Synthesis, Substitution and Cyclization Reactions Starting from 5-Unsubstituted Pyrido[3,2,1-*jk*]carbazolone

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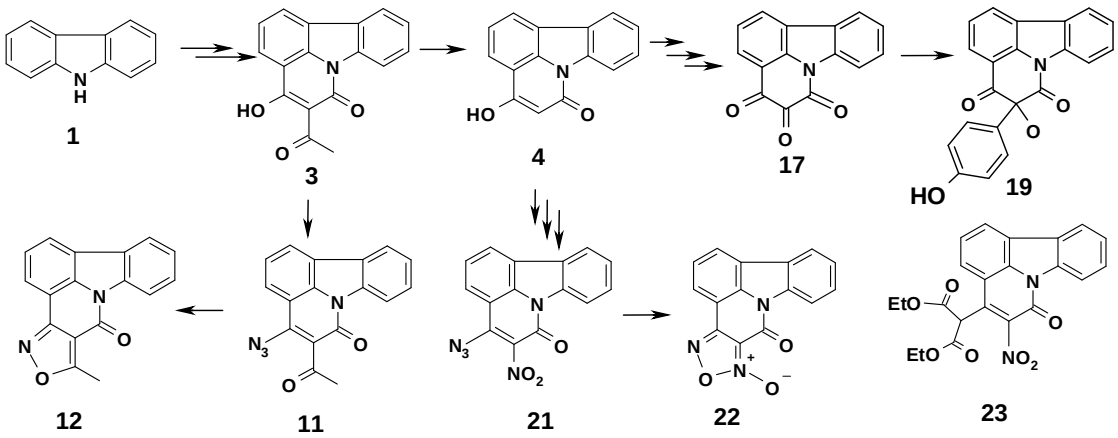
Abstract



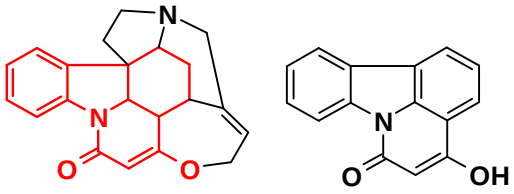
The synthesis of 5-unsubstituted pyrido[3,2,1-jk]carbazol-6-one **4** can be achieved by the reaction of carbazole (**1**) and malonate derivatives, either in a 3-step synthesis via 5-acetyl-pyrido[3,2,1-jk]carbazolone **3** or in a 1-step reaction from **1** and malonic acid.

5-Acetyl derivative can be transformed to 4-azido-pyrido[3,2,1-jk]carbazolone **11**, which cyclizes by thermal decomposition to isoxazolo-pyrido[3,2,1-jk]carbazolone **12.** The thermolysis conditions were investigated by differential scanning calorimetry (DSC). Nitration of pyrido[3,2,1-jk]carbazol-6-one **4** and subsequent introduction of azide leads to azido derivative **21**, which cyclizes on thermolysis to furazan-oxide derivative **22**. Again the thermolysis conditions were investigated by DSC.

5-Chloro-5-nitro-pyrido[3,2,1-jk]carbazole-4,6-dione, obtained from **4** by subsequent nitration and chlorination, forms on oxidative thermolysis reaction pyrido[3,2,1-jk]carbazole-4,5,6-trione **17**, which reacts e.g. with phenole by acylation to give 5-hydroxy-5-(p-hydroxyphenyl)-pyrido[3,2,1-jk]-carbazole-4,6-dione **19**. A further C-C-coupling at position 4 starts from 4-chloro-5-nitro-pyrido[3,2,1-jk]carbazol-6-one, which gives e.g. with diethyl malonate 5-nitro-6-oxopyrido[3,2,1-*jk*]carbazol-4-yl)-malonate **23**.

Introduction

Pyrido[3,2,1-jk]carbazol-6-one is part of the heterocyclic skeleton of natural products such as Strychnos alkaloids [1] (red lines) with the biological interesting combination of an indole and a 2-pyridone structure. Some pyrido-carbazole derivatives have found interest in pharmacological investigations [2] and in dyes [3] chemistry.



