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4-Cyano-6-methoxyquinolones: Syntheses and Luminescence Properties

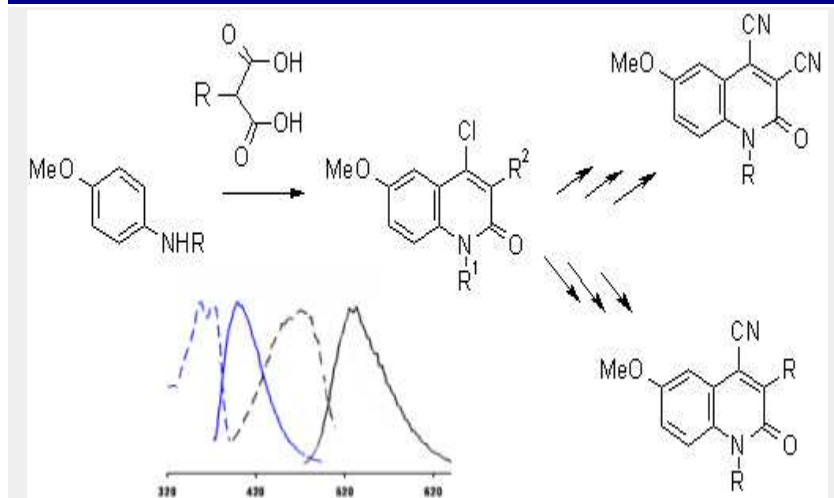**Guy Crépin ENOUA, Georg URAY, and Wolfgang STADLBAUER**[*]

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Abstract

Cyano functionalized 6-methoxyquinolin-2-ones were synthesized from malonic acid derivatives and p-anisidines in multistep reactions via 4-chloro-6-methoxyquinolin-2-ones. Introduction of cyano substituents resulted in 3,4-dicyano-6-methoxyquinolin-2-ones or 4-cyano-6-methoxyquinolin-2-ones, depending on the substituents in position 3 and 1. The study of the fluorescence properties of 3,4-dicyano-6-methoxyquinolone showed emission values up to 550 nm (**black curve**) combined with large Stoke's shifts , whereas 4-cyano-6-methoxyquinolones gave lower values (e.g. blue curve) comparable to earlier findings.

General Aspects
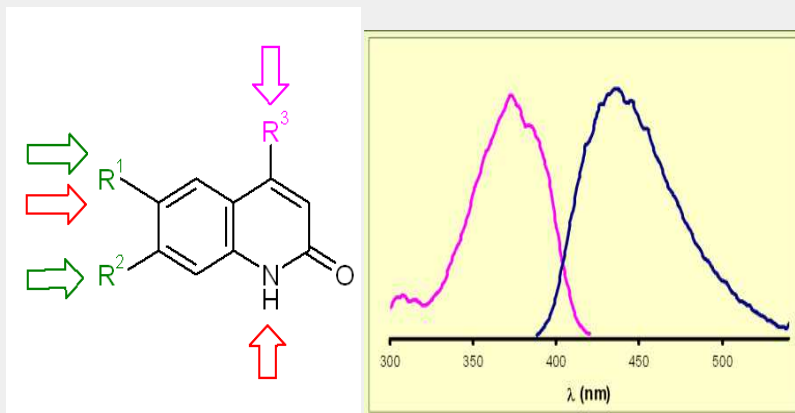
Compared with similar coumarin fluorophors, simple carbostyrils (quinolin-2-ones) have the big disadvantage of shorter emission wavelengths. Recently we reported about the synthesis and on the vastly improved luminescence properties of a number of quinolin-2-one systems [1-6]

These properties we could achieve by suitable substituents, e.g. acceptor groups such as trifluoromethyl or cyano in position 4 (R^3, pink arrow) and donor groups such as methoxy or amino in position 6 and 7 (R^1, R^2, green arrow) [1-6].

