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Concave Reagents - 14 [1]. Concave Pyridines with a 2,6-Diarylpyridine Core.

Ulrich Lüning*, Roland Baumstark and Wolfgang Schyja

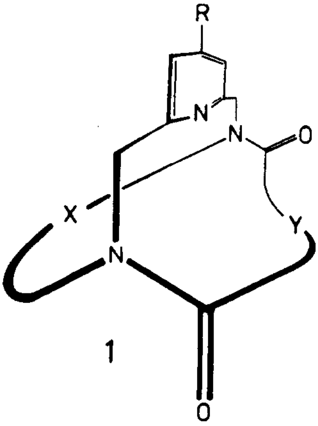
Chemisches Laboratorium, Albertstraße 21, D-79104 Freiburg (Germany)

Abstract: A new type of concave pyridine **4** based on a 2,6-diarylpyridine system is described. By cyclization of a C_5-unit **5** or **6** with ammonium acetate a tetra-*ortho*-methoxy-substituted 2,6-diarylpyridine **7** was obtained. Deprotection of the phenol functions and bimacrocyclization with the diiodide **9** gave **4a** which catalyzes the addition of alcohols to diphenylketene.

To increase the selectivity of standard reagents of organic chemistry, standard functional groups have been embedded in a concave environment [2]. Thus concave pyridines **1** [2a, 3] have been synthesized and their behavior has been investigated in model reactions, in a base catalyzed alcohol addition to a ketene [4] and in a proton transfer reaction [5]. The concave shielding of the pyridine led to changes in reactivity *and* selectivity.

But the concave pyridines **1** contain amide functions as bridgeheads which lead to the following problems: (i) Amide functions may also be catalytically active, e. g. in the addition of alcohols to ketenes [4]. (ii) The existence of two amide groups in the concave pyridines **1** leads to the formation of conformers (*EE*, *ZE*, *ZZ*) [2a, 3] which are stable on the NMR time scale.

Closely related to the concave pyridines **1** are concave 1,10-phenanthrolines **2** [3a, 6]. To solve the conformer problem in **2**, the amide bridgeheads were exchanged by trisubstituted phenylrings leading to the concave 1,10-phenanthrolines **3** [6a]. An analogous class of pyridines **4** should therefore contain a 2,6-diarylpyridine unit (a 2'-aza-*m*-terphenyl [7]) where each phenyl ring is disubstituted. But in contrast to the synthesis of analogous 1,10-phenanthrolines **3**, the incorporation of such aryl groups into the C-2 and C-6 position of an already existing pyridine system was not successful up to now. Therefore, a different approach [8] for the synthesis of 2'-aza-*m*-terphenyls has been chosen: the construction of a C_5-unit with subsequent cyclization by reaction with ammonia.



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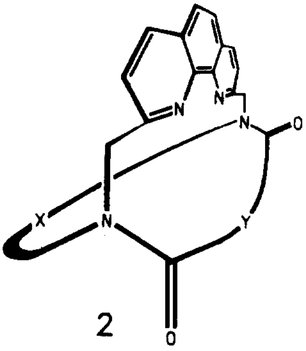

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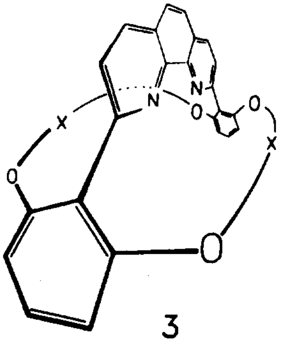

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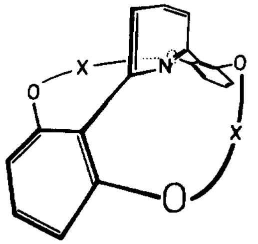
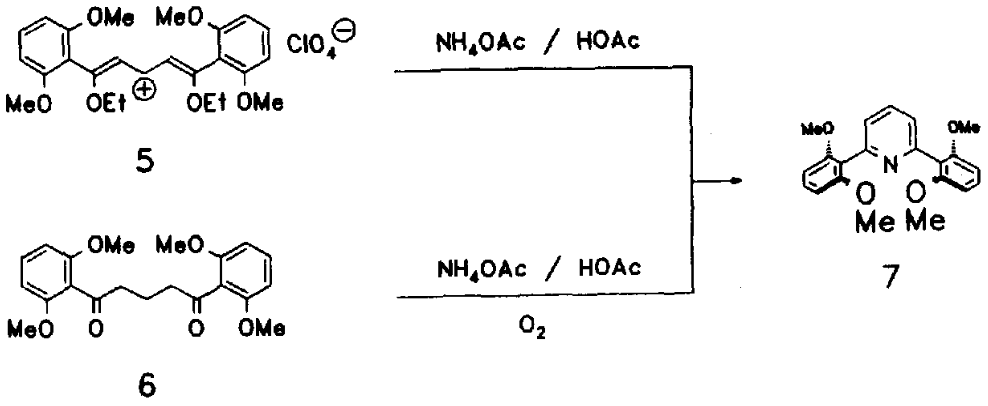


