Diastereoselective Photocyclization to Dihydroindolinols

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Dedicated to Prof. U. Schmidt on the occasion of his 75 birthday

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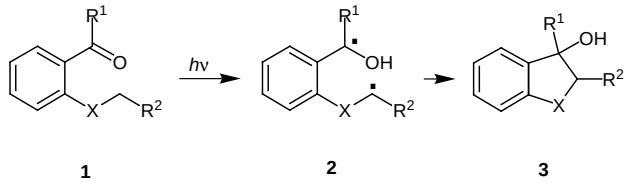
Abstract: Photocyclization of substituted *o*-aminophenylketone **1b** leads in high yields to indolinol **3b**. Depending upon the substituent R^2 and on the solvent either *cis*-products (**10**: R^2=COX) or *trans*-products (**12**: R^2=Ph) are formed predominantly.

Keywords: cyclizations, diastereoselectivity, indoles, substituent effect, photochemistry

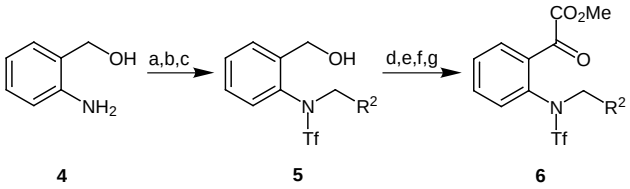
Dihydrobenzofuranols **3a** can be easily synthesized by Norrish-Yang photocyclization of phenylketones **1a**, whereby biradicals **2a** are the decisive intermediates.[1,2] Surprisingly, analogous photocyclizations of **1b** leading to dihydroindolinols **3b** were impossible until now.[3,4]



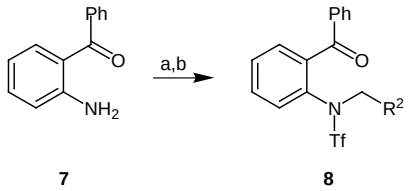
Scheme 1

Because some antagonists of neurotransmitters have dihydroindolinols as substructures,[5] it was appealing to find out whether appropriate conditions for a photoinduced ring closure of **1b** exist. From studies of photocyclization reactions of amino acids it is known that strong electron-withdrawing substituents at the nitrogen atom increase the yield of photocylization products.[6] We therefore introduced a trifluoromethanesulfonyl group at the aniline nitrogen of **1b** and observed photocyclizations to dihydroindolinols **3b** in high yields and high stereoselectivities. The phenyl ketones **6** and **8** were synthesized using standard procedures.[7,8,9]

Photolysis[10] of the ester or amide containing phenyl ketones **9a-c** led predominantly to *cis*-products *cis*-**10a-c** (Table 1).[11] Thus, from amide **9c** the *cis*-isomer **10c** is formed in 90% yield with a 98:2 *cis*:*trans* stereoselectivity. This *cis*-orientation of the OH- and the COX-groups is not unexpected because OH is less bulky than CO_2Me or Ph and it can form H-bridges with the COX substituent.



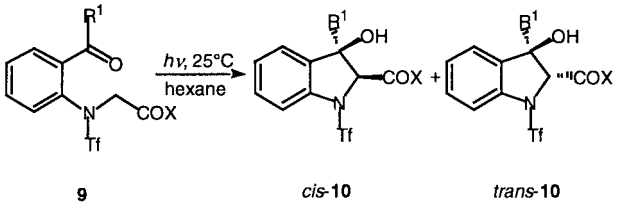
a: TBDMS-Cl, imidazole, 96%, b: Tf_2O, Na_2CO_3, 55%, c: Br-CH_2-R^2, K_2CO_3; HF, pyridine, 86-91%, d: PDC, 90-91%, e: NaCN, NH_4Cl, 84-96%, f: CH_3OH/HCl, 72-75%, g: CrO_3 / H_2SO_4, 20°C, 86-90%



a: Tf_2O, pyridine, 53%, b: Br-CH_2-R^2, K_2CO_3, 81-99%

Scheme 2

Table 1 Photocyclization of *o*-Carboxymethylaminophenylketones **9**

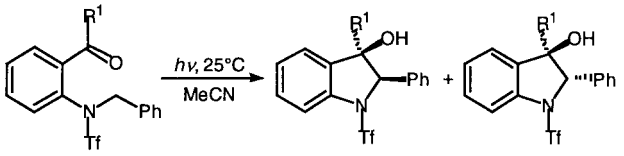


	R^1	X	*cis* : *trans*-**10**[a]	yield of **10** (%)
a	CO_2Me	OMe	71 : 29	85
b	Ph	OMe	92 : 8	83
c	Ph	$N(CH_2)_4$	98 : 2	90

[a] Determined by GC and ^{1}H-NMR spectroscopy.

Surprisingly, the corresponding phenyl substituted photoeducts **11a**,**b** yielded mainly *trans*-**12a**,**b**,[12] the less stable products where the bulky groups R^1 and Ph are *cis* to each other (Table 2). Starting from **11a** products **12a** are formed in 90% yield with a 4:96 *cis*:*trans* ratio.

Table 2 Photocyclization of *o*-Benzylaminophenylketones **11**

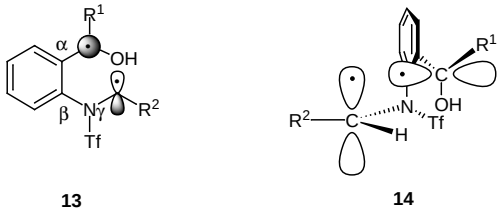


11 *cis*-**12** *trans*-**12**

	R^1	*cis* : *trans*-**12**[a]	yield of **12** (%)
a	CO_2Me	4 : 96	75
b	Ph	11 : 89	79[b]

[a] Determined by GC and ^{1}H-NMR spectroscopy. [b] Dehydration to the indole is observed during work up.

