[A####]

Cyclization of 4-Azido-3-nitroquinolines to Oxadiazolo[3,4-c] quinolines

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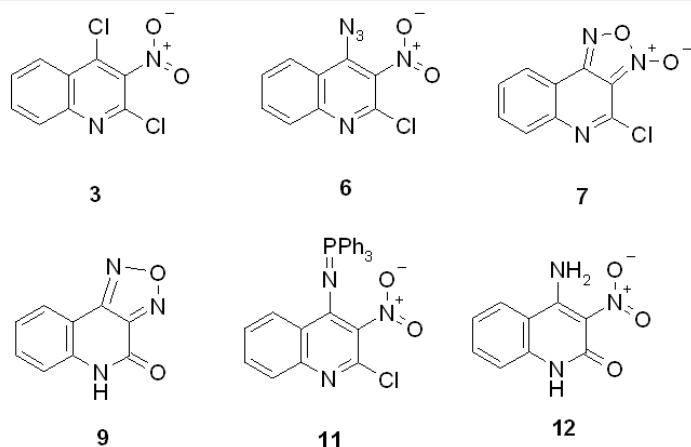E-mail: wolfgang.stadlbauer@uni-graz.at

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Abstract

3-Nitro-4-chloroquinoline **3** was converted to the azides **5/6**. The azides were cyclized on thermolysis to furoxanes **7/8**. Deoxygenation to furazane **9** was achieved by reaction with triphenylphosphane. The reaction conditions were studied by differential scanning calorimetry (DSC). The azides **5/6** gave with triphenylphosphane the phosphazenes **10/11**, which were cleaved to the aminoquinolone **12**.

Introduction
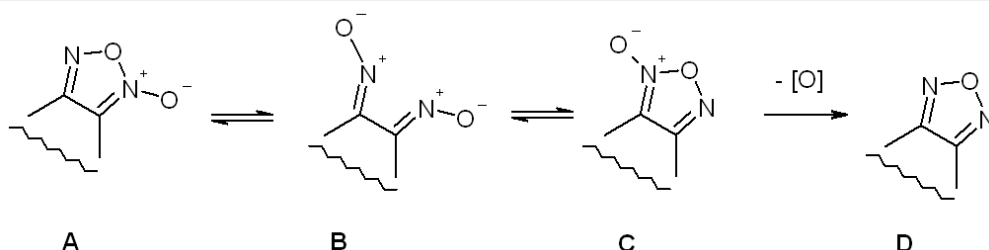
The synthesis of furoxanes (furazan 2-oxides, 1,2,5-oxadiazole 2-oxides) have found great interest in the last decades because of their theoretical and synthetical capability. Theoretical and spectroscopical investigations deal mainly with isomerization and ring opening topics (**A, B, C**) [1], synthetic interest was directed either to further ring closure reactions or to the problem of deoxygenation to furazanes **D** [2]. In a few cases, furoxanes are reported to show biological activity [3]. Reviews can be found in ref. [4].