These molecules gave excitation maxima at ~380 (pink curve) and emission maxima at 440 nm (blue curve).
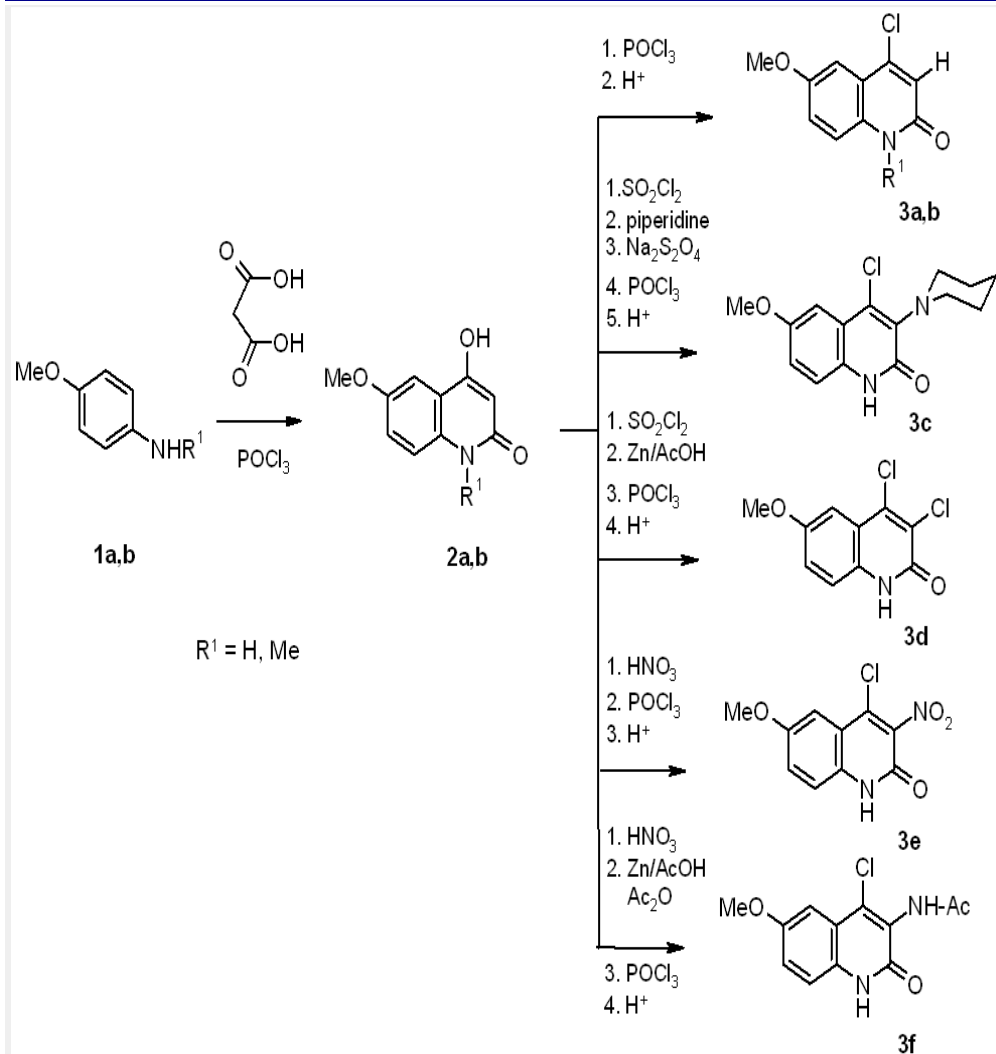
Tethers in position 1 and 6 (red arrows) allowed the connection to biological materials such as peptides, proteins and carbohydrates [1-3]

The general advantages of carbostyril systems are a high stability against chemicals, thermal and photochemical stress, insensitivity to O_2 quenching, independence of luminescence in the pH region 3-9, large Stoke's shifts, and sufficient quantum yields.
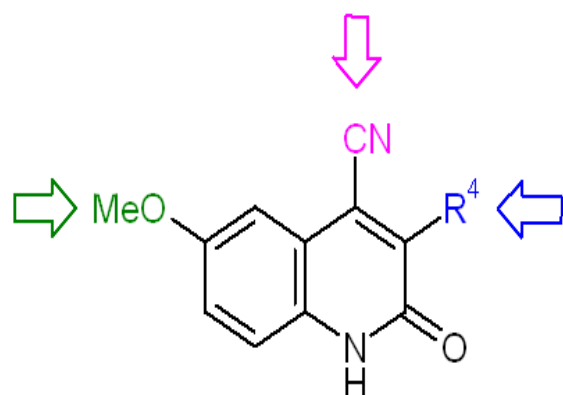
In this work we present a study about carbostyrils with a cyano group as an acceptor group in position 4 (pink arrow) and a methoxy group as donor in position 6 (green arrow). Different substituents (with either donor or acceptor properties) in position 3 (blue arrow) should allow additional fine-tuning of the fluorescence properties.