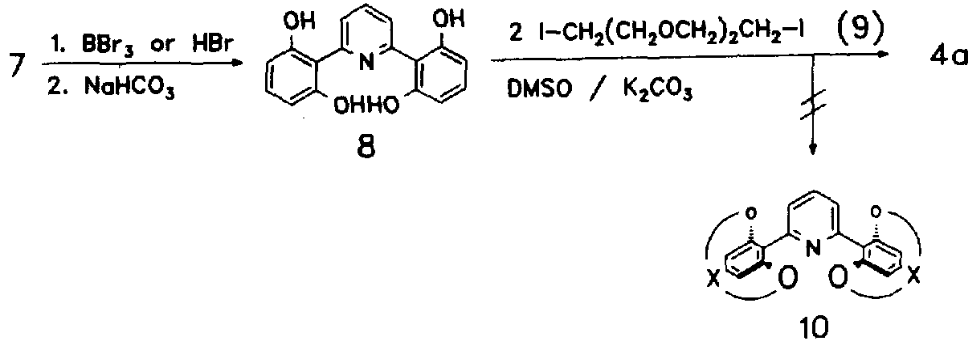
4

4a: X = $CH_2(CH_2OCH_2)_2CH_2$

Diarylpyridine **7** could be synthesized from two different C_5-units, from the pentadienylium salt **5** [9] and from the 1,5-diketone **6** [10]. In both cases, for the cyclization to pyridine **7**, ammonium acetate in acetic acid was used as the nitrogen source. When the diketone **6** was used, the intermediate nitrogen heterocycle is a dihydropyridine, but the reaction was carried out in the presence of air and thus the fully aromatized pyridine **7** was obtained. Due to the two aryl rings in 2,6-position, pyridine **7** is a strongly shielded pyridine. But in comparison to 2,6-di-*tert*-butylpyridine it is distinctly more basic (see below).

The ether groups of the tetramethoxy derivative **7** were cleavable by BBr_3 or HBr in comparable yields of 60 - 70 %. The tetraphenol **8** was then doubly bridged with an α,ω-diiodide **9** in DMSO with K_2CO_3 as a base to give the concave pyridine **4a**. In this reaction, the non-macrocyclic precursor **8** was transformed into a bimacrocycle **4a** in one reaction step. Therefore, the yield of 22 % is acceptable. The new concave pyridine **4a** was characterized [11] by IR, NMR, MS and elemental analysis. Furthermore, nuclear Overhauser effects proved that the concave, bimacrocyclic pyridine **4a** was formed. The NOE data ruled out the other possibilty of bridging the four phenol functions with the diiodide: the formation of a bis meta-cyclophane **10** [12] by linkage of the phenol groups within *one* aryl ring.





The new concave pyridine **4a** and its precursor **7** are strong bases in comparison to the concave pyridines **1**; their basicities were at least two orders of magnitude larger than pyridine itself. When **4a** was tested as catalyst for the base catalyzed addition of alcohols to diphenylketene, **4a** showed catalysis comparable to the concave pyridines **1** [4, 13]. The cavity of **4a** seems to be rather large because **4a** catalyzed the addition of isopropanol almost as good as the addition of ethanol.

With the incorporation of aryl bridgeheads into concave pyridines an interesting new class of concave bases (pyridino-bridged crown ethers, cryptand-like cyclophanes) has been made available which is reactive in base catalyzed additions of alcohols to ketenes. Because also the addition of a secondary alcohol could be catalyzed, and because the chains X in the concave pyridines **4** can easily be made chiral [14], one should now be able to investigate also enantioselectivity in this reaction.

