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Tuning the keto equilibrium in 4-substituted dipicolinic acid derivatives

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The synthesis of 4-substituted dipicolinic acid derivatives requiring palladium catalysis is described. A keto–enol equilibrium has been observed, depending on the nature of the 2,6-position substituents.

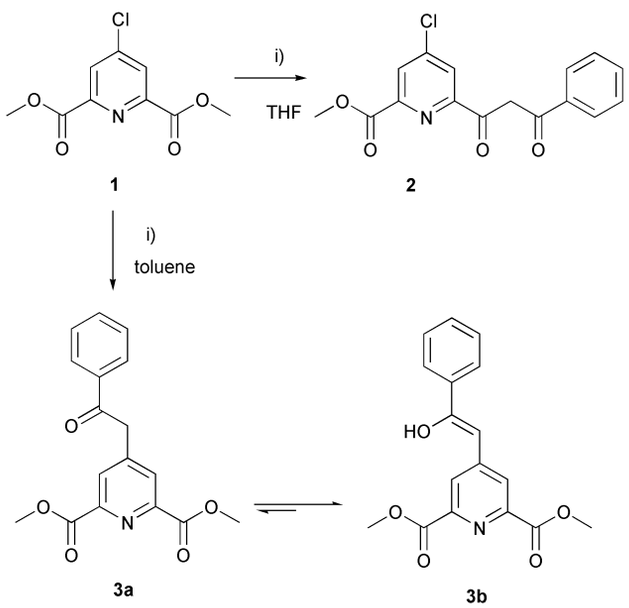
Introduction

The tridentate aromatic anion dipicolinate (dpa) forms stable nine-coordinate complexes with lanthanide ions in water.[1] In $[Ln(dpa)_3]^{3-}$, the ligand strands are helically wrapped around the metal ion, generating chiral assemblies, as demonstrated by circularly polarized luminescence.[2] Several luminescent compounds have been studied which incorporate the $[Ln(dpa)_3]^{3-}$ complex anion, for instance 3d–4f complexes[3] or invisible inks for bar codes.[4] Present interest in the design of lanthanide-containing luminescent probes for biomedical analyses[5] makes complexes based on the tris(dipicolinate) framework quite attractive in view of the sizeable quantum yield of the parent compounds (12% for Eu and 21% for Tb),[6] and of the relative ease with which the 4 position of the pyridine moiety can be substituted. Indeed, varying the substituent in this position allows one to finely tune the photophysical properties of the resulting complexes.[7] Moreover, functional groups may be introduced in this position for chiral resolution[8] or for coupling with biological materials,[9] yielding bifunctional chelators *e.g.* for immunoassays.[10] Lanthanide-containing luminescent probes rely on the antenna effect[11] to sensitize the metal-centred luminescence and it has been demonstrated that phenylphenacyl and phenacyl groups grafted onto a calixarene[12] or cyclen[13] framework are very effective in transferring energy onto these metal ions. We have therefore undertaken efforts to attach these functional groups in the 4-position of pyridine-2,6-dicarboxamide and we discuss here the synthesis of these chelating agents, as well as their keto–enol tautomerism which, until now, has not attracted attention, although this phenomenon has been well studied for similar heterocycles.[14]

Results and discussion

Our first attempt to create a C–C bond, starting from 4-chloropyridine-2,6-dicarboxylic acid dimethyl ester which is easily obtained from 4-hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid), consisted of adding acetophenolate to 4-chloropyridine-2,6-dicarboxylic acid dimethyl ester **1** according to a procedure that we recently reported.[15] However, this reaction led to 4-chloro-6-(3-oxo-3-phenylpropionyl)pyridine-2-carboxylic acid methyl ester **2** only and no substitution of the chlorine was observed (Scheme 1). We therefore turned to the use of palladium catalysis. The experiments were conducted under an inert atmosphere in the presence of acetophenone, NaO^{t}Bu or NaHMDS (sodium bis(trimethylsilyl)amide) as base, a palladium catalyst either generated *in situ* from $Pd(OAc)_2$ and a phosphine co-ligand, or commercially available, $(Ph_3P)_2PdCl_2$ in THF or toluene. The results are summarised in Table 1.

