Functionalized Terpyridines

DOI: 10.1002/anie.201403403

Unprecedented Strong Lewis Bases—Synthesis and Methyl Cation Affinities of Dimethylamino-Substituted Terpyridines**

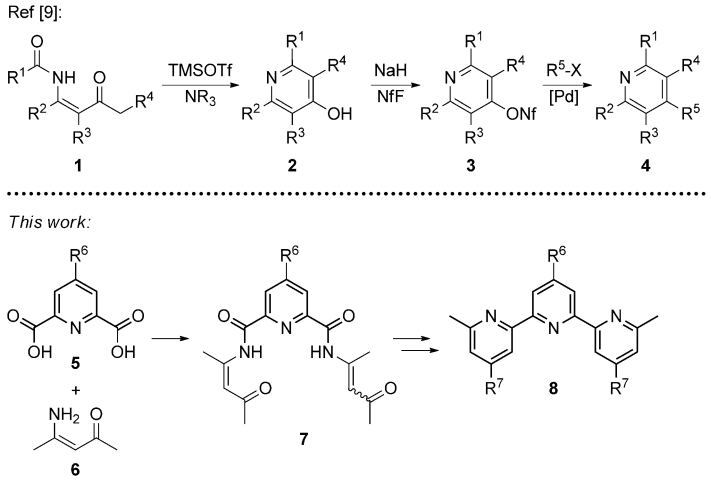
Paul Hommes, Christina Fischer, Christoph Lindner, Hendrik Zipse, and Hans-Ulrich Reissig**

Dedicated to Professor Wolfgang Steglich

Abstract: *A versatile method for the synthesis of functionalized 2,2′:6′,2″-terpyridines by assembly of the terminal pyridine rings is presented. The cyclization precursors—bis-β-ketoenamides—are prepared from 4-substituted 2,6-pyridinedicarboxylic acids and acetylacetone or its corresponding enamino ketone. Treatment with trimethylsilyl trifluoromethanesulfonate induces a twofold intramolecular condensation providing an efficient access to 4,4″-di- and 4,4′,4″-trifunctionalized 6,6″-dimethyl-2,2′:6′,2″-terpyridines. Using this method, hitherto unknown 4,4″-bis(dimethylamino)- and 4,4′,4″-tris(dimethylamino)terpyridines have been prepared that show remarkably high calculated Lewis basicities.*

Due to their ability to form stable complexes with various transition-metal ions of different oxidation states, 2,2′:6′,2″-terpyridines have evolved to one of the most important classes of chelating ligands during the last two decades.[1] Many polypyridyl complexes show remarkable electronic, photophysical, and redox properties that may be fine-tuned by the choice of substituents at the pyridine rings. This resulted in the development of numerous promising applications of terpyridine metal complexes.[2] The number of new applications[3] continues to increase, but efficient syntheses of functionalized terpyridine ligands and the accessible structural diversity are still limited. Two strategies are common:[1a,4] traditional ring-assembly methods[5] (formation of the inner or the terminal pyridine rings by condensations of pyridine-containing precursors or by cycloadditions), and cross-coupling reactions using functionalized pyridine building blocks. Due to the inherent reactivity of metalated 2-pyridyl species,[6] the latter approach was restricted to Stille reactions for a long time,[7] but recent progress in cross-coupling approaches[8] is likely to overcome this limitation. Despite these synthetic strategies, a fast and efficient synthesis of multifunctionalized terpyridines remains a challenge. The vast majority of applications feature terpyridines that are linked to other functional entities via the 4′-position.

In this context we explored the potential of our approach to polysubstituted pyridine derivatives with regard to the synthesis of multifunctionalized terpyridines. The method is based upon the TMSOTf-promoted cyclocondensation of β-ketoenamides **1** to 4-hydroxypyridines **2** (Scheme 1, top)[9] which may be functionalized by palladium-catalyzed cross-coupling reactions[10] of the 4-pyridyl nonaflates **3**.[11] Encouraged by the successful preparation of one 2,2′:6′,2″-terpyridine derivative by this method,[9d] we envisioned a new general approach for the preparation of 4,4″-di- and 4,4′,4″-trifunctionalized 2,2′:6′,2″-terpyridines **8** from pyridine-2,6-dicarboxylic acids **5** and β-enaminoketone **6**[12] (Scheme 1, bottom).



