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Fluorescence Properties of 6-Methoxy-4-p-toluenesulfonyl-carbostyrils and 6-Methoxy-4-p-toluenesulfonyloxy-carbostyrils

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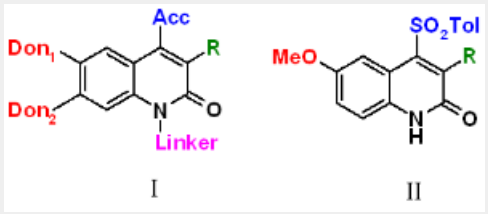
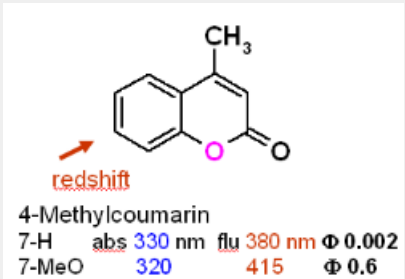
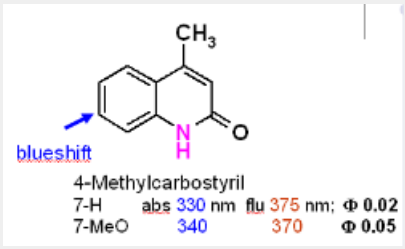
Abstract



The research on fluorescent carbostyrils of the general type I has been going on in our work group for several years [1]. In the course of these investigations we found that carbostyrils of type II having a 4-p-toluenesulfonyl group in position 4 - formed as not isolated intermediates in many cases during our investigations of strongly fluorescent 4-cyano-carbostyrils [2] - showed surprisingly strong fluorescence: they exhibit long-wave absorption and fluorescence properties, and high quantum yields. These findings prompted us to investigate the synthesis and luminescence properties of 4-p-toluenesulfonyl-carbostyrils of type II dependent on the nature of substituents in position 3.

Introduction



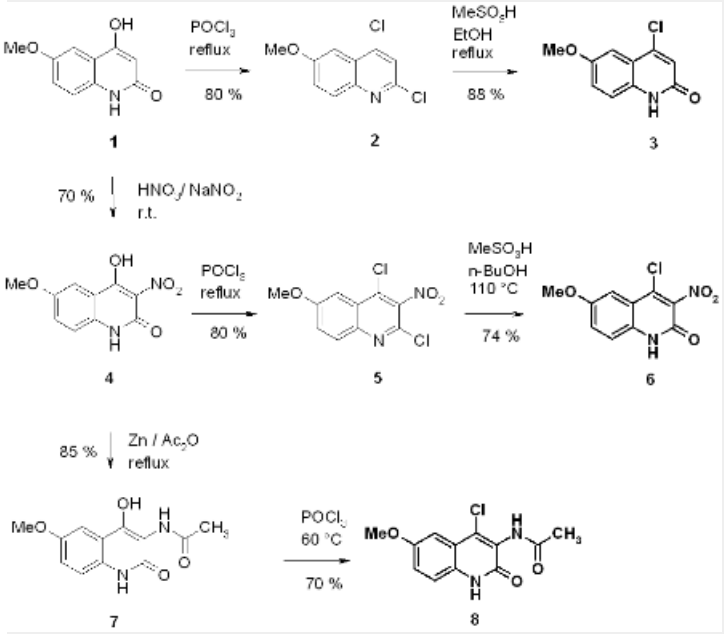


Coumarin fluorophors (upper formula) are widely used e.g. as optical brighteners [3] and laser dyes [4]. However they have the disadvantage of poor stability against chemicals. 7-Methoxycarbostyrils (lower formula) show similar emission wavelengths, but have the big disadvantage of much lower quantum yields, as shown in the adjacent scheme. Advantages of carbostyril systems are high stability against chemicals and independence of luminescence in a broad pH region. Such properties make them interesting for the use as probes in biological, biochemistry and medicine applications [5].

In our recent investigations we were able to combine the carbostyril moiety with suitable substituents to get vastly improved luminescence and photophysical properties in order to construct labelled biological materials [1,2,6]: the fluorescence is comparable with the most advanced umbelliferones, but the nitrogen analogues have much better stability. These carbostyril molecules gave excitation / emission maxima up to ~530 nm, together with large Stokes' shifts and sufficient quantum yields up to Φ = 0.5.
Recently the group of Bannwarth [7] used our fluorescent carbostyrils, incorporated in peptides, in a Fluorescence-Resonance-Energy Transfer (FRET)-system for distance determinations on the molecular level.