Recently, we published the synthesis and reactions of 5-substituted 4-hydroxypyrido[3,2,1-jk]-carbazol-6-ones which were obtained by cyclocondensation of 2-alkyl- or 2-aryl malonates and carbazole [4]. The approach to 5-unsubstituted derivatives was found to require other reaction pathways which want to show in this contribution. Furthermore, the substitution at C-5 of 4-hydroxypyrido[3,2,1-jk]carbazol-6-ones and further reactions lead to new and interesting structures.

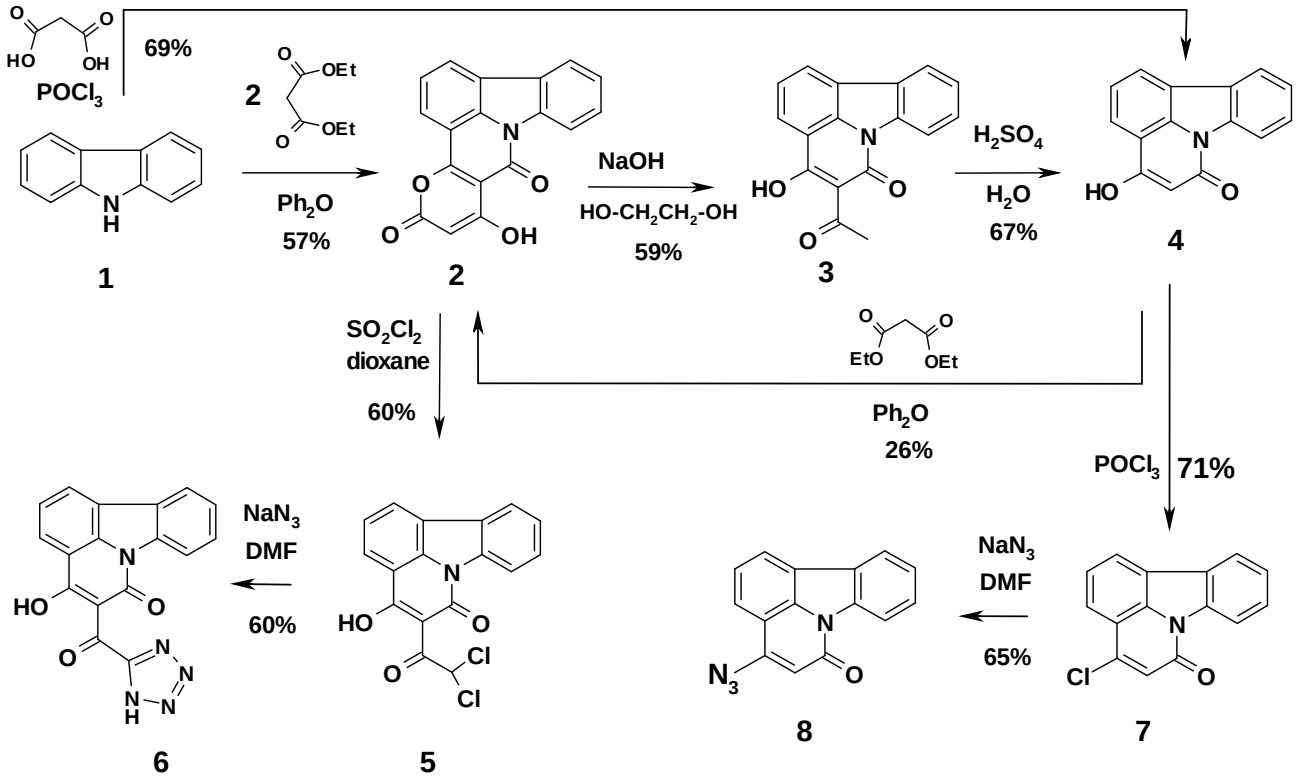
Results and Discussion

1. Formation of pyrido[3,2,1-jk]carbazol-6-one from carbazole and malonates

Whereas 2-substituted malonates react in a thermal 1:1 cyclocondensation reaction with carbazole **1** to 5-substituted 4-hydroxy-pyrido[3,2,1-jk]carbazol-6-ones [4], 5-unsubstituted could not obtained in such an easy way. Cyclocondensation of 2-unsubstituted diethyl malonate with carbazole **1** gave in a 1:1 reaction a mixture of compounds, which could not be separated. In a 2:1 cyclocondensation, however, a single compound **2** was obtained, which was shown to consist of one molecule of carbazole (**1**) and two molecules deriving from malonate. The structure was assigned to 7-hydroxy-5H,8H-pyrano[2',3':4,5]pyrido[3,2,1-jk]carbazole-5,8-dione (**2**), a structure similar as obtained from e.g. quinoline systems [5]. In ref. [5] we could show that the use of boiling diphenyl ether (bp. 250 °C) as solvent gave the best results, when the formed four molecules of ethanol removed by distillation.

