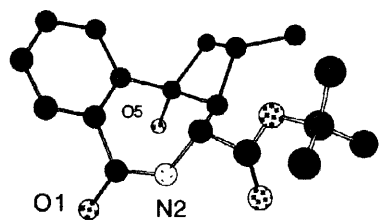


Fig. 3. Crystal structure of compound **5**

ACKNOWLEDGEMENT

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REFERENCES and NOTES

1. Part of the Ph.D. thesis of A. H., Univ. of Würzburg, 1996, and the projected Ph.D. thesis of W. K., Univ. of Cologne.

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3. The term *Yang cyclization* has been suggested by P. J. Wagner (ref. 2a) for the 1,4-biradical combination process of Norrish II biradicals.
4. e.g. Griesbeck, A. G., Henz, A., Hirt, J., Ptatschek, V., Engel, T., Löffler, D., Schneider, F. W. *Tetrahedron* **1994**, *50*, 701-714.
5. Griesbeck, A. G., Hirt, J., Peters, K., Peters, E.-M., von Schnering, H. G. *Chem. Eur J.* **1996**, *2*, 1388.
6. Booth, H., *Org. Magn. Res.* **1979**, *12*, 63.
7. The crystals of **2**[14] ($C_{18}H_{23}NO_2$, M = 285.39, from acetone) are monoclinic, space group $P2_1/n$, a = 1202.5(7), b = 1600.5(8), c = 876.6(3) pm; β= 109.53(3)°; V = 1590(1)x10^6 pm^3; Z = 4; d_{calc} = 1.192 g/cm^3. Data collection: Siemens R3m/V diffractometer, MoK_α, graphite monochromator, Wyckoff-scan, theta range [°] : 1.75-27.5, crystal dimensions: 0.2 x 1.15 x 0.15 mm; no. refl. measd.: 4010, no. unique refl.: 3645, no. refl. $F>3\sigma(F)$: 2679; R, R_w: 0.058, 0.054.- m.p.: 234-235°C.- IR (CCl_4): 2930, 1725, 1690, 1640, 1380, 1355, 1340 cm^{-1}.- ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.92 (s, 9H), 1.25 (m, 2H), 1.43 (m, 1H), 1.65-2.39 (4 m, 4H), 2.56 (m, 1H), 4.20 (m, 1H), 6.57 (s, 1H), 7.52-7.89 (m, 4H).- ^{13}C NMR ($CDCl_3$, 63 MHz) δ 21.1 (t), 23.5 (t), 29.8 (t), 27.4 (q), 32.7 (s), 47.3 (d), 47.8 (d), 56.5 (d), 128.0 (d), 129.4 (d), 132.0 (d), 132.1 (s), 137.2 (s), 170.1 (s), 205.1 (s).
8. This strict behaviour is less pronounced for ketones which have been intensively investigated in the solid state; e.g.: Scheffer, J. R., *Org. Photochem.* **1987**, *8*, 249.
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10. Griesbeck, A. G., Mauder, H., Müller, I. *Chem. Ber.* **1992**, *125*, 2467.
11. Lewis, F. D., Hilliard, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 3852.
12. Griesbeck, A. G., Hirt, J., Kramer, W., Dallakian, P. *Tetrahedron*, submitted.
13. The crystals of **5**[14] ($C_{18}H_{23}NO_4$, M = 317.38, from acetone) are monoclinic, space group $P2_1$, a = 847.5(1), b = 1042.7(2), c = 1060.4(2) pm; β = 111.851(5)°; V = 869.7(4)x10^6 pm^3; Z = 2; d_{calc} = 1.212 g/cm^3. Data collection: Siemens R3m/V diffractometer, MoK_α, graphite monochromator, Wyckoff-scan, theta range [°] : 1.75-27.5, crystal dimensions: 0.4 x 0.45 x 0.75 mm; no. refl. measd.: 4260, no. unique refl.: 3990, no. refl. $F>3\sigma(F)$: 3710; R, R_w: 0.048, 0.048.- m.p.: 203-204°C.-IR (CCl_4): 3398, 2926, 2855, 1734, 1719, 1651, 1459, 1370, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.90 (m, 1H), 1.20 (d, 6.0 Hz, 3H), 1.46 (s, 9H), 1.93 (m, 1H), 2.54 (dd, 8.4, 11.5 Hz, 1H), 3.07 (dd, 6.2, 11.5 Hz, 1H), 4.67 (dd, 5.8, 11.5 Hz, 1H), 7.38-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 20.6 (q), 25.5 (d), 27.9 (q), 40.0 (t), 57.7 (d), 61.7 (d), 74.3 (s), 83.3 (s), 125.1 (d), 129. 1(d), 130.8 (d), 130.9 (d), 134.9 (s), 138.8 (s), 169.0 (s), 170.0 (s).
14. The coordinates of **2** and **5** can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.