Aim of this study: In this contribution new types of the acceptor group (**Acc** in structure I) in position 4 such as *toluenesulfonyl* (e.g. structure II) and *toluenesulfonyloxy* groups are investigated, which were in earlier investigations applied as intermediates [1,2] for e.g. strong fluorescent cyano-carbostyrils. Observations during the reaction sequences revealed that they have already similar strong fluorescence properties as the desired target molecules.

Results and Discussion



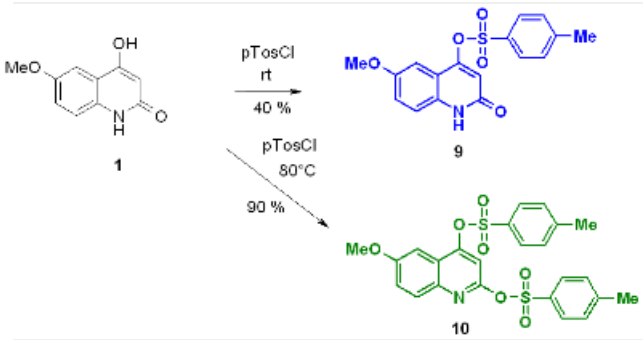
Starting materials for the synthesis of toluenesulfonyloxy and toluenesulfonyl carbostyrils were either 4-hydroxycarbostyril **1** or 4-hydroxy-3-nitrocarbostyril **4**; as more reactive compounds 4-chloro derivatives **3**, **6** and **8** were applied.

4-Hydroxycarbostryil **1** was prepared from p-anisidine, malonic acid and phosphoroxy chloride as condensation agent [2b, 8]. Chlorination with phosphoroxychloride gave the 2,4-dichloro derivative **2**, which was hydrolyzed with methanesulfonic acid regioselectively at position 2 to give the reactive intermediate, 4-chlorocarboystyril **3**.

To compare the influence of various substituents in pos 3 with the basic ring system of **1** and **3** having in position 3 hydrogen, with an electron acceptor group in position 3, the 3-nitro derivative **4** was prepared by nitration of **1**, and which was subsequently 2,4-di-chlorinated and hydrolyzed in position 2 to yield selectively the 4-chloro-3-nitrocarbostyril **6**.

As electron donor derivative, the 3-acetylaminocarbosytril **7** was obtained from the 3-nitro derivative **4** by reduction with zinc in the presence of acetic anhydride. The reactive 3-acetylamino-4-chlorocarbostyril **8** was obtained directly from **7** by regioselective chlorination.

4-Tosyloxy-quinolines 9 and 10



*Preparation of 4-tosyloxy quinolines **9** and **10**:*

*Tosylation of 4-hydroxycarbostyril **1** with tosylchloride gave either **4-tosyloxycarbostyril 9** or 2,4-ditosyloxyquinoline 10, depending on the reaction temperature and reaction time.*

*Tosylation of the 4-hydroxy-3-nitrocarbostyril **4** did not stop at the tosylation step, but gave further reactions; e.g. with pyridine or triethylamine as catalyst, the basic residue was introduced as substituent in position 4 to give again strongly fluorescent compounds (λ_{max}/flu = 450-460 nm).*

*With acetylaminocarbostyril **7** no consistent 4-hydroxy-3-acetylamino product could be isolated.*

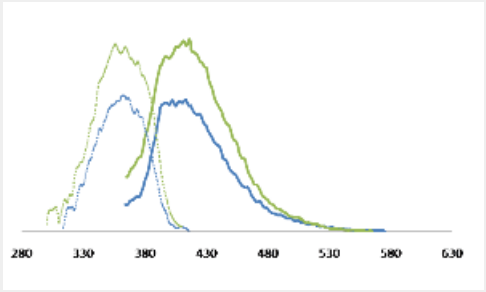
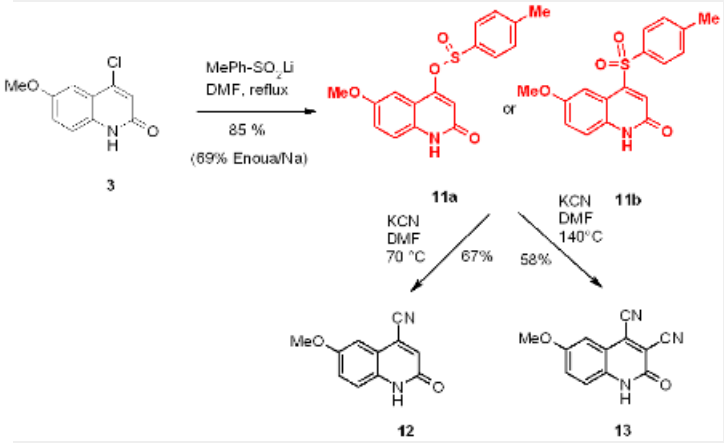