Pyrano-pyridocarbazole **2** having a lactone structure, reacted as cyclic ester with sodium or potassium hydroxide by hydrolytic ring opening. Best results were obtained using glycole as solvent to obtain a higher reaction temperature and shorter reaction time. Acidification with hydrochloric acid resulted in the formation of acetoacetic acid as substituent, which decarboxylated spontaneously to give the 5-acetyl-pyridocarbazole **3**. Because strong foaming by evolution of carbon dioxide accompanied this reaction, there must be taken care to perform this reaction slowly.

The 5-acetyl group can be removed in a smooth reaction with 90% sulfuric acid at 140 °C by ipso-substitution and results in an overall yield of 5-unsubstituted pyridocarbazole **4** in about 25% after 3 steps.



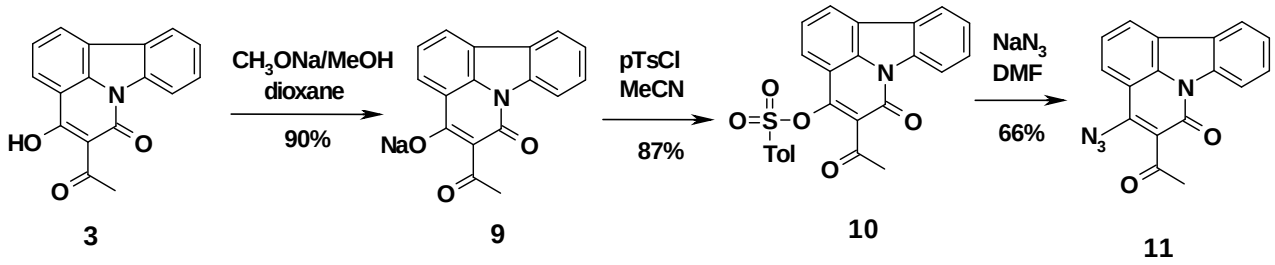
We made several attempts to obtain **4** in a shorter reaction sequence using several reactive malonic acid derivatives (e.g. trichlorophenyl esters or ketene-carboxylates) and catalysts [10]. The best result was obtained by reaction of malonic acid and carbazole (**1**) with phosphoryl chloride as condensation agent, which gave after optimization a 69% yield of **4**, together with a diamide of malonic acid with two molecules of carbazole (**1**), accompanied with small amounts of 4-chloro-pyrido[3,2,1-jk]carbazol-6-one (**7**). However, the enforcement of this reaction gave differing yields and purities depending on the accuracy and work-up which was sometimes cumbersome. 4-Chloro-pyridocarbazolone **7** was obtained in good yields from **4** by reaction with boiling phosphoryl chloride. The exchange of the chloro atom against the azide group proceeded in a nucleophilic reaction with sodium azide in dimethylformamide to produce 4-azido-pyridocarbazolone **8**. Condensation of pyridocarbazole **4** with malonate gave in moderate yield 7-hydroxy-pyranopyridocarbazoledione **2**, which proved the structure of **4**.