The photochemistry starts by intramolecular H-abstraction from triplet ketones.[13] For a cyclization of the intermediate biradical a triplet-singlet interconversion has to occur. This interconversion is favored by a twisted conformation **13** in which two radical p-orbitals can interact with each other.[14] *Ab initio* calculations[15] demonstrate that in analogous monoradicals the barriers of rotation around the benzylic α-bond are much higher than those around the β- and γ-bonds. If this holds also for triplet biradical **13**, the conformation **14** in which the OH-group adopts a sterically favorable conformation can be reached easily. Triplet-singlet interconversion of **14** and a rapid cyclization of the singlet biradical[16] leads to the thermodynamically less favored *trans*-products (**11** → *trans*-**12**). In reactions where R^2 carries a carbonyl group intramolecular H-bridging between the hydroxyl and carbonyl groups can overcompensate the steric effect.[2] This leads to a predominant formation of *cis*-products (**9** → *cis*-**10**).



13 **14**

Figure

In polar solvents the amount of *trans*-products increases because polar solvents increase the bulk of the OH-group by solvation and break possible H-bridges between the hydroxyl and carbonyl groups.[2] These solvent effects are shown in Table 3.

Table 3 Solvent Effect on the *trans* : *cis*-Ratio[a]

solvent	**10b**	**10c**	**12a**	**12b**
n-hexane	0.08	< 0.02	3.8	2.7
toluene	0.09	< 0.02	4.7	4.1
t-BuOH	0.56	0.12	16	6.0
MeCN	0.91	0.56	27	8.0

[a] Determined by GC and ^{1}H-NMR spectroscopy.

In conclusion, the photocyclization of *o*-aminophenylketones **9** and **11** afforded in high yields and high stereoselectivities the corresponding dihydroindolinols **10** and **12**, respectively.

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(9) All compounds were characterized by NMR, IR, MS and elementary analysis.

(10) General procedure for the irradiation of ketones **9** and **11**: Compounds **9** and **11** (*ca.* 4 mg in 1 ml solvent) were dissolved in MeCN, toluene or chloroform (HPLC grade), rinsed with argon for 15 min and irradiated with a 500 W-mercury-arc lamp (*OSRAM* HBO-500) using a WG 320 filter (*Schott*). Evaporation of the solvent, followed by flash chromatography afforded the racemic products **10** or **12**. For simplicity only one enantiomer is depicted.

(11) The structures of products *trans*-**10a**, *trans*-**10b** and *cis*-**10c** were confirmed with X-ray crystal analyses. Detailed data were deposited in the *Cambridge Crystallographic Data Base*: *trans*-**10a** (*No.* CCDC-125683), *trans*-**10b** (*No.* CCDC-125680) and *cis*-**10c** (*No.* CCDC-125681).The products *cis*-**10b** and *cis*-**10c** exhibit a NOE effect of 5% between H-C(2) and the aromatic *ortho*-protons of the phenyl group (R^1 = Ph) whereas the spectra of *trans*-**10b** and *trans*-**10c** show a NOE effect of 2-4% between H-C(2) and the hydroxyl proton. Representative data for *cis*- and *trans*-compounds: *cis*-**10a**: m.p. 116–118°C; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.7, 165.9 (2s), 140.1 (s), 131.5 (d), 129.7 (s), 125.8 (d), 124.3 (d), 119.8 (q), 114.4 (d), 79.7 (s), 70.5 (d), 54.4, 53.1 (2q). *trans*-**10a**: m.p. 153–154°C; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 166.8 (2s), 140.2 (s), 131.5 (d); 130.3 (s), 126.1 (d), 124.5 (d), 119.9 (q), 115.0 (d), 82.3 (s), 75.0 (d), 54.1, 53.3 (2q).

(12) Indolinol *trans*-**12a** was converted into the appropriate benzoyl ester according to Danishefsky, S. J.; De Ninno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3029. The structure of this ester was determined by X-ray analysis (*No.* CCDC-125682). Product *trans*-**12b** exhibits a NOE of 6% between the hydroxyl proton and H-C(2). Additionally, the $^3J_{C,H}$-coupling constant of approximately 1.4 Hz between the quaternary carbon atom of the phenyl group at C(3) and the proton at C(2) corresponds to the expected dihedral angle of 120° for *trans*-**12b**. Representative data for *cis*- and *trans*-compounds: *cis*-**12a**: ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.0 (s), 140.6 (s), 134.5 (s), 131.2 (d), 131.0 (s), 129.1 (d), 128.6 (d, 2xC), 127.5 (d), 126.0 (d, 2xC), 125.0 (d), 119.8 (q), 114.8 (d), 80.8 (s), 73.7 (d), 54.1 (q). *trans*-**12a**: m.p. 83–84°C; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4 (s), 141.4 (s), 135.5 (s); 131.3 (d), 129.8 (s), 128.8 (d), 128.4 (d, 2xC), 126.3 (d, 3xC), 126.2 (d), 120.1 (q), 115.0 (d), 85.4 (s), 78.9 (d), 52.9 (q).

(13) Quenching experiments with 2,5-dimethyl-2,4-hexadiene showed that the hydrogen abstraction occurred from the triplet state of the ketone. Triplet energies of 62.5 kcal mol^{-1} and 67.5 kcal mol^{-1} for **9a** and **11a**, respectively, were determined by measurement of phosphorescence spectra performed in Et_2O/*i*-pentane/EtOH 5:5:2 at 77 K.

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