Scheme 1. β-Ketoenamides **1** and **7** as precursors for highly substituted pyridine derivatives **4** and of 4,4′,4″-trisubstituted 6,6″-dimethyl-2,2′:6′,2″-terpyridines **8**. TMSOTf = trimethylsilyl trifluoromethanesulfonate; NfF = nonafluorobutanesulfonyl fluoride.

Following our interest in 4-(dimethylamino)pyridine (DMAP) analogues[13] we selected dimethylamino-substituted terpyridines as targets. The electron-donating effect of amino groups in *para*-position to the pyridine nitrogen atoms in terpyridines enhances their σ-donor character and strongly

[*] Dr. P. Hommes, C. Fischer, Prof. Dr. H.-U. Reissig
Institut für Chemie und Biochemie, Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
E-mail: hans.reissig@chemie.fu-berlin.de
Dr. C. Lindner, Prof. Dr. H. Zipse
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, 81377 München (Germany)
E-mail: zipse@cup.uni-muenchen.de
Dr. P. Hommes
Current address: Helmholtz-Zentrum Geesthacht
Institut für Biomaterialforschung
Kantstrasse 55, 14513 Teltow (Germany)

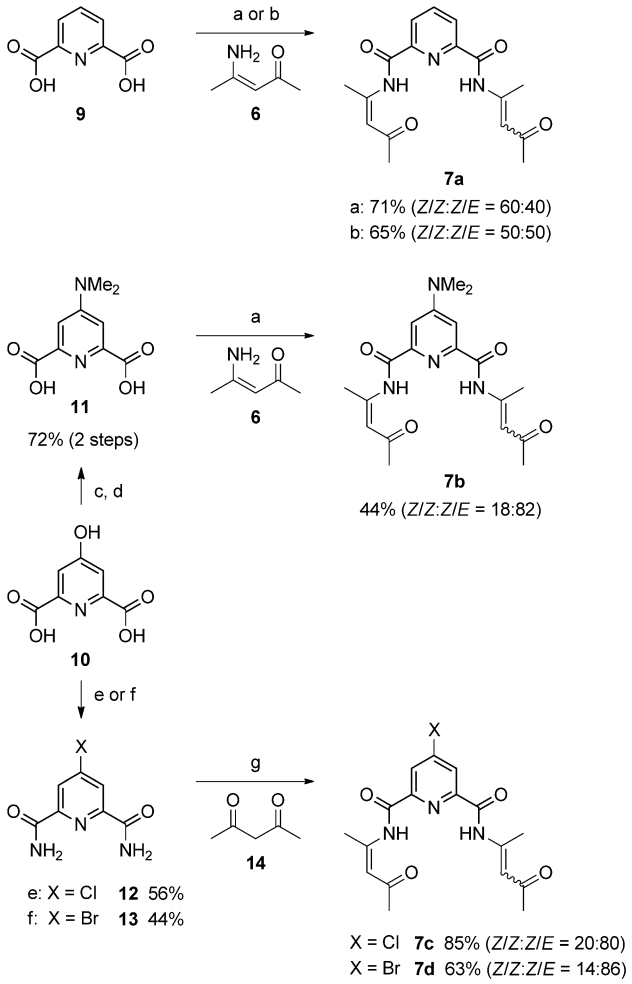
[**] This work was supported by the Deutsche Forschungsgemeinschaft and Bayer HealthCare.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403403.