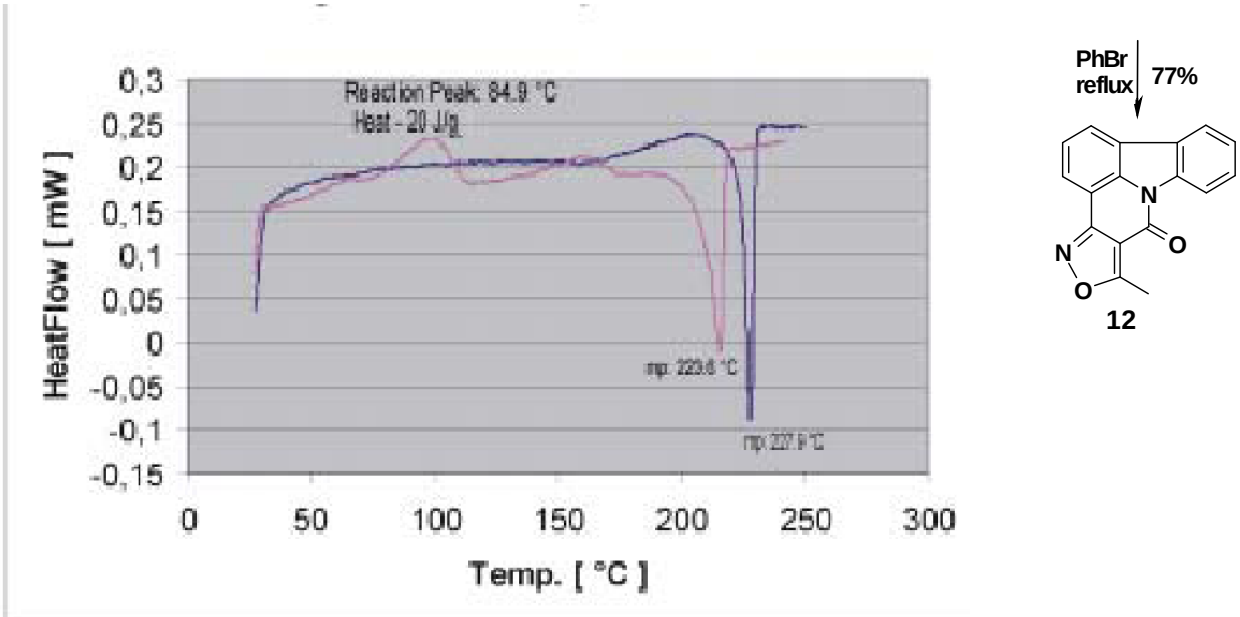
A further method for the degradation of the pyrano ring was developed when pyrano-pyridocarbazole **2** was brought to reaction with sulfuryl chloride. In contrast to similar reactions described below, not only electrophilic chlorination at the dicarbonyl-methylene group took place, but also ring opening of the lactone ring and decarboxylation, probably caused by sulfuric acid formed during the reaction. As product, 5-dichloroacetyl-pyridocarbazole **5** was obtained. When both chloro atoms where exchanged against azide groups by reaction with sodium azide, the tetrazolylcarbonyl derivative **6** was formed by elimination of nitrogen. Tetrazole **6** reveals structural relationship to tetrazoles which show biological activity [6].

2. Thermal ring closure reaction of 5-acetylpyrido[3,2,1-jk]carbazol-6-one

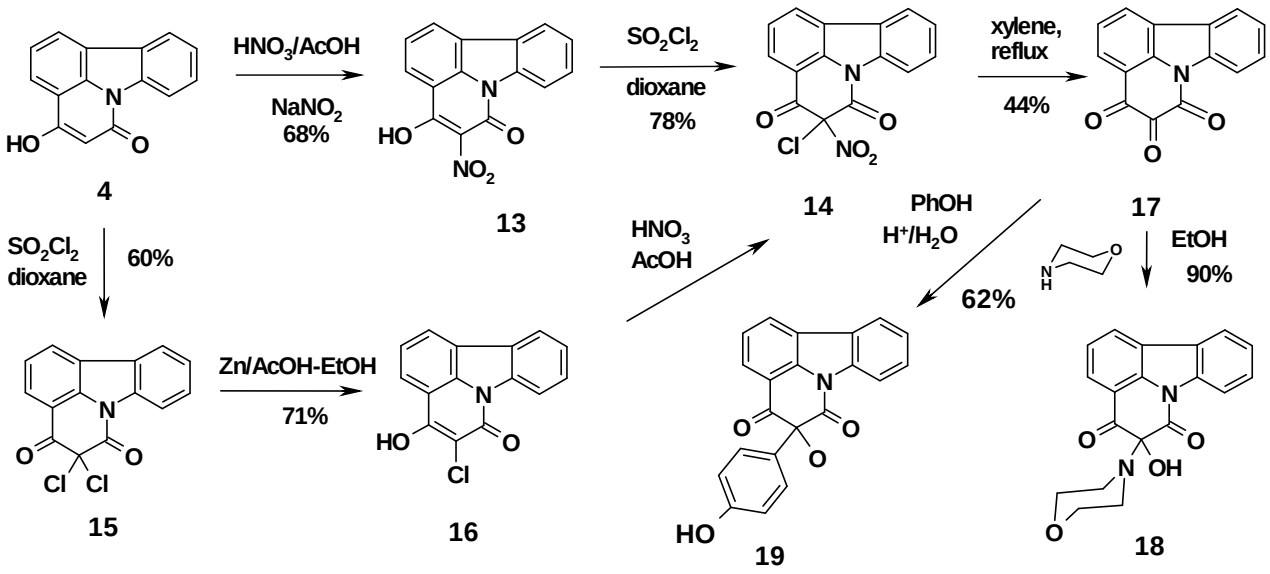
Recently we published a series of cyclization reactions of azides with reactive ortho-substituents [7, 8]. The acetyl group in acetyl-pyridocarbazolone **3** is one of these structure elements, which should react with azido groups in an electrocyclic reaction to isoxazoles. The conversion of the 4-hydroxy group to a reactive intermediate was rather difficult: chlorination with phosphoryl chloride or tosylation with tosyl chloride did not work because hydrogen bondings betweeen the acetyl group and the 4-hydroxy group prevented a reaction. A successful way was found by a 2-step reaction, first converting the hydroxy group with sodium methanolate at room temperature to its sodium salt **9**, which could then be tosylated under reflux to give tosylate **10**, which proved to be a very reactive intermediate. The tosyloxy group was exchanged against the azido group in dimethylformamide at room temperature to form 4-azido compound **11**.