Diagram 1: Absorption and emission spectra of 4-tosyloxycarbostyril **9** andr 2,4-ditosyloxyquinoline **10**

*Absorption and emission spectra of 4-tosyloxycarbostyril **9** and 2,4-ditosyloxyquinoline **10***

*Tosyloxycarbostyril **9** shows an average blue fluorescence of 425 nm and a Stokes' shift of 58 nm, however a very low quantum yield of Φ = 0.02, which is not sufficient for many luminescence purposes.*
*Surprisingly, 2,4-ditosyloxyquinoline **10** has similar values (fluorescence at 420 nm, a Stokes' shift of 60 nm and a similar quantum yield). This means that in these tosyl structures the carbostyril system has no advantage regarding fluorescence properties over a simple quinoline system.*

4-Toluenesulfonyl-carbostyril 11



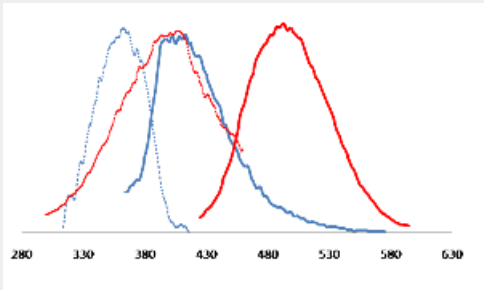


Diagram 2: Comparison of absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** and 4-tosyloxycarbostyril **9**

Preparation of 4-toluenesulfonylcarbostyril 11:

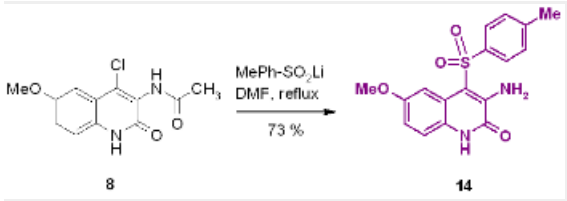
4-Toluenesulfonylcarbostyril **11** was detected as strong fluorescent intermediate in the reaction of 4-chlorocarbostyril **3** with potassium cyanide using sodium p-toluenesulfinate as catalyst [8]. Finishing the reaction, 3,4-dicyanocarbostyril **13** was formed as product. With lithium p-toluenesulfinate, the intermediate **11** was isolated in excellent yield. In a further reaction with potassium cyanide - depending on the reaction conditions - either 4-cyanocarbostyril **12** or 3,4-dicyanocarbostyril **13** were obtained as products in good yields.

The structure elucidation of **11** on the basis of ^{13}C nmr spectra and infrared spectra revealed that the formed compound **11** has not the toluenesulfinyloxy structure **11a** but the isomeric toluenesulfonyl structure **11b**. This fact was also supported by a literature search which showed that alkyl and aryl halides were found to react with sulfinates to sulfones [9].

*Comparison of absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** and 4-tosyloxycarbostyril **9**:*

In diagram 2, the absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** are compared with the spectra of tosyloxycarbostyril **9**. It is visible that a strong red shift of 65 nm to 490 nm took place in **11**, leading to a Stokes' shift of 95 nm. The quantum yield of **11** with Φ = 0.18 has nearly the tenfold value of tosyloxycarbostyril **9**.