In this contribution, we describe the

Results and Discussion

Introduction of the azide group in quinolines and quinolones

The synthesis of 4-azidoquinolines **5** and **6** starts from 4-hydroxy-2-quinolone (**1**). The first reaction step is the introduction of the nitro group in position 3 in the neighborship position of the later planned azido group. Nitration to **2** was regioselectively performed at position 3 by reaction of conc. nitric acid using sodium nitrite as catalyst, which allows to carry out the reaction at room temperature and avoided further nitration in the benzo part of the quinoline nucleus [5]. Older nitration procedures described in the literature, without sodium nitrite, suffer from multi-nitrated by-products in position 6 and 8 [6].
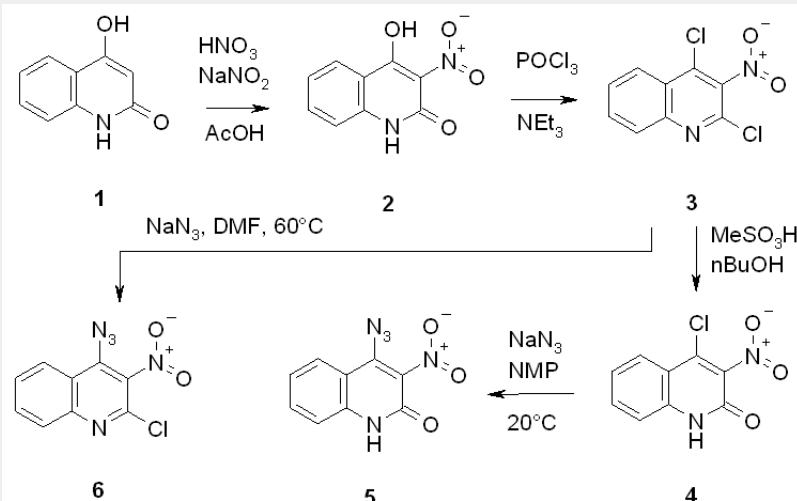
The key step for the introduction of the azido group is the transformation of the hydroxyquinolone **2** into a reactive intermediate. We chose the introduction of chloro as good leaving group, because experiments with other leaving groups such as tosylate or mesylate gave mixtures of multi-acylated products due to the reactive positions at N-1 and O-2. Also chlorination needs further activation because the 4-hydroxy group is rather inreactive because of hydrogen bondings to the nitro group [5]. With triethylamine as a base, the hydrogen bondings can be cleaved and a bis-chlorination at position 2 and 4 takes place by exchange of both oxygen functions to yield 2,4-dichloro-3-nitroquinoline **3**. Reaction of **3** with sodium azide in DMF at 60 °C gives in a nucleophilic displacement reaction 88% yield regioselectively 4-azidoquinoline **6**. The chloro atom in position 2 is not affected [7]. Chloroquinolone **4**, which was obtained from dichloroquinoline **3** by regioselective hydrolysis, reacts already at room temperature with sodium azide to azidoquinolone **5** with a yield of 80%.
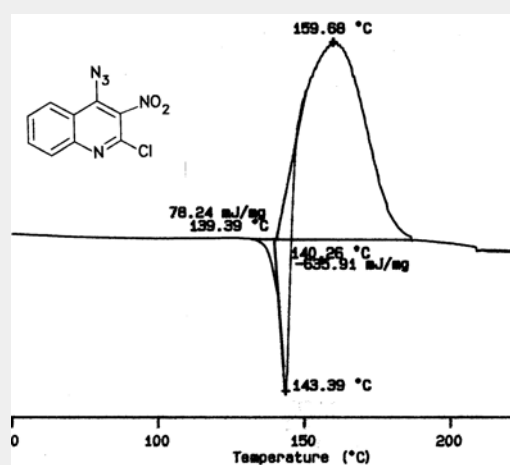
Determination of the cyclization conditions by differential scanning calorimetry (DSC)

Thermolysis of azides with reactive ortho-substituents is known to give ring closure products [8]. Depending on the ortho-substituent the mechanism is either a nitrene or an electrocyclic mechanism. In the case of acyl- or nitro substituents, the reaction follows an electrocyclic mechanism to give isoxazoles or oxadiazoles [9].

Because azide decomposition is a strong exothermic reaction, we have introduced some years ago the determination of temperatures and reaction enthalpies for such reactions by differential scanning calorimetry (DSC) to follow such reactions [10]. The reaction conditions can be easily obtained from the DSC diagram of azidoquinoline **6**. The diagram of **6** (upper curve) gives an onset of the exothermic reaction area at 143°C with a peak maximum at 160°C and it shows further that no
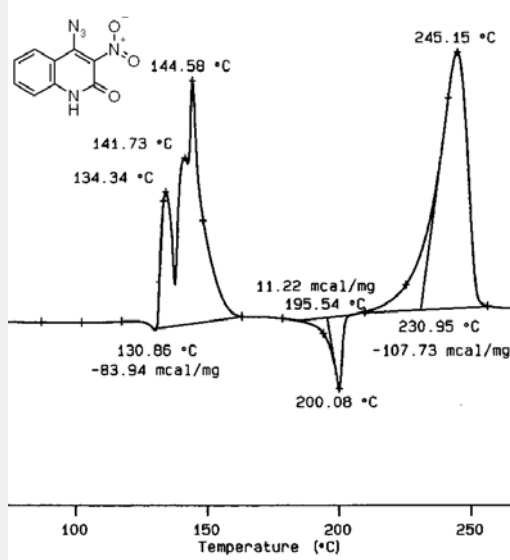
follow-up reactions have to be suspected.

Similar values for the cyclization were obtained from the azidoquinolone **5** (lower curve, with an onset at 130°C), however, in this case, further decomposition reactions are observed after the first reaction maximum of 134°C.

Ring closure reactions from azides to furoxanes and deoxygenation with the help of DSC data

According to the DSC data we decided to use for the cyclization of azidoquinoline **6** refluxing bromobenzene and obtained an excellent yield of 83% of the cyclized furoxane **7**.