The reaction is solvent dependant, whatever the base is: in



i): $PhCOCH_3$, NaO^{t}Bu or NaHMDS, $Pd(OAc)_2$ and $P(^tBu)_3$ or $(Ph_3P)_2PdCl_2$

Scheme 1

THF, chlorine is substituted leading to **3** (entries 1 and 2). On the contrary, in toluene, β-diketone **2** is the major product (entries 3 and 4). The same product **2** is obtained with mixed solvents (entries 5 and 6). These results can be explained by differences in the solvation of the sodium cation. In a non-solvating solvent such as toluene, the sodium ion is stabilised in the presence of the β-diketonate, and the resulting complex becomes the thermodynamically stable product, while THF stabilises the metal ion under its solvate form $[Na(THF)_n]^+$ so that there is no competition between the Claisen condensation and the chlorine substitution, the latter apparently leading to the thermodynamically preferred products. The reaction has to be performed at room temperature otherwise, upon warming, **2** again becomes the major compound.

An increasing number of publications are dealing with C–C bond formation assisted by palladium catalysts, namely for the α-arylation of ketones. The choice of base is critical to avoid the Claisen condensation of a ketone enolate with an aryl halide fitted with ester or nitrile functions. For instance, Fox *et al.* have demonstrated that NaHMDS is preferred over NaO^{t}Bu.[16] We have, nevertheless, tested both bases. In THF, the desired product **3** was isolated with both bases, the yields being larger with NaO^{t}Bu (entries 1 and 2); in the case of NaHMDS, unreacted

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Table 1 Reaction conditions for the addition of acetophenolate to 4-chloropyridine-2,6-dicarboxylic acid dimethyl ester in the presence of a palladium catalyst and yields of the isolated products

Entry	Base	Eq.	Solvent	**2**	**3**
1	NaHMDS	2.2[a]	THF	15%	25%
2	NaO^{t}Bu	2.2[a] or [b]	THF	<5%	42%
3	NaHMDS	2.2[a]	Toluene	42%	8%
4	NaO^{t}Bu	2.2[a] or [b]	Toluene	56%	12%
5	NaHMDS	2.2[a]	Toluene–THF 50 : 50	39%	10%
6	NaO^{t}Bu	2.2[a]	Toluene–THF 50 : 50	41%	11%
7	NaO^{t}Bu	1[a] or [b]	THF	<5%	37%

[a] $Pd(OAc)_2$ + $P(^tBu)_3$ 1%. [b] $(PPh_3)_2PdCl_2$ 1 mol%.

Table 2 Ketone : enol percentages in various solvents as determined by ^{1}H-NMR

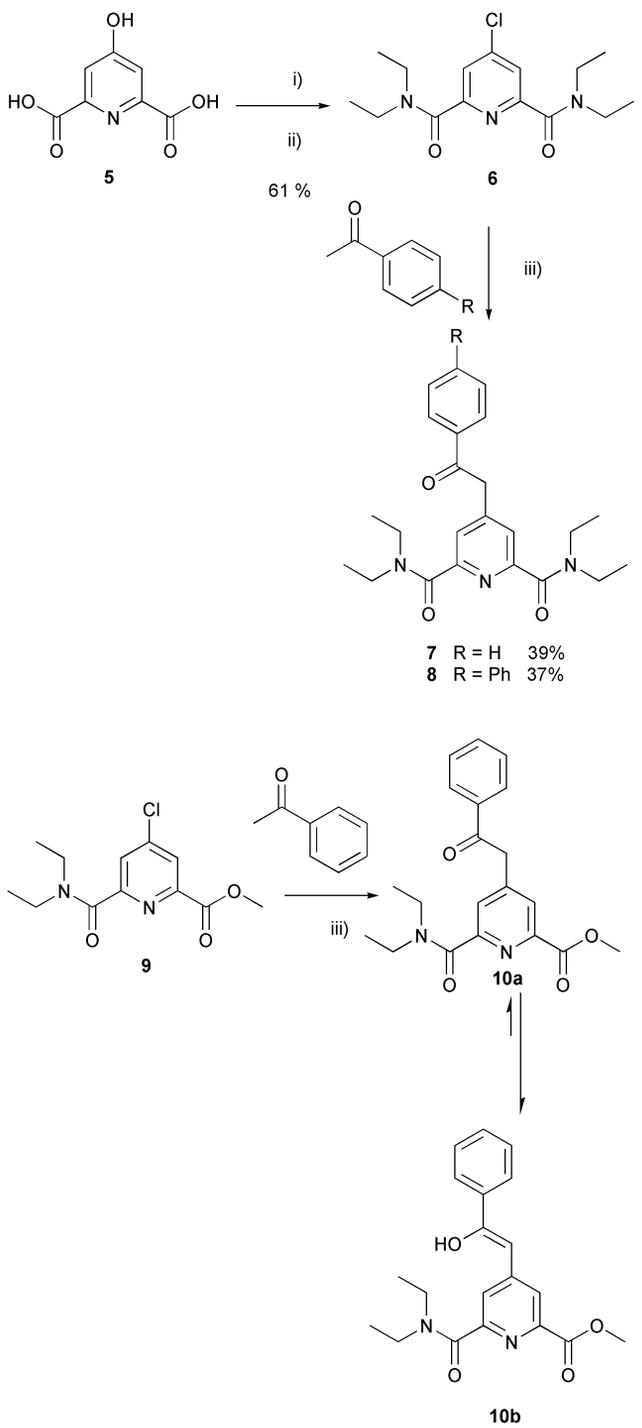
Solvent	**3a : 3b**	**7**	**8**	**10a : 10b**
$CDCl_3$	4.5 : 95.5	100	100	20 : 80
CD_3CN	8 : 92	100	100	30 : 70
DMSO d_6	29 : 71	100	100	43 : 57