1. POCl$_3$
2. H$^+$

3a,b

1. SO$_2$Cl$_2$
2. piperidine
3. Na$_2$S$_2$O$_4$
4. POCl$_3$
5. H$^+$

3c

1. SO$_2$Cl$_2$
2. Zn/AcOH
3. POCl$_3$
4. H$^+$

3d

1. HNO$_3$
2. POCl$_3$
3. H$^+$

3e

1. HNO$_3$
2. Zn/AcOH
Ac$_2$O
3. POCl$_3$
4. H$^+$

3f

1a,b

2a,b

R^1 = H, Me

The syntheses of 4-chloro-6-methoxyquinolones having either hydrogen, acceptor or donor substituents in position 3, started from p-anisidine or its N-methyl derivative **1a,b** (R^1 = H, Me) and malonic acid, which gave in the first step 3-unsubstituted 4-hydroxycarbostyrils **2a,b**.

Suitable substituents at position 3 of 4-hydroxycarbostyril **2a** (R^1= H) were obtained by multistep syntheses:

Chlorination with sulfuryl chloride, followed
a) either by amination with piperidine and reduction, or
b) by reduction of the dichloro intermediate
gave 3-piperidino and 3-chlorocarbostyril derivatives of **2**.

Nitration in position 3, alternatively followed by reduction, gave 3-nitro- and 3-acetylamino carbostyril derivatives of **2**.

All these 4-hydroxycarbostyrils were chlorinated with phosphoryl chloride at position 2 and 4, and subsequently hydrolyzed in acidic media regioselectively at position 2 to give 4-chloro-2-quinolones **3a-f**.

4a-c

1a

5a-c

1. POCl$_3$
2. H$^+$

R^2 = H, Cl, MeO

6a-c
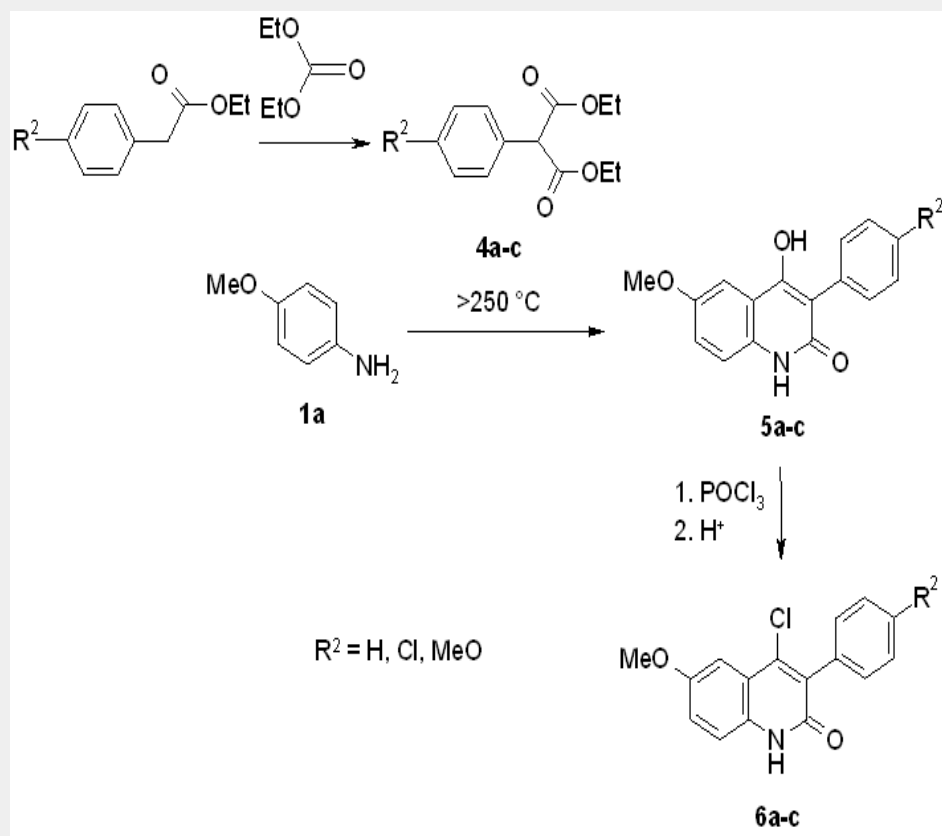
Another approach to 3-donor or acceptor-substituted carbostyrils is the synthesis of 3-arylsubstituted 4-hydroxycarbostyrils **5** having substituents in the phenyl ring which are connected via the conjugated bonds to the carbostyril dye system.