Azidoquinolone **5** was cyclized in boiling xylene to use more conservative reaction conditions. The furoxane **8** was obtained in 37% yield only with a lot of by-products. Lower cyclization temperatures gave no better results because of prolonged reaction times, which caused probably other azide decomposition mechanisms.
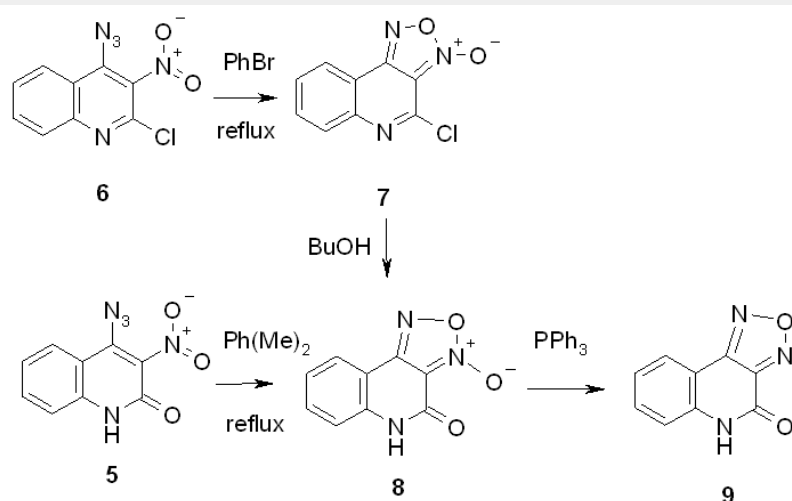
Surprisingly, on purification of **7** by recrystallization in n-butanol, we revealed, that chloroquinoline **7** was hydrolyzed to quinolone **8**, which resulted in a much better overall yield by using the reaction sequence from dichloroquinoline **3** to chloro-azide **6**, cylization to chloro-furoxane **7** and hydrolysis to quinolone **8**.

To obtain a deoxygenation of furoxanes to furazans, several procedures are decribed in the literature. In our case, the easiest and most successful pathway was found in the reaction of furoxanes with triphenylphosphane.
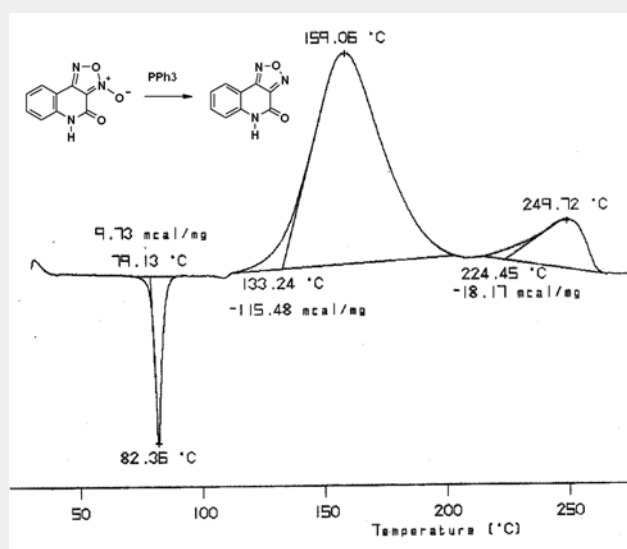
The reaction conditions were again found with the help of DSC, but in this case we studied the behaviour of the reaction mixture with all reactants, not only the thermal decomposition of the furoxanes. This experiment showed, that the reaction onset of **8** to **9** as a mixture with triphenylphosphane was visible at 133°C and a peak maximum at 159°C (see upper DSC curve). The simple thermolysis of **8** without reactants starts about 100°C higher (see lower DSC curve). We obtained in the synthetic procedure the best results on heating in refluxing dichlorobenzene; oxadiazolo-quinolone **9** was formed in 90% yield. The structure was confirmed by spectral data. In addition, the DSC curve gives the information that after the deoxygenation reaction at 242°C (onset) a decomposition reaction starts (lower curve).
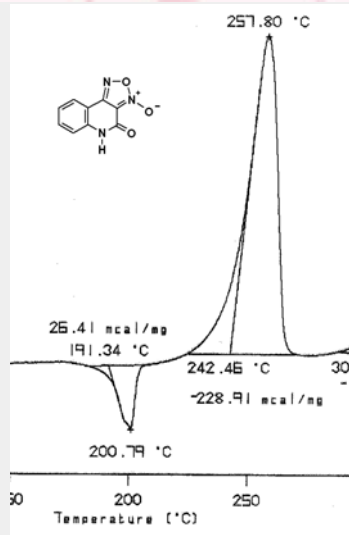
Conversion of azides to amines via a Staudinger reaction to phosphazenes