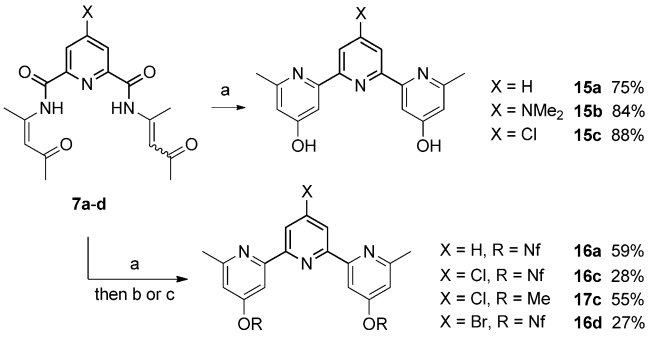
influences the photophysical[14] and other properties[15] of transition-metal complexes.

The synthesis of suitable cyclization precursors for this approach starts from commercially available pyridine-2,6-dicarboxylic acid (**9**) and chelidamic acid (**10**) (Scheme 2).[16] As reported, bis-β-ketoenamide **7a** can be prepared by reacting pyridine-2,6-dicarbonyl dichloride with acetylacetone-derived enaminoketone **6**.[9d] Alternatively, **7a** may be synthesized from **9** and **6** using the coupling agent BOP. The 4-dimethylamino-substituted bis-β-ketoenamide **7b** was synthesized by acylation of **6** with the dichloride of 4-(dimethylamino)pyridine-2,6-dicarboxylic acid (**11**), which is available from chelidamic acid (**10**) in two steps.[17] The halogenated bis-β-ketoenamides **7c** and **7d** were prepared from **10** using a slightly different approach, since the synthesis from 4-halogenated pyridine-2,6-dicarboxylic acids as described for **7a** and **7b** was rather inefficient. After halogenation of **10** the halogenated diacyl halides were treated with ammonia to give compounds **12** and **13**, which were condensed with acetylacetone (**14**)[18] affording the bis-β-ketoenamides **7c** and **7d**. All bis-β-ketoenamides were obtained as mixtures of *Z*/*Z* and *Z*/*E* isomers.[9d,19]

We investigated the crucial TMSOTf-promoted cyclocondensation[20] of precursors **7a–7d** (Scheme 3). The expected 4,4″-dihydroxy-6,6″-dimethyl-substituted terpyridines **15a–c** were obtained in very good yields (75–88%).



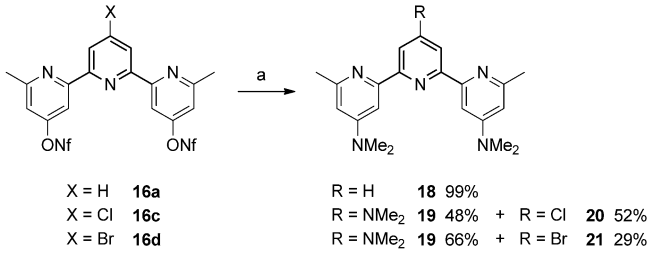
Scheme 2. Preparation of bis-β-ketoenamides **7a–d** starting from pyridine-2,6-dicarboxylic acids. Reagents and conditions: a) 1. $SOCl_2$, reflux, 2 d; 2. **6** (2 equiv), NEt_3, CH_2Cl_2, 0°C to RT, overnight. b) **6** (2 equiv), BOP, NEt_3, CH_2Cl_2, RT, 2 d. c) 1. $PhPOCl_2$, 120°C, 3 h; ii) H_2O, RT, 1 h (84%). d) $HNMe_2$ (40%$_{aq}$), sealed tube, 160°C, 2 d (86%). e) 1. $SOCl_2$, DMF (cat.), reflux, 1 d; 2. NH_3 (25%$_{aq}$), CH_2Cl_2, 0°C to RT, 2 d. f) 1. PBr_5, 90°C, 6 h; 2. $CHCl_3$, EtOH, RT, 15 min; 3. NH_3 (25%$_{aq}$), 0°C, 30 min. g) **14** (excess), PTSA (cat.), toluene, reflux, overnight. BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate; PTSA = *p*-toluenesulfonic acid.