The synthesis started from suitable substituted arylacetates which gave with diethyl carbonate arylmalonates **4**. Thermal cyclization of malonates with p-anisidine **1a** gave 4-hydroxycarbostyrils **5** [7].

4-Hydroxycarbostyrils **5** were converted in a 2-step reaction to 4-chloro derivatives **6**: 2,4-bischlorination with phosphoryl chloride was followed by a regioselective hydrolysis of the 2-chloro substituent to give 4-chlorocarbostyrils **6a-c**.

KCN

p-Toluene sulfinate Na

X = H, Cl, NO$_2$, NH-Ac

3a,c-f

7a
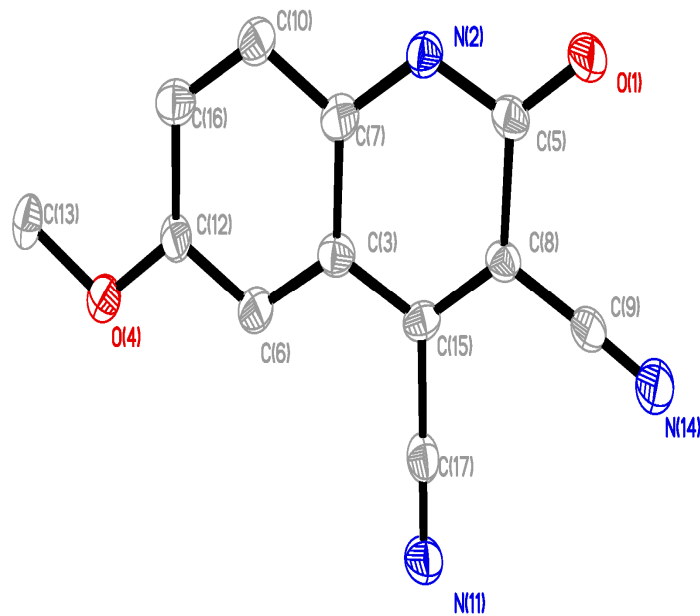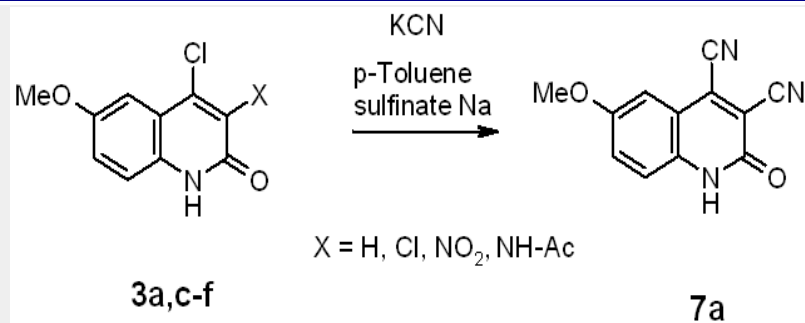
The introduction of the cyano group in position 4 of 4-chlorocarbostyrils **3a-f** was carried out by reaction with potassium cyanide in the presence of sodium p-toluene sulfinate similar as recently described [3].

Unexpectedly, in the 6-methoxycarbostyril series substituents in position 3 such as hydrogen, piperidino-, chloro-, nitro- and acetylamino groups were also exchanged against the cyano group: in all cases the red-colored (and yellow-green fluorescing) 3,4-dicyanocarbostryil **7a** was isolated. Infrared signals of both cyano groups were very weak and therefore the structure of **7a** was confirmed by ^{13}C nmr and X-ray analysis, together with mass spectral data and elemental analysis.