The ring closure reaction of **11** was investigated by differential scanning calorimetry (DSC) to obtain the hint on the cyclization temperature and possible further decomposition. The DSC diagram of **11** (red curve) shows, that no melting point of **11** can be observed, but cyclization takes place already at rather low temperatures of 85 °C (onset) with a reaction peak at about 101 °C. The reaction enthalpy is rather low with -21 mcal/g. A small decomposition area is visible at about 160 °C, followed by a melting area at 223 °C (-36 mcal/mg) and a further decomposition at 330 °C (110 mcal/mg). From this information, the decomposition of the azide was performed in refluxing bromobenzene to obtain in good yields 6-methyl-7H-isoxazolo[3',4':4,5]pyrido[3,2,1-jk]carbazol-7-one **12**. The DSC diagram of isoxazole **12** (blue curve) showed only a melting area at 224 °C (onset) and 256°C (peak maximum).





3. Electrophilic substitutions at C-5 of 4-hydroxypyrido[3,2,1-jk]carbazol-6-one

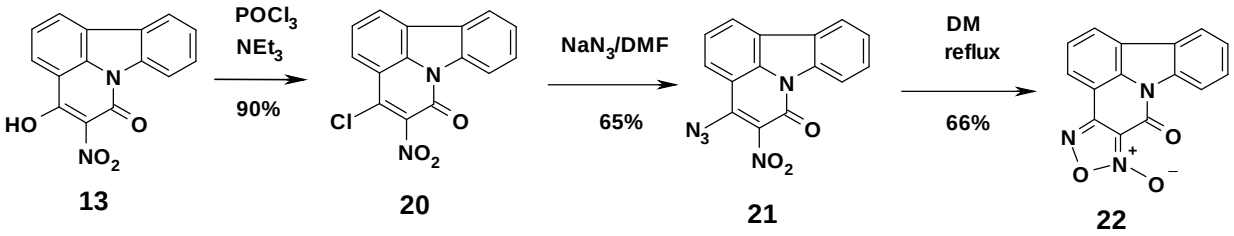


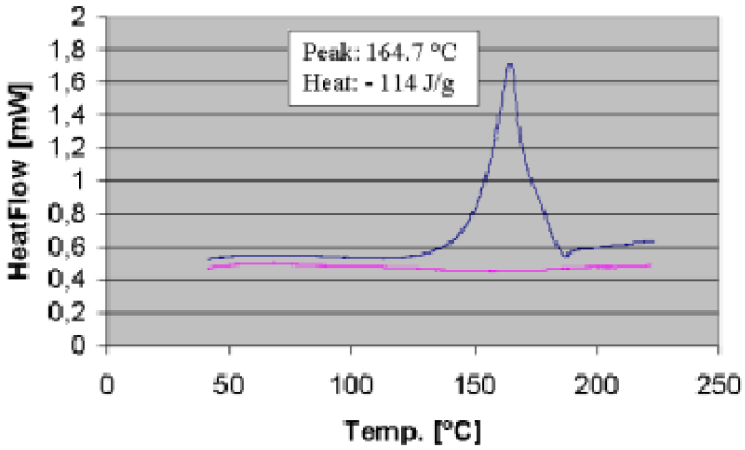
4-Hydroxy-pyridocarbazolone **4** reacts with nitric acid in acetic acid in the presence of sodium nitrite at position 5 to give 5-nitro-pyridocarbazolone **13**. Electrophilic chlorination of **13** with sulfuryl chloride in dioxane at about 50°C yields 5-chloro-5-nitro-pyridocarbazoledione **14**. Another pathway to **14** with the reversed order of nitration and chlorination starts first with the reaction of sulfuryl chloride with **4** to give 5,5-dichloro-pyridocarbazoledione **15**, which can be converted to the monochloro derivative **16** by reduction with zinc in acetic acid. Nitration with nitric acid in acetic acid attacks again position 5 and gives 5-chloro-5-nitro-pyridocarbazoledione **14**.