The conversion of azides to amines can be carried out by reductive reaction conditions. However, in this case sensitive substituents such as halogens or nitro groups are usually attacked too. For this purpose, the Staudinger reaction [11] from azides to phosphazenes is a good choice, because the key step is an intramolecular redox reaction between the azide and the phosphane moiety which does not affect neighbor groups.
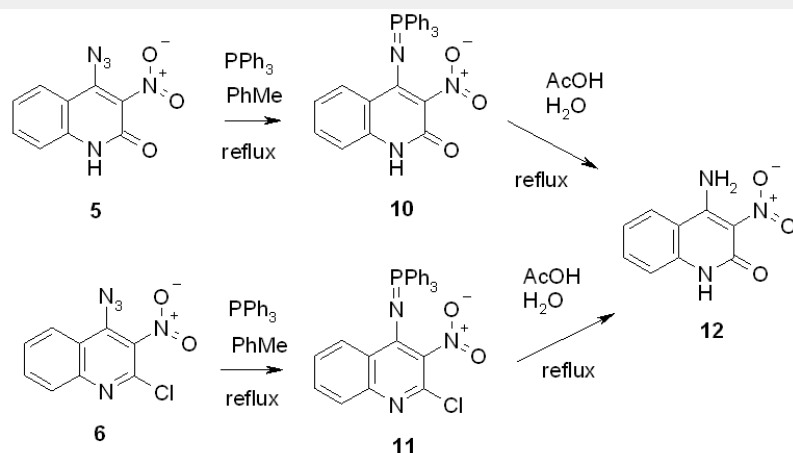
In our case, the quinoline nucleus contains both a nitro group and a chloro substituent, which are sensitive to reduction conditions. When azido-nitroquinolone 5 was treated with triphenylphosphane, the Staudinger reaction product 10 was obtained in about 80% yield. On hydrolysis in acidic medium, the former azido group formed an amino group in 12, which opens interesting pathways to compounds with multiple reaction centers.

Azido-chloro-nitroquinoline 6 gave in similar yields the phosphazene 11. However, on hydrolysis not onyl the phosphazene bonding was cleaved, but also the chloro substituent was hydrolyzed which resulted again in the amino-nitro-quinolone 12. The yield is also comparable (76%), the only advantage of this reaction path is, that the over-all reaction from 3 to 12 via 6 is one step shorter.

Experimental

General. Melting points were determined using a Stuart SMP3 Melting Point Apparatus in open capillary tubes. Calorimetric data were obtained on a Rheometric Scientific DSC-Plus instrument with the differential scanning calorimetry software Orchestrator V6.2.2. The differential scanning calorimetry plots were recorded between 25–400 °C, with a heating rate of 2-10 °C/min, and 1.5-3 mg compound in sealed aluminium crucibles (11 bar). IR spectra were recorded using a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. NMR spectra were recorded on a Bruker Avance III (300 MHz 1H, 75 MHz 13C) or on a Bruker Avance DRX 500 instrument (500 MHz 1H, 125 MHz 13C). 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 obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen, or AP-ES electrospray method). Dry column flash chromatography was carried out on silica gel 60 H (5-40 mm) (Merck, Darmstadt, Germany). All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F 254 plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 µm) column, running an acetonitrile/water gradient (30-100% acetonitrile). Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

4-Hydroxy-3-nitroquinolin-2(1H)-one (**2**) was prepared from **1** according to ref. [5]

2,4-Dichloro-3-nitro-quinoline (**3**) was prepared from **2** according to ref. [7]

4-Chloro-3-nitro-1H-quinolin-2-one (**4**) was prepared from (**3**) in n-butanol / methanesulfonic acid at 110 °C; yield: 49%, mp 265°C (EtOH). 1H-NMR (DMSO): 7.10 (t, J= 7.2 Hz, 7-H), 7.26 (d, J = 7.1 Hz, 8-H), 7.48 (t, J= 7.2 Hz, 6-H), 7.73 (d, J = 7.1 Hz, 5-H), 13.0 (s, NH); ir: 3436 s, 2924 w, 1666 m, 1636 w, 1599s; MS (APCI, neg): m/e (%) = 223 (100), 225 (32).

4-Azido-3-nitro-1H-quinolin-2-one (**5**) was prepared from 2.5 mmol (**4**) and 3.1 mmol sodium azide in N-methylpyrrolidone at 20°C; yield: 81%, mp (dec) 245°C (EtOH). 1H-NMR (DMSO): 7.43-7.65 (m, 7-H, 8-H), 7.73 (t, J= 7.2 Hz, 6-H), 7.97 (d, J= 7.1 Hz, 5-H); ir: 3435 s, 2125 (m), 1666 s, 1600 m.