3-Amino-4-toluenesulfonyl carbostyril 14



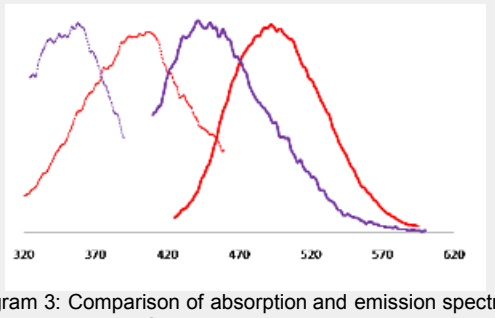


Diagram 3: Comparison of absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** and 3-amino-4-toluenesulfonylcarbostyril **14**

*Preparation of 3-amino-4-toluenesulfonylcarbostyril **14***

To study the influence of an electron donating substituent in position 3 of the carbostyril system, 3-acetylamino-4-chlorocarbostyril **8** was reacted with lithium p-toluenesulfinate. In good yields the deacetylated 3-amino-4-toluenesulfonylcarbostyril **14** was been formed.

In order to study the influence of an electron withdrawing substituent, the 4-chloro-3-nitrocarbostyril **6** was reacted with sodium or lithium p-toluenesulfinate. The reaction of this 3-nitro derivative **6**, however, gave under various reaction conditions in all cases mixtures of compounds which could not be separated as single products. Similar mixtures were obtained when the 2,4-dichloro-3-nitroquinoline **5** was brought to reaction with sodium or lithium p-toluenesulfinate.

*Comparison of absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** and 3-amino-4-toluenesulfonylcarbostyril **14**:*

The comparison of absorption and emission spectra of 4-toluenesulfonylcarbostyril **11** and 3-amino-4-toluenesulfonylcarbostyril **14** reveals, that a significant blueshift was caused by the 3-amino substituent: the fluorescence maximum was lowered from 490 to 455 nm. However, the Stokes' shift remains similar with 99 nm, and the quantum yield of **14** with Φ = 0.10 has half the value of 3-H-carbostyril **11**.

Conclusion

6-Methoxy-4-toluenesulfonylcarbostyrils and 6-methoxy-4-tosyloxycarbostyrils are obtained in good yields by simple synthetic procedures.

The fluorescence investigations on 6-methoxy-4-toluenesulfonylcarbostyrils reveal excellent properties of 4-toluenesulfonylcarbostyrils both for excitation and fluorescence values: up to 490 nm emission maximum, suitable quantum yield (about 20% in acetonitrile), and a Stokes' shift of about 90 nm, together with good chemical stability. This hitherto unknown fact is caused by the 4-toluenesulfonyl substituent in position 4 acting as a strong electron acceptor group. Further investigations are in progress to explore the properties of 6,7-dimethoxy derivatives, which in many cases have a slightly blue-shifted fluorescence maximum, but significantly higher quantum yields [8].

These characteristics make the 4-toluenesulfonylcarbostyril structure useful as a new alternative to radioactive probes, to other fluorescent dyes, for biological investigations and also as donor in energy transfer experiments.

6-Methoxy-4-tosyloxycarbostyrils possess too low quantum yields to be useful as fluorescence probes, probably caused by the obviously unsufficient acceptor properties of the 4-tosyloxy group.

Experimental

Spectral measurements

UV/vis spectra: Shimadzu UV/VIS scanning spectrophotometer UV-2101 PC; concentration: 0.01 mg/mL.

Excitation and emission spectra: Perkin-Elmer LS50B luminescence spectrofluorometer. concentration: 1x 10^{-5} M, DMSO or MeCN.
Determination of quantum yields: emission signals were set in relation to the known signal of 6,7-dimethoxy-1-methyl-4-trifluoromethyl carbostyril [1] under the same conditions.

General procedure for tosylate 9
A mixture of 4-hydroxy-6-methoxyquinolin-2(1H)-one (**1**), p-tosyl chloride and 4-(N,N-dimethyl)aminopyridine in dry pyridine was stirred for several hours at ambient temperature. Then the mixture was poured into ice/water, the solid filtered by suction and washed with water. The solid was purified in a Soxhlet extractor with cyclohexane to afford the tosylate as insoluble solid. The yield was 40 %, colorless prisms (recrystallization from dioxane).

General procedure for sulfones 11 and 14
A mixture of 4-chloro-6-methoxyquinolin-2(1H)-one (**3**) and lithium p-toluenesulfinate in dry dimethylformamide was heated under reflux for several hours. The reaction mixture was cooled to room temperature and poured into ice/water. The precipitate was filtered by suction, washed with water, and the residue dissolved in refluxing dioxane and filtered. The dioxane filtrate was poured onto ice/water, the precipitate filtered by suction and washed with water. The yield was 73-85 %.

Acknowledgement

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