starting material was recovered. We have also tested the number of equivalents of base needed (entries 2 and 7). In the case of methyl alkyl ketones, the enolate ion of the product is formed preferentially to the enolate of the starting ketone with one equivalent of base, the enolate of the product being an active reagent for the arylation process.[17] Therefore, two equivalents of alkoxide base ensure that all the ketone exists in its enolate form. In our experiments, the yield of the desired product **3** was only slightly improved with 2.2 equivalents compared with 1. We also observed the formation of an unstable product identified as being the 4-(2-oxo-2-phenylethyl)pyridine-2,6-dicarboxylic acid monomethyl ester **4** from its mass spectrum and ^{1}H/^{13}C-NMR spectra. If a larger amount of base is used (>4 eq.), **4** becomes the major product of the reaction. In summary, the best conditions were determined to be 2.2 equivalents of the alkoxide base and 1 mol% of catalyst, the exact nature of which is not so important.

Tuning the ketone–enol equilibrium

In fact, **3** was isolated as a mixture of 4-(2-oxo-2-phenylethyl)-pyridine-2,6-dicarboxylic acid dimethyl ester **3a** and (*Z*)-4-(2-hydroxy-2-phenylvinyl)pyridine-2,6-dicarboxylic acid dimethyl ester **3b** (Scheme 1), the equilibrium being displaced in favour of the *Z*-enol isomer, according to ^{1}H and ^{13}C-NMR spectra. The ratio of the keto *vs.* enol compound depends upon the polarity of the solvent, as reported in Table 2. Such a keto–enol tautomerism has been observed in the case of phenacylpyridines,[14,18] for which the enol form is favoured in apolar solvents, while polar solvents favour the keto form.[19] According to the NMR spectra, only the *Z*-enol isomer of **3b** was observed, the formation of the *E* isomer being totally prevented, probably because of steric hindrance generated by the phenyl moiety.

To test the influence of the 2,6 substituents, 4-chloro-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide **6** was also synthesized and reacted with acetophenone under the same experimental conditions as those optimized for **1** (Scheme 2). This reaction resulted in the isolation of 4-(2-oxo-2-phenylethyl)-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide **7** in 39% yield. No reaction occurs in the absence of the palladium catalyst. On the other hand, compound **6** does not react with 1-(biphenyl-4-yl)ethanone under the same experimental conditions, 4-[2-(biphenyl-4-yl)-2-oxoethyl]-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide **8** is only isolated as a trace. A more substantial yield (37%) can be obtained however, if the mixture is refluxed for 3 days in THF.



i) $PhPOCl_2$, ii) Et_2NH
iii) $Pd(OAc)_2$ and $P(^tBu)_3$ or PPh_3, 2 NaO^tBu , THF

Scheme 2

According to NMR and IR studies, **7** and **8** are only present as ketones and no keto–enolic equilibrium is observed, whatever the solvent is. This demonstrates that, compared with amide substituents, the electron-withdrawing ability of the ester groups provides considerable stabilization of the enol form. Finally, if the same experiment is performed with the 4-chloro-6-diethylcarbamoylpyridine-2-carboxylic acid methyl ester **9**, the major product recovered is the enol 6-diethylcarbamoyl-4-(2-hydroxy-2-phenylvinyl)pyridine-2-carboxylic acid methyl ester **10**, but the percentage of the keto form is larger than with (**3**) (see Table 2). Thus, if a single ester moiety provides sufficient π delocalization to induce a large proportion of the enol form, the cumulative effect of two such groups is needed to solely produce the enol form. This probably results from the low electron density on the oxygen atom of the carbonyl function of the ester compared with that found in carboxamides.[20]

Conclusion

In conclusion, we have synthesised a new family of dipicolinic acid derivatives substituted in the 4-position by a chromophoric group. The use of a palladium catalyst enables the formation of the C–C bond and, depending of the nature of the 2,6 substituents, ester or amide, either the ketone or the enol form is favoured. Therefore the light-harvesting properties of these molecules can be modulated, which is of great interest for the design of lanthanide-containing luminescent probes. Work is in progress towards this goal and will be reported elsewhere.