4-Azido-2-chloro-3-nitro-quinoline (**6**) was prepared from 13 mmol (**3**) and 13 mmol sodium azide in DMF at 60°C; yield: 74%, mp 137-139°C (EtOH). 1H-NMR (DMSO): 7.48-7.59 (m, 7-H, 8-H), 7.76 (t, J = 7.1 Hz, 6-H), 8.06 (d, J = 7.2 Hz, 5-H); ir (KBr): 3228 s, 2126 s, 1610 w, 1566 m; MS (APCI, pos): m/e (%) = 231 (100), 134 (48); DSC: mp onset 139.39°C, max. 143.39, enthalpy 78 mJ/mg; cyclization onset 140.26, max. 159.88, enthalpy -636; decomposition onset 225°C. DSC in diphenylether solution: cyclization onset 105.63, max. 146.60°C.

4-Chloro[1,2,5]oxadiazolo[3,4-c]quinoline 3-oxide (**7**) was prepared from 6 mmol **6** in refluxing bromobenzene; yield 83%, mp 159°C (ethanol). 1H-NMR (DMSO): 7.80-7.91 (m, 7-H, 8-H), 8.03 (d, J = 7.1 Hz, 6-H), 8.33 (dd, J = 7.1 and 1.5 Hz, 1H, 9-H); ir: 3466 s, 1629 s, 1604 m, 1568 m.

[1,2,5]Oxadiazolo[3,4-c]quinolin-4(5H)-one 3-oxide (**8**) was prepared either
a) from 10 mmol **5** in refluxing brombenzene; yield 38%, mp 252°C toluene)
or
b) from 10 mmol **7** in refluxing 1-butanol; yield 54%, mp 258°C (ethanol). 1H-NMR (DMSO): 7.30-7.39 (m, 6-H, 8-H), 7.63 (t, J= 7.5 Hz, 7-H), 8.06 (dd, J = 1.6 and 7.3 Hz, 9-H), 11.95 (s, NH); ir: 3450 s, 1699 s, 1657 m, 1612 s, 1542 w.

[1,2,5]Oxadiazolo[3,4-c]quinolin-4(5H)-one (**9**) was prepared from 10 mmol **8** and 10 mmol triphenylphosphane in refluxing 1,2-dichlorobenzene; yield: 28%, yellow prisms, mp 225°C (ligroin). 1H-NMR (DMSO): 7.29-7.41 (m, 6-H, 8-H), 7.56 (t, J= 7.5 Hz, 7-H), 8.04 (dd, J = 1.6 and 7.3 Hz, 9-H), 12.04 (s, NH); 13C-NMR (DMSO, 75 MHz)): 107.3 (ArH), 111.6 (ArH), 116.9 (ArH), 122.9 (ArH) 124.2(ArH), 132.6 (ArH), 137.4 (C-9a), 148.4 (C-3a), 154.1 (C-4); MS (APCI, neg): m/e(%)= 186 (40); IR: 3445 s, 3221 s, 1712 s, 1666 m, 1634 m, 1611 w.

3-Nitro-4-triphenylphosphoranylideneamino-2-quinolone (**10**) was prepared from 10 mmol **5** and 10 mmol triphenylphosphane in refluxing toluene; yield 78%, mp 235°C (toluene). ir: 3120 w, 2980 w, 1640 s, 1620 s, 1600 s; 1H-NMR (DMSO-d6): 6.90, 6,95 (2 d, J = 7 Hz, 1 H, 8-H), 7.35 (m, 7-H, 8-H), 7.65 - 7.85 (m, 16 H, 5-H, Aryl H), 11.50 (s, NH).

2-Chloro-3-nitro-4-triphenylphosphoranylidenamino-quinoline (**11**) was prepared from 10 mmol **6** and 10 mmol triphenylphosphane in refluxing toluene; yield 72%, mp 189-190°C (toluene); ir: 1560 m, 1530 s, 1500 s, 1480 s, 1435 s.

4-Amino-3-nitro-1H-quinolin-2-one (**12**) was prepared
a) from 10 mmol **10** in refluxing AcOH/water (4:1); yield 83%.
or
b) from 10 mmol **11** in refluxing AcOH/water (4:1); yield 68%.
mp 304°C (AcOH); ir: 3290 m, 3200 - 3120 m, br, 1650 sh, 1610 s; 1H-NMR (DMSO): 7.15 - 7.30 (m, 2 ArH), 7.55 - 7-65 (m, 8-H), 8.25 (dd, J = 7 and 1.5 Hz, 5-H), 8.45 (s, br, 2 H, NH2), 11.30 (s, 1 H, NH).

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