Scheme 3. Cyclization of the bis-β-ketoenamides **7a–d** to 4,4″-dihydroxy-2,2′:6′,2″-terpyridines **15a–c** and bisnonaflates **16a**, **16c** and **16d** or dimethoxy compound **17c**. Reagents and conditions: a) TMSOTf, DIPEA, DCE, reflux, 3 d. b) NaH, NfF, THF, RT, overnight. c) MeI, K_2CO_3, acetone, reflux, overnight. DCE = 1,2-Dichloroethane; DIPEA = *N*,*N*-diisopropylethylamine.

For an easy purification and to allow subsequent reactions in 4- and 4″-position we also subjected the crude dihydroxyterpyridines to nonaflations using NaH and NfF. For **7a** the desired terpyridyl bisnonaflate **16a** was obtained in 59% yield over two steps, but the halogenated compounds **16c** and **16d** were isolated only in moderate yields. Apparently, the nonaflation of the crude cyclization products is inefficient under these conditions. Unfortunately, nonaflation of purified **15c** was also inefficient and did not provide a significantly higher yield of **16c** (see SI for details). In contrast, the alkylation of the 4′-chloro-4,4″-dihydroxyterpyridine **15c** with methyl iodide was fairly efficient, providing the corresponding dimethoxy derivative **17c** in 55% yield over two steps. To our surprise the employed nonaflation conditions failed completely with 4,4″-dihydroxy-4′-dimethylamino-terpyridine **15b**.[21] Even though optimization of the nonaflation step is still required the presented cyclization–nonaflation sequence offers a concise access to functionalized 6,6″-dimethyl-2,2′:6′,2″-terpyridines from simple precursors.

For the preparation of dimethylamino-substituted terpyridines[22] we subjected the terpyridyl bisnonaflates to an aromatic nucleophilic substitution reaction with dimethylamine. After precursor **16a** had been heated with an excess of the amine in THF, 4,4″-bis(dimethylamino)-terpyridine **18** was obtained in excellent yield (Scheme 4). Whereas under the same reaction conditions the nonafloxy groups of the terminal pyridine rings of **16c** and **16d** were readily displaced,



Scheme 4. Synthesis of dimethylamino-substituted terpyridines **18** and **19**. Reagents and conditions: a) $HNMe_2$ (2 M in THF), sealed tube, 70 °C, 2 d.

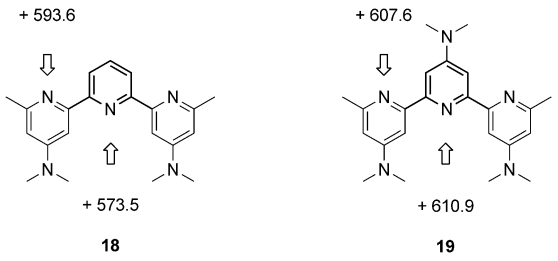


Figure 1. Calculated methyl cation affinities (MCA in kJ mol^{-1}) for dimethylamino-substituted terpyridines **18** and **19**.

nucleophilic substitution at the central halogenated pyridine core was incomplete. The desired 4,4′,4″-tris(dimethylamino)terpyridine **19** was obtained as mixture with the corresponding 4′-chloroterpyridine **20** and the 4′-bromo derivative **21**. The reaction of **16c** gave a product ratio of ca. 1:1 whilst that of **16d** provided a ratio of about 2:1 in favor of the desired product **19**. In both cases treatment of the mixtures with an excess of dimethylamine did not alter the product ratios, indicating that **19** was not formed from **20** or **21**. Once the dimethylamino substituents are present at the terminal pyridine rings, the resulting electronic deactivation of the central core towards nucleophilic attack apparently inhibits further displacement of the 4′-halo substituents. It seems that the 4′-bromo substituent of **16d** is displaced slightly faster than the 4′-chloro substituent of **16c**.[23] Compounds **19** and **20** or **21**, respectively, can easily be separated by column chromatography.