Experimental

General methods

Reactions were conducted under an inert atmosphere with standard Schlenk and drybox techniques. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Palladium catalysts obtained from Fluka or Strem gave the most reproducible results. ESI-MS spectra were measured on a Finnigan SSQ 710C spectrometer on 10^{-4} M solutions in methanol; the capillary temperature was set to 200 °C and the acceleration potential to 4.5 kV. ^{1}H and ^{13}C-NMR spectra were recorded at 25 °C on a Bruker AV, 400 MHz. Chemical shifts are reported in parts per million with respect to TMS. *J* values are given in Hertz. Elemental analyses were performed by Dr H. Eder (Microchemical Laboratory, University of Geneva).

4-(2-Oxo-2-phenylethyl)pyridine-2,6-dicarboxylic acid dimethyl ester (3)

Sodium *tert*-butoxide (186 mg, 1.9 mmol), $(Ph_3P)_2PdCl_2$ (12.2 mg, 17.6 μmol) or $Pd(OAc)_2$ (3.6 mg, 17.6 μmol) and $P(^tBu)_3$ (2.8 mg, 17.6 μmol), acetophenone (116 mg 0.96 mmol) and THF (3 mL) were added in a dry flask to 4-chloropyridine-2,6-dicarboxylic acid dimethyl ester (200 mg, 0.86 mmol). The mixture was stirred under N_2 for 12 h at rt, the solvent was removed and the crude product dissolved in 100 mL dichloromethane, washed with 2 × 50 mL 0.1 M HCl and then with 2 × 50 mL water. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. After purification by silica gel chromatography (MeOH–CH_2Cl_2 1 : 99), **3** was isolated as a pale yellow product (115 mg, 42%). Anal. Calcd for $C_{17}H_{15}NO_5$ (%): C 65.17, H 4.83, N 4.47, found: C 64.98, H 4.95, N 4.37, ESI-MS: *m*/*z* = 314.07 $[M + H]^+$ (Calc. 314.10), δ_H (400 MHz, $CDCl_3$, ppm): (**3a**) 8.09 (2H, d, *J* 7.1 Hz), 7.85 (1H, d, *J* 2.7 Hz), 7.76 (1H, d, *J* 2.7 Hz), 7.58 (1H, m, *J* 7.8 Hz), 7.51 (2H, m, *J* 7.9 Hz), 7.50 (1H, s), 4.05 and 4.00 (2 × 3H, s), δ_C: 186.4, 182.9, 167.7, 165.3, 154.6, 149.3, 135.0, 132.8, 128.7, 128.6, 127.6, 113.9, 110.6, 94.1, 55.9 and 53.0, δ_H (400 MHz, DMSO-d_6, ppm): (**3a**): 7.97 (2H, d, *J* 7.2 Hz), 7.68 (1H, d, *J* 2.4 Hz), 7.65 (1H, d, *J* 2,4 Hz), 7.58 (1H, m), 7.54 (2H, m), 4.88 (2H, s), 4.02 and 3.75 (2 × 3H, s); (**3b**): 8.02 (2H, d, *J* 7.3 Hz), 7.79 (1H, d, *J* 2.4 Hz), 7.72 (1H, d, *J* 2,4 Hz), 7.69 (1H, m), 7.60 (2H, d, *J* 7.8 Hz), 7.50 (1H, s), 4.05 and 4.00 (2 × 3H, s).

4-Chloro-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide (6)

Chelidamic acid monohydrate (1000 mg, 4.9 mmol) and *P,P*-dichlorophenylphosphine oxide (8 mL, 5.7 mmol) were heated at 130 °C for 2 h, the solution was cooled to rt and freshly distilled diethylamine (10 mL) was added very carefully. The solution was further stirred for 2 h and evaporated. The brown residue was diluted with dichloromethane, and washed with water. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The solid was dissolved in diethyl ether and the insoluble products eliminated by filtration. After slow evaporation of the solvent, **6** was obtained as shiny crystals (1200 mg, 78%). Anal. Calcd for $C_{15}H_{22}ClN_3O_2$ (%): C 57.78, H 7.11, N 13.48, found: C 57.74, H 7.04, N 13.44, δ_H (400 MHz, $CDCl_3$, ppm): 7.63 (2H, s), 3.54 and 3.33 (2 × 4H, q, *J* 7.1 Hz), 1.25 and 1.15 (2 × 6H, t, *J* 7.1 Hz), δ_C (400 MHz, $CDCl_3$, ppm): 166.78, 154.76, 146.0, 124.1, 43.2, 40.2, 14.2 and 12.7, ESI-MS: *m*/*z* = 312.18 $[M + H]^+$ (Calc. 312.15).

