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A new versatile methodology for the synthesis of 4-halogenated-6-diethylcarbamoylpyridine-2-carboxylic acids

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Abstract—Convenient syntheses of dipicolinic or chelidamic acid derivatives including 4-X-6-diethylcarbamoyl-pyridine-2-carboxylic acid (X = H, Cl, Br) and 4-chloro-6-(3-oxo-3-phenylpropionyl)pyridine-2-carboxylic acid methyl ester are described. These compounds are important synthons for the synthesis of non-symmetric tridentate aromatic chelating agents as well as for the design of ditopic ligands targeted for the elaboration of functional dimetallic helicates. © 2001 Elsevier Science Ltd. All rights reserved.

Benzimidazole based compounds are versatile molecules that can be conveniently synthesised by a Phillips reaction.[1,2] In particular, they are adequate ligands for the complexation of whole ranges of d- and f-transition metal ions. Recently, they have been used for the construction of two- and three-dimensional supramolecular networks encapsulating trivalent lanthanide ions, Ln(III),[3] for the design of tripodal ligands, for the complexation of Ln(III) ions,[4,5] in the synthesis of spin-crossover Fe(II) compounds,[6,7] or in the preparation of bis ligands for the selective complexation of Zn(II).[8] Benzimidazole nucleic acid analogues have been recently synthesised that form duplex complexes with RNA,[9] and the condensation of two benzimidazole moieties results in the formation of interesting macrocyclic ligands.[10] During the last decade, we have been tailoring ditopic ligands derived from bis(benzimidazolyl)pyridine for the design of 4f–4f and 3d–4f bimetallic functional edifices with luminescent and/or magnetic properties.[11–13] Asymmetrically substituted synthons derived from chelidamic acid (**1**) or dipicolinic acid (**2**) and containing carboxamide binding units are known to enhance lanthanide luminescence, but are not easily obtained. Here we report a new and convenient way of synthesising these compounds in good yield.

The synthesis of 6-diethylcarbamoyl-pyridine-2-carboxylic acid (**5a**), we previously reported, consisted of a monoesterification of dipicolinic acid followed by coupling between its acylchloride and diethylamine, the resulting product being hydrolysed in potassium hydroxide.[13] We have now found that adding 1.1 equiv. of amide anion of diethylamine, readily obtained with *n*-butyllithium, to pyridine-2,6-dicarboxylic acid dimethyl ester (**3a**)[14] in THF gives 6-diethylcarbamoyl-pyridine-2-carboxylic acid methyl ester (**4a**),[15] which can easily be hydrolysed into (**5a**) (Fig. 1).[16] This new strategy produces a much better yield than previously reported (Table 1) and requires one step less.

Moreover, the same reaction can be extended to functionalising the 4-position of the pyridine, namely for obtaining 4-chloro-6-diethylcarbamoyl-pyridine-2-carboxylic acid methyl ester (**4b**)[17] or 4-bromo-6-diethylcarbamoyl-pyridine-2-carboxylic acid methyl ester (**4c**).[18] These compounds can also be directly hydrolysed into the corresponding acids (**5b**) and (**5c**). The previously described synthesis of (**5b**) and (**5c**) includes monoesterification of the carboxylic moieties followed by conversion of the other carboxylic moiety into acyl chloride, reaction with diethylamine in presence of triethylamine and a final saponification of the ester moiety.[13] The new synthetic path proposed here is more convenient, being shorter (three steps instead of six) and providing substantially better yields than obtained earlier (Table 1).[13]

When using 1.1 equiv. of amide ion and 4-halogenated-pyridine-2,6-dicarboxylic acid dimethyl ester (**3b**) or (**3c**), no halogen substitution is observed, even when starting from the very active bromo derivative. In the previous procedure, bromide was readily substituted in the presence of chlorinating agents or even in