The Brønsted basicities of dimethylamino-substituted pyridines **18** and **19** should be high due to the electron-donating nature of the substituents. This is reflected by the chemical shifts observed in the NMR spectra of **18** and **19** (see Figure S1 in the SI). The preliminary results of transprotonation experiments with **18** studied by ^{1}H NMR spectroscopy,[24] however, indicate that the pK_{aH} of the protonated species of **18** and **19** should be rather similar to that of DMAP (pK_{aH} = 17.7 (MeCN);[25] see Figure S2 in the SI). Due to a very fast transprotonation between DMAP and the dimethylamino-substituted terpyridine in MeCN and the poor solubility of neutral **18** and **19** in non-chlorinated solvents, we have not been able to determine the exact pK_{aH} values by this method.

Methyl cation affinities (MCA) of **18** and **19** were calculated as a measure of the Lewis basicities of these compounds. The MCA of a Lewis base (LB) is obtained as the reaction enthalpy (298.15 K at 1 bar) for the transformation shown in Equation (1). This definition is in analogy to that for proton affinities (PA) and implies large positive energies for strong Lewis bases.

$$\overset{\oplus}{\mathrm{LB{-}CH_3}} \xrightarrow{\Delta H_{298}} \mathrm{LB} + \overset{\oplus}{\mathrm{CH_3}} \qquad (1)$$

The MCA values for terpyridines **18** and **19** calculated at the MP2(FC)/6-31 + G(2d,p)//B98/6-31G(d) level of theory[26,27] (Boltzmann-averaged) are shown in Figure 1. When compared with MCA values of common nitrogen Lewis bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (+609.6 kJ mol^{-1}) and electron-rich pyridines such as DMAP (+581.2 kJ mol^{-1}) we note that the two terpyridines **18** (+593.6 and +573.5 kJ mol^{-1}) and **19** (+607.6 and +610.9 kJ mol^{-1}) studied here are among the most Lewis basic pyridine derivatives studied so far.[26,28] These remarkably high values are quite surprising, in particular because of the significant difference to the structurally related subunit DMAP. MCA values calculated for less substituted terpyridines (see SI for details) indicate that the high Lewis basicity of the central pyridine ring in **19** is due to the donor substituent at 4′-position, but it also benefits from the donor substituents of the two outer pyridine rings.

Inspection of the preferred conformations of neutral and *N*-methylated **19** in Figure 2 indicates that reactions of the pyridine nitrogen atoms in **19** may be accompanied by a sizeable steric effect. Whereas for neutral parent compound **19** a planar transoid conformation of the conjugated pyridine rings is predicted, *N*-methylation slightly twists the reacting pyridine ring out of conjugation with its direct neighbors. A cisoid conformation of the pyridine rings is adopted in this case (Figure 2b and c), to reduce steric interactions of the newly attached methyl group and the neighboring pyridine rings. An electrostatic attraction between the *N*-methyl group and the electron-donating nitrogen atoms of the adjacent pyridine rings also contributes to the stabilization of the cisoid conformation. The high methyl cation affinities indicate that compounds **18** and **19** should be excellent ligands for positively charged central atoms and that they are likely to stabilize new entities in an unprecedented manner.

As demonstrated in many examples,[9,29] 4-pyridyl nonaflates are excellent candidates for palladium-catalyzed reactions (Scheme 1). Scheme 5 shows examples for terpyridyl bisnonaflate **16a**.[30] Reductive removal[31] of the nonafloxy substituents of **16a** efficiently provided 6,6″-dimethylterpyridine **22**[32] in 86% yield. Compound **16a** was also subjected to a Suzuki coupling with 4-fluorophenylboronic acid to give terpyridine **23** in excellent yield and Stille coupling with a (trifluorovinyl)stannane[33] provided terpyridine **24** in 70% yield. We also subjected 4′-bromoterpyridine **21** to a Sonogashira coupling with an alkyne affording terpyridine **25** in 72% yield. These examples show that compounds such as **16a** and **21** can lead to libraries of novel terpyridine derivatives. The 6,6″-methyl groups of terpyridines should allow further reactions giving compounds with two additional donor moieties.[9d,34]