We assume that the mechanism proceeds via a Meisenheimer type sulfinyl addition of p-toluene sulfinate in position 3, followed by elimination of the 3-substituent. This could also explain the 3-cyanation of 3-unsubstituted carbostyril **3a** to **7a**.
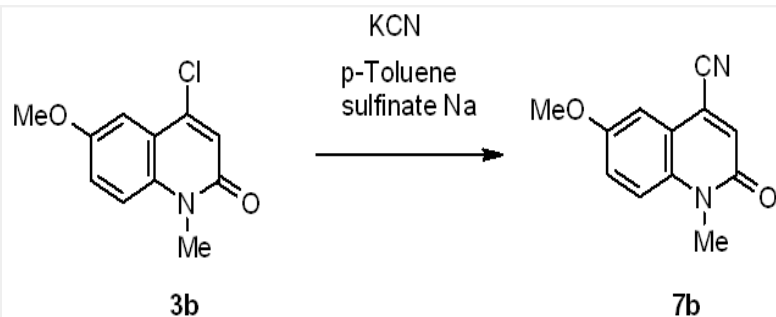
Surprisingly, in the case of 1-methyl-4-chloro-6-methoxycarbostyril **3b**, only the usual mono-substitution at position 4 took place which forms **7b**.

A similar clean mono-substitution was observed with 7-methoxycarbostyril **8**: 4-cyanocarbostyril **7c** was obtained in good yield; In cases **7b,c** mono-substitution was easily confirmed due to the presence of the 3-H signal in ^{1}H nmr.
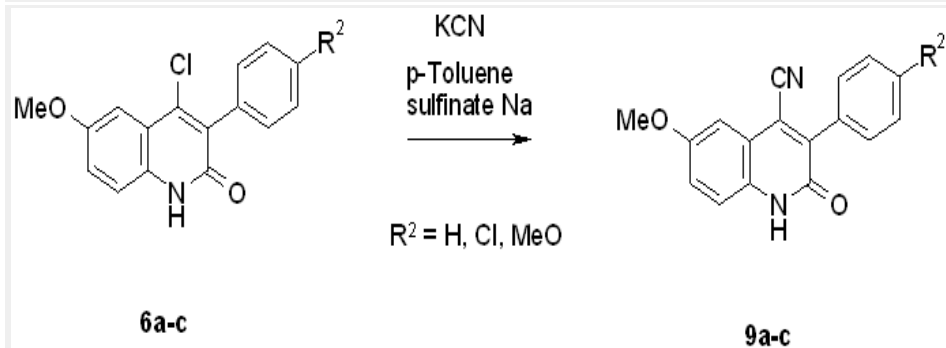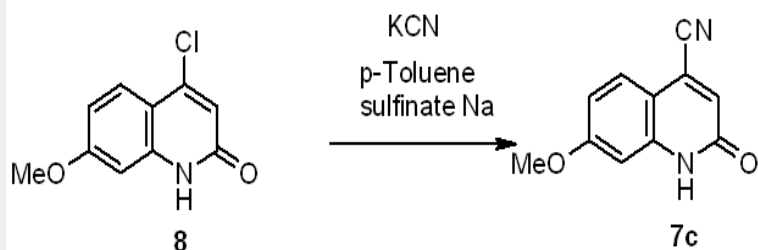
Also 3-aryl-4-chlorocarbostyrils **6a-c** could be converted to mono-cyano carbostyrils **9a-c** with H, chloro and methoxy as substituents at the 3-phenyl ring. Again the p-toluene sulfinate mediated substitution of the 4-chloro substituent worked cleanly and the phenyl ring and its substituents remained unaffected.