This chloro-nitro derivative **14** could be shown to be rather sensitive to thermolysis, and gives in refluxing xylene the trioxo derivative, pyrido[3,2,1-jk]carbazole-4,5,6-trione **17**. Addition of morpholine at the 5-carbonyl group of the trioxo compound **17** gives as half-aminal 5-hydroxy-5-morpholino-pyridocarbazoledione **18**. The reaction with phenol in the presence of conc. sulfuric acid resulted in an addition reaction of the 5-carbonyl group at the aromatic ring in p-position of the phenol group, and produced 5-p-hydroxyphenyl-5-hydroxy derivative **19**. Such structures are related to a series of heterocycles with bioactive properties [9].

4. Thermal cyclization of 4-azido-5-nitropyrido[3,2,1-jk]carbazol-6-one

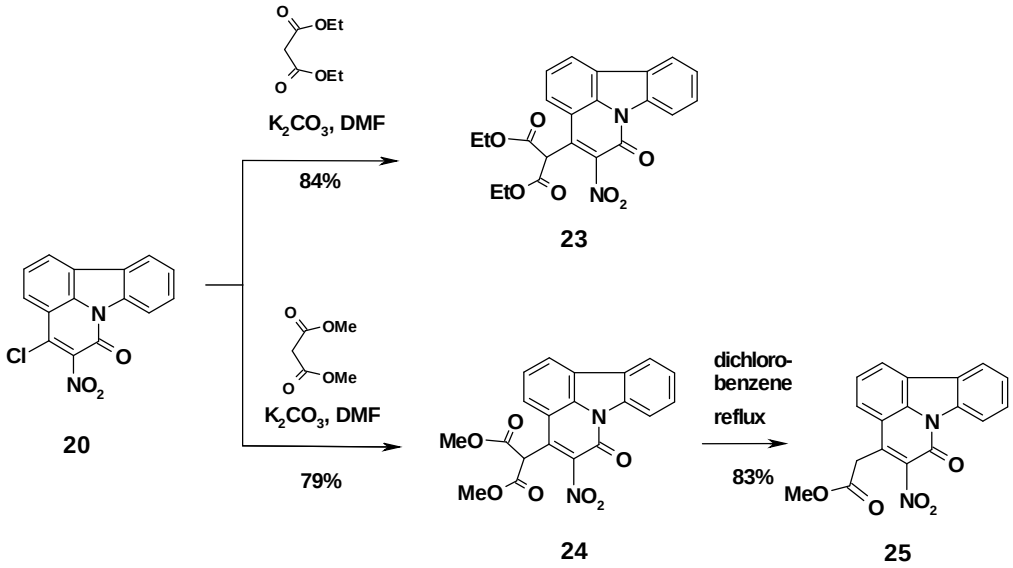
When 5-nitro-pyridocarbazolone **13** was brought to reaction with phosphoryl chloride in order to obtain as reactive intermediate 4-chloro-5-nitropyridocarbazolone **20**, again this reaction was hindered by hydrogen bondings between the nitro and the hydroxy group. Addition of triethylamine destroyed these bondings and nucleophilic chlorination takes place in excellent yields in position 4. The exchange of the chloro atom against the azide group was easily achieved with sodium azide in dimethylformamide suspension. The end of the reaction is not easily determined from the reaction mixture, because in the same manner as sodium azide reacts, sodium chloride is formed. Also TLC check is not easy because both molecules have a very similar R_f-value.