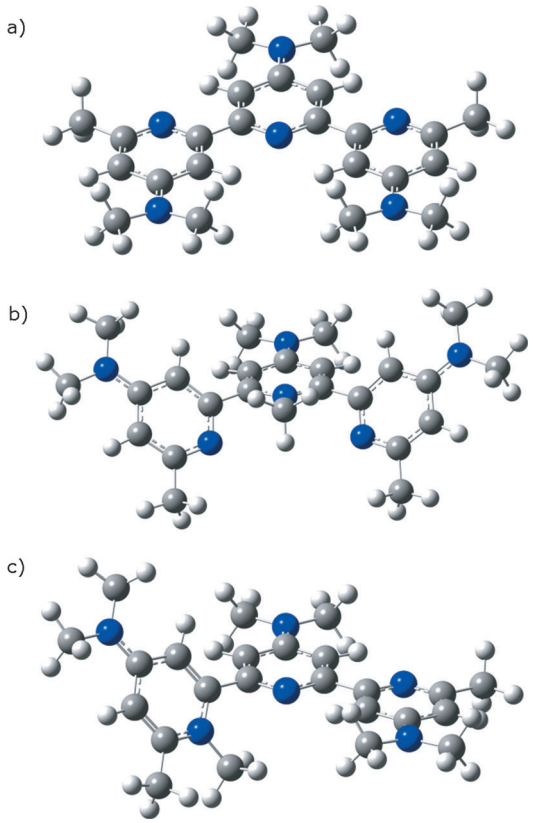
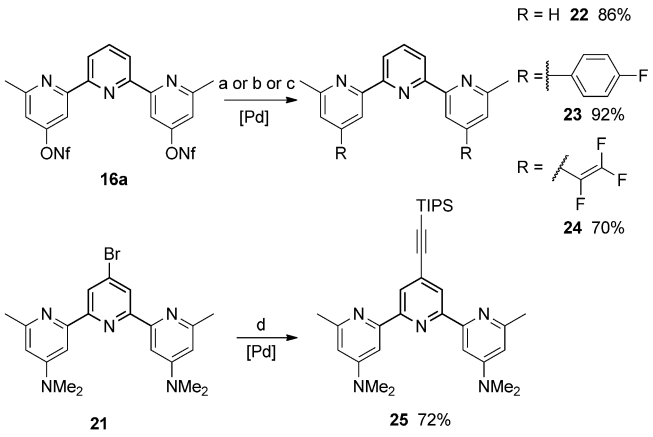


Figure 2. Predicted conformations of neutral **19** (a) and the two *N*-methylated species of **19** (b) and (c).



Scheme 5. Transition-metal-catalyzed reactions of the terpyridines **16a** and **21**. Reagents and conditions: a) HCO_2H, NEt_3, dppp, $Pd(OAc)_2$, DMF, 80 °C, 2 h. b) 4-$FC_6H_4B(OH)_2$, $[Pd(PPh_3)_4]$, K_2CO_3, DMF, 90 °C, 2 h. c) $Bu_3SnCF{=}CF_2$, $[Pd(PPh_3)_4]$, DMF, 60 °C, 1 h. d) $HC{\equiv}CSi(iPr)_3$, iPr_2NH, $[PdCl_2(PPh_3)_2]$, CuI, THF, reflux, 24 h. dppp = 1,3-Bis(diphenylphosphino)propane; TIPS = triisopropylsilyl.

In conclusion, our results reveal that the new approach to functionalized 2,2′:6′,2″-terpyridines will enhance the accessibility of tailor-made ligands and hence it is a valuable addition to established strategies. The prepared 4-dimethylamino-substituted derivatives are compounds that deserve further studies as ligands for metal ions and other central atoms. Although the Brønsted basicity is only in the range of DMAP the very high calculated methyl cation affinities promise unprecedented Lewis base properties.

Received: March 17, 2014
Published online: June 4, 2014

Keywords: cross-coupling · DMAP analogues · ketoenamides · Lewis bases · terpyridines

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