References and Footnotes

1. Concave Reagents 13: U. Lüning, H. Baumgartner, submitted to *Synlett*.
2. a) U. Lüning, *Liebigs Ann. Chem.* **1987**, 949. - b) U. Lüning, R. Baumstark, C. Wangnick, M. Müller, W. Schyja, M. Gerst, M. Gelbert, *Pure Appl. Chem.* **1993**, 65, 527. - c) U. Lüning, *GIT Fachz. Lab.* **1993**, 173.

3. U. Lüning, R. Baumstark, M. Müller, *Liebigs Ann. Chem.* **1991**, 987. - b) U. Lüning, R. Baumstark, K. Peters, H. G. v. Schnering, *Liebigs Ann. Chem.* **1990**, 129.
4. U. Lüning, R. Baumstark, W. Schyja, *Liebigs Ann. Chem.* **1991**, 999.
5. a) U. Lüning, M. Müller, *Angew. Chem.* **1992**, *104*, 99; *Int. Ed. Engl.* **1992**, *31*, 80. - b) U. Lüning, F. Schillinger, *Chem. Ber.* **1990**, *123*, 2073. - c) U. Lüning, R. Baumstark, M. Müller, C. Wangnick, F. Schillinger, *Chem. Ber.* **1990**, *123*, 221.
6. a) U. Lüning, M. Müller, *Chem. Ber.* **1990**, *123*, 643. - b) U. Lüning, M. Müller, *Liebigs Ann. Chem.* **1989**, 367.
7. Also concave acids derived from 2,6-diaryl benzoic acid have been synthesized (via 2'-functionalization of a *m*-terphenyl). For *m*-terphenyl based concave acids see: U. Lüning, C. Wangnick, *Liebigs Ann. Chem.* **1992**, 481; U. Lüning, C. Wangnick, K. Peters, H. G. v. Schnering, *Chem. Ber.* **1991**, *124*, 397, for *m*-terphenyls with other substituents in 2'-position see: [1].
8. For pyridine syntheses see: Houben-Weyl, *Methoden der organischen Chemie*, Ed.: R. P. Kreher, Erw. u. Folgeband z. 4. Aufl. *E7b*, *Teil 2*, Thieme Verlag, Stuttgart - New York, **1992**.
9. U. Lüning, R. Baumstark, *Tetrahedron Lett.* **1993**, preceeding paper.
10. W. Schyja, *dissertation*, Universität Freiburg, in preparation. **6** was synthesized by addition of two equivalents of 1,3-dimethoxy-2-phenyl lithium to glutar dialdehyde, and subsequent oxidation with $KMnO_4/CuSO_4$.
11. *6,9,12,15,21,24,27,30-Octaoxa-38-azapentacyclo[14.14.7.$1^{32,36}$.$0^{5,31}$.$0^{16,37}$]octatriaconta-1(31),2,4,16(37),17,19,32(38),33,35-nonaene* **4a**: M. p. 217 - 219°C. - IR (KBr): ν = 1595, 1450 (arom.), 1255, 1100 (C-O). - MS (EI, 70 eV): m/z (%) = 524 (31), 523 (100), 522 (27), 480 (15), 436 (29), 435 (93). - ^1H NMR (250 MHz, $CDCl_3$) : δ = 1.77 (br. s, ca. 2 H), 3.22 - 3.55 (m, 8 H), 3.56 - 3.98 (m, 8 H), 3.98 - 4.14 (m, 8 H), 6.57 (d, J = 8.0 Hz, 4 H), 7.22, 7.25 (d, J = 7.5 Hz, t, J = 8 Hz, 4 H), 7.71 (t, J = 7.5 Hz, 1 H).

    $C_{29}H_{33}NO_8 \cdot 0.5\ H_2O$ (523.58 + 9.01) Calcd. C, 65.40; H, 6.43; N, 2.63. Found C, 65.37; H, 6.30; N, 2.67 %.
12. See also the discussion for analogous concave 1,10-phenanthrolines **3**, ref. [6a].
13. The experiments were carried out as described [4]: 25°C, [ketene] = 4 mM, [alcohol] = 50 mM, [**4a**] = 4.4 mM (EtOH-run), k_{obs} (EtOH) = $1.25 \cdot 10^{-3}\ s^{-2}$, [**4a**] = 4.5 mM (iPrOH-run), k_{obs} (iPrOH) = $6.7 \cdot 10^{-4}\ s^{-1}$.
14. An analogous chiral concave 1,10-phenanthroline **3** could be synthesized by using (*R*,*R*)-4,5-dimethyl-3,6-dioxaoctane bridges X, see M. Müller, *dissertation*, Universität Freiburg, **1991**.

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