4-(2-Oxo-2-phenylethyl)-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide (7)

The same procedure as that described for the synthesis of **3** was used, starting from **6** (265 mg, 0.86 mmol). After chromatography, 4-(2-oxo-2-phenylethyl)-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide **7** was recrystallized by diethyl ether diffusion in ethanol (132 mg, 39%). Anal. Calcd for $C_{23}H_{29}N_3O_3$ (%): C 69.85, H 7.39, N 10.62, found: C 69.14, H 7.00, N 10.64, δ_H (400 MHz, $CDCl_3$, ppm): 8.0 (2H, dd, *J* 7.0 and 2 Hz), 7.60 (1H, m), 7.54 (2H, s), 7.49 (2H, m), 4.34 (2H, s), 3.56 and 3.34 (2 × 4H, q, *J* 7.0 Hz), 1.25 and 1.14 (2 × 6H, t, *J* 7.0 Hz), δ_C: 167.9, 153.7, 145.7, 133.8, 128.9, 128.4, 124.9, 44.3, 43.3, 40.1, 14.2 and 12.7, ESI-MS: *m*/*z* = 396.37 $[M + H]^+$ (Calc. 396.49).

4-[2-(Biphenyl-4-yl)-2-oxoethyl]-*N,N,N′,N′*-tetraethylpyridine-2,6-dicarboxamide (8)

Compound **6** (265 mg, 0.86 mmol), sodium *tert*-butoxide (186 mg, 1.9 mmol), Ph_3P (4.6 mg, 17.6 μmol), $Pd(OAc)_2$ (3.6 mg, 17.6 μmol), 1-(biphenyl-4-yl)ethanone (160 mg, 0.95 mmol) and THF (10 mL) were combined in a dry flask. The mixture was refluxed under N_2 for 18 h, the solvent was removed and the crude product dissolved in 20 mL of dichloromethane, washed with 2 × 10 mL of 0.1 M HCl, then with 2 × 10 mL of water. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. After purification by silica gel chromatography (MeOH–CH_2Cl_2 1 : 99) the compound was precipitated in dichloromethane–pentane (150 mg, 37%). Anal. Calcd for $C_{29}H_{33}N_3O_3$ (%): C 73.86, H 7.05, N 8.9, found: C 74.44, H 7.05, N 9.91, δ_H (400 MHz, $CDCl_3$, ppm): 8.06 (2H, dd, *J* 8.3 and 1.2 Hz), 7.71 (2H, dd, *J* 9.3 and 1.2 Hz), 7.57 (2H, s), 7.48 (2H, m), 7.42 (1H, m), 3.56 and 3.35 (2 × 4H, q, *J* 7.0 Hz), 1.25 and 1.15 (3 × 6H, t, *J* 7.0 Hz), δ_C: 195.1, 168.4, 154.1, 146.8, 146.2, 140.0, 135.2, 129.4, 127.9, 127.7, 125.4, 44.8, 43.7, 40.6, 14.6 and 13.2, ESI-MS: *m*/*z* = 472.34 $[M + H]^+$ (Calc. 472.26).

6-Diethylcarbamoyl-4-(2-hydroxy-2-phenylvinyl)pyridine-2-carboxylic acid methyl ester (10)

The same procedure as that described for the synthesis of **3** was used, starting from 4-chloro-6-diethylcarbamoylpyridine-2-carboxylic acid methyl ester **9**.[15] Yield: 32% after chromatography (silica gel CH_2Cl_2–MeOH 98 : 2 v/v). δ_H (400 MHz, $CDCl_3$, ppm): 8.03 (2H, d), 7.72 (1H, s), 7.53–7.27 (4H, m), 7.28 (1H, d), 3.96 (3H, s), 3.62 and 3.44 (2 × 4H, q, 7.0 Hz) and 1.32 (12H, t, 7.0 Hz), δ_C: 183.1, 153.9, 132.5, 128.7, 127.7, 123.2,

111.7, 109.1, 93.6, 54.1, 43.3, 40.4, 13.7 and 12.5, ESI-MS : $m/z = 355.27$ $[M + H]^+$ (Calc. 355.17).

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