Thermolysis of nitro compounds with ortho-azido groups is known to lead to furoxanes, however the thermal conditions must be carefully selected otherwise decomposition reactions take place [7, 8]. The thermal conditions for the cyclization of the azide in structure **21** to the furoxane in **22** were again determined by DSC. In this reaction, only a strong exothermic cyclization reaction (blue curve) was observed at 140° (onset) and 165 °C (peak maximum), with a reaction enthalpy of - 114 J/g. The DSC diagram of furoxane **22** (red curve) does not show any signals up to 225 °C.

5. C-C Coupling of 4-chloro-5-nitropyridocarbazolone with malonates to (5-nitro-6-oxopyrido[3,2,1-*jk*]carbazol-4-yl)malonates



4-Chloro-quinolones and quinolines have recently shown to react with CH-acidic compounds such as malonates, cyanoacetates, malononitriles or cyclic CH-acidic derivatives (e.g. dimedone) in a

nucleophilic C-C coupling reaction to give 4-heteroarylsubstituted quinolones [11]. In a similar way, 4-chloro-5-nitro-pyridocarbazolone **20** reacts with diethyl malonate to form 5-nitro-6-oxopyrido-carbazol-4-yl)-malonate **23**. When dimethyl malonate was used, 4-pyridocarbazolyl-malonate **24** was obtained, which gave on thermolysis in refluxing dichlorobenzene by elimination of the methyl group and decarboxylation 4-pyridocarbazolyl-acetate **25**.

Conclusions

We could show in this contribution, that the hitherto unknown 5-unsubstituted pyrido[3,2,1-jk]carbazol-6-one **4** can be obtained in two pathways from carbazole (**1**) and malonic acid derivatives. The structure shows two reactive sites: in an electrophilic substitution, position 5 can be attacked to give e.g. 5-nitro or 5-chloro compounds. Position 4, which bears a reactive hydroxy group, can be attacked in a nucleophilic substitution to form chloro-, tosyloxy-, azido compounds, or gives with CH-acidic compounds a C-C coupling. These reactive intermediate undergo thermolytic reactions, which were investigated by differential scanning colorimetry (DSC).

Methods and Experimental

DSC measurements

DSC (differential scanning calorimetry data) were obtained with a Perkin Elmer Pyris 1 DSC instrument with the Pyris Software for Windows (Pyris Thermal Analysis System) V3.72. The DSC plots were recorded between 25-600 °C, with a heating rate of 2-10 °C/min, and 1.5-3 mg compound in sealed aluminium crucibles (11 bar).

Spectral measurements

IR spectra were taken on a Bruker Alpha-P with Attenuated Total Reflectance (ATR) measurement, using a reflexion method.
NMR spectra were measured on a Bruker AMX 360 instrument (360 MHz ^{1}H, 90 MHz ^{13}C), a Bruker Avance III instrument (300 MHz ^{1}H), or a Bruker Avance DRX 500 instrument (500 MHz ^{1}H, 125 MHz ^{13}C). Chemical shifts are given in ppm (δ) from the internal TMS standard.
Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria.
Mass spectra were taken on a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen, or AP-ES electrospray method).

Analytics

For analytical HPLC, a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) was used on a Pathfinder AS reversed phase (4.6150 mm, 5 µm) column, running an acetonitrile/water gradient (30-100% acetonitrile).
Thin layer chromatography was carried out on 0.2 mm silica gel F 254 plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection.

Preparation examples

4-Hydroxypyrido[3,2,1-jk]carbazole-6-one (**4**). *Method A*: To a mixture of carbazole (**1**), malonic acid and naphthalene, phosphoryl chloride was added and heated. After cooling, the residue poured onto ice/water. The solid was dissolved in sodium hydroxide, remaining insoluble by-products filtered off and the filtrate acidified which yielded 69 % of **4**. *Method B*: A solution of 5-acetylpyridocarbazolone **3** in sulfuric acid was heated, then cooled to room temperature and poured into ice/water and the solid filtered to yield 67% of **4**.

Dry column flash chromatography was carried out on silica gel 60 H (5-40 μm) (Merck, Darmstadt, Germany).

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