Fluorescence Properties
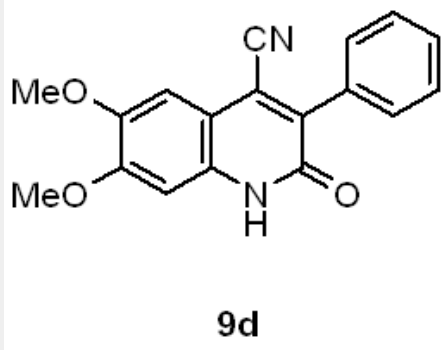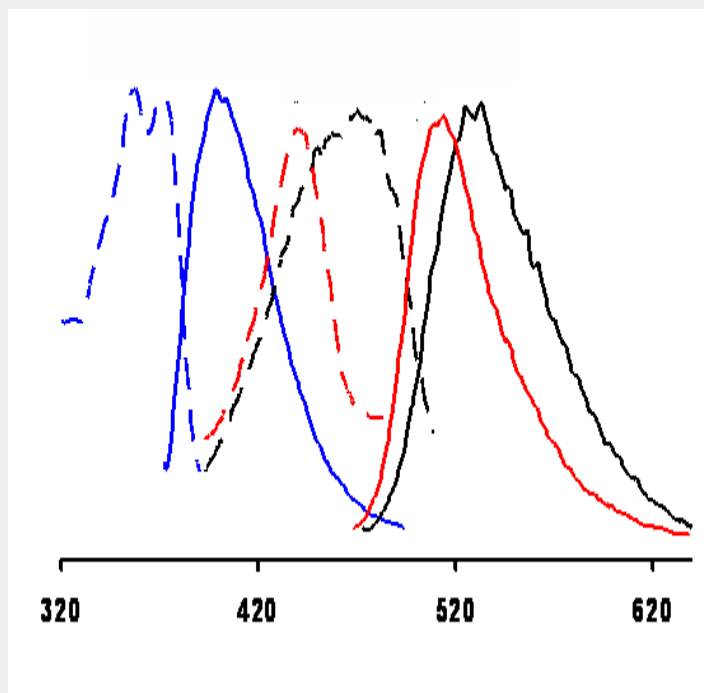
The electronic spectra show that 3,4-dicyanocarbostyril **7a** (**black curves**) has very interesting luminescence properties: λ_{max} of excitation was found in the region of ~440-470 nm (dotted **black** line; depending on the solvent), λ_{max} of emission in the region of ~530-560 nm (full **black** line). Hence the emission wavelength has a redshift of more than 100 nm compared with all methoxy substituted carbostyrils we have recently investigated [1-6]. Also the Stoke's shift of about 100 nm is remarkable. Disappointing is the rather low quantum yield of ~10%. This is most probably caused by lack of an electron donating substituent in position 7.

These luminescence properties of dicyanocarbostyril **7a** are similar to *fluorescein* [8]: Excitation and emission at pH 3.4 is shown as red curves (λ_{max} excitation 450 nm and emission at 510 nm, $\Phi = 0.3$, H_2O, zero in DMSO). The pure high yielding dianion can only be observed in alkaline medium (492 and 511 nm, $\Phi = 0.85$, 0.1 N NaOH).

For comparison, short wavelength absorbing and emitting 3-unsubstituted 4-cyanocarbostyrils **7b** (6-methoxy) and **7c** (7-methoxy) are surprisingly similar to each other (blue curve, **7b** only): excitation values are ~ 355 nm, emission values are ~ 420 nm , again with rather low quantum yields of ~10%.

Luminescence spectra of all 3-aryl-4-cyanocarbostyrils **9a-c** show excitation maxima at ~410 nm, and emission values at about ~500 nm; quantum yields are again low <10%. The influence of substituents at the aryl ring is weak and has almost no influence on the luminescence properties.

A comparison with 4-cyano-6,7-dimethoxy-3-phenylcarbostyril **9d** shows similar excitation and emission values (400/485 nm) and quantum yields of ~50% as already found in 3-unsubstituted 4-cyano-6,7-dimethoxycarbostyrils [3]. We expect approximately these quantum yields in a 6,7-electron rich substituted 3,4-dicyano analogue.

Experimental

General:
UV/VIS spectra: Shimadzu spectrophotometer UV-2101 PC; concentration: 1×10^{-4} M.
Excitation and emission spectra: Shimadzu RF-5001 PC spectrofluorometer; concentration: 1×10^{-5} M, DMSO.
Determination of quantum yields: emission signals were set in relation to the known signal of 6,7-dimethoxy-1-methyl-4-trifluoromethyl carbostyril under the same conditions.

General procedure for the synthesis of 4-cyanocarbostyrils (**7, 9**).
5 mmoles of the appropriate 4-chlorocarbostyril (**3 or 6**), 5 mmoles of sodium p-toluenesulfinate, and 12 mmoles of potassium cyanide in dry DMF were heated for several hours with vigorous stirring, cooled to room temperature, poured into ice/water, and acidified with conc. hydrochloric acid. The precipitate was filtered by suction, washed with water and dried to afford red or yellow prisms.

Acknowledgement

References

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