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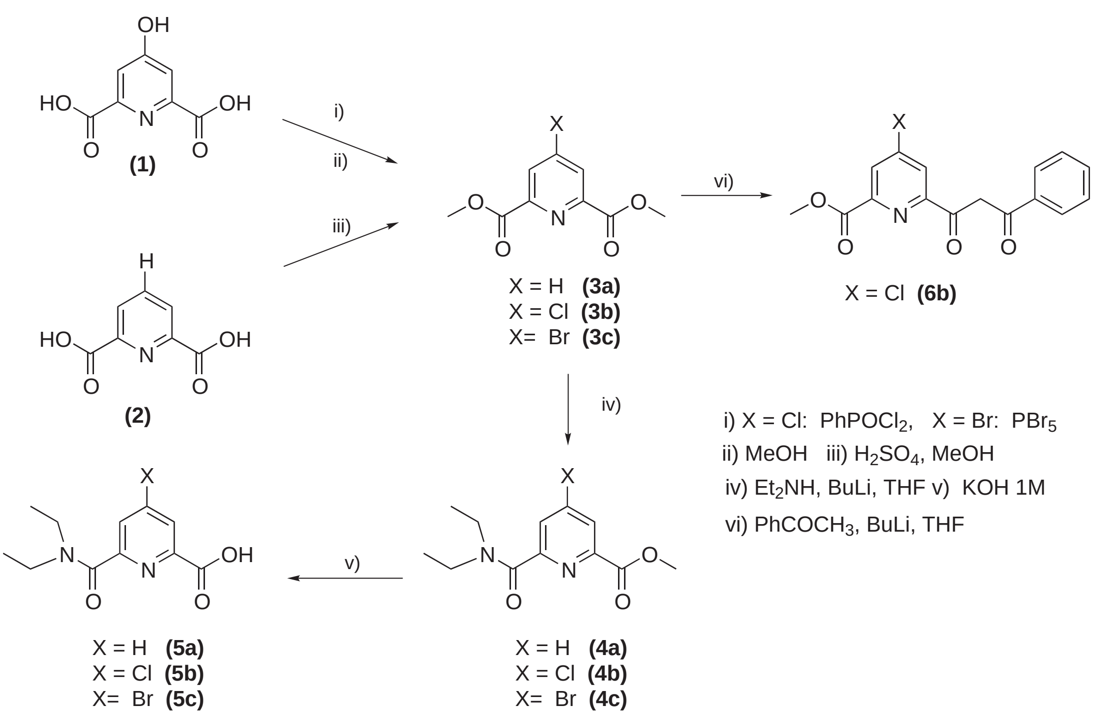

Figure 1.

Table 1. Synthesis of asymmetrically substituted derivatives of dipicolinic and chelidamic acids

Reactant	Nucleophilic agent	Product	This work yield (%)	Literature yield (%)
X=H (**2a**)	1.1 equiv. Et_2NH, BuLi, THF	**5a**	56.1	35.4[16]
X=Br (**3c**)	1.1 equiv. Et_2NH, BuLi, THF	**5c**	28.4	16.2[13]
X=Cl (**3b**)	1.1 equiv. Et_2NH, BuLi, THF	**5b**	58.0	46.7[13]
X=Cl (**3b**)	1.1 equiv. $PhCOCH_3$, BuLi, THF	**6b**	60.0	–
X=Cl (**3b**)	1.1 equiv. $PhCOCH_3$, NaOEt, EtOH	**6b**	50.2	–
X=Cl (**3b**)	2.2 equiv. $PhCOCH_3$, BuLi, THF	**6b**	60.8	–

dichloromethane so that oxallylbromide had to be used instead of acylchloride, and this should not be left too long in dichloromethane.[13] Despite these precautions the yield was low. Such a problem is avoided with the new synthesis (Fig. 1).

When using an excess of amide ion, simultaneous substitution of the two diester and chloride functions occurred.

Among bifunctional chelating agents used for the enhancement of lanthanide ion luminescence, dipicolinic acid, chelidamic acid or β-diketonates proved to be good candidates.[19] For this reason we have applied the described strategy to the synthesis of β-diketones by adding acetophenolate (obtained by addition of either BuLi in THF or sodium ethanolate in ethanol to acetophenone) to 4-chloro-pyridine-2,6-dicarboxylic acid dimethyl ester (**3b**). 4-Chloro-6-(3-oxo-3-phenylpropionyl)pyridine-2-carboxylic acid methyl ester (**6b**) was obtained as pale yellow crystals (Table 1).[20] When 2.2 equiv. of acetophenolate were added instead of 1.1 equiv., the same product (**6b**) was isolated with no substitution of the chloride or of the other ester moiety.

In conclusion, the new methodology for the synthesis of asymmetrically substituted derivatives of dipicolinic and chelidamic acids proved to be efficient and versatile since both carboxamide and β-diketone products were obtained. Thanks to the halo-substituent, these synthons are valuable for producing compounds in which both the pK_a of the carboxylic acid and the light-harvesting properties can be modulated. Furthermore, they can be used to introduce activated groups in ditopic chelating agents or coupling groups to form covalent linkages with biological material. Work is under way to develop such ligands and will be reported elsewhere.

Acknowledgements

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14. General procedure: an *n*-butyllithium solution 1.6 M in hexane (2.39 mmol) is added slowly under a nitrogen atmosphere to a mixture of diethylamine (2.39 mmol) in freshly distilled tetrahydrofuran (50 mL). After 10 min stirring, this yellow mixture is added very slowly under controlled atmosphere and with vigorous stirring to a solution of the 4-X-2,6-dimethylpyridindicarboxylate (X = H, Cl, Br) (2.17 mmol) in tetrahydrofuran (20 mL). The mixture becomes brown and is stirred at room temperature for 12 h. After solvent evaporation, a white–beige solid is obtained, dichloromethane is added and the solution is washed with a half-saturated solution of ammonium chloride (3×35 mL). The organic phase is dried on anhydrous disodium sulphate, filtered and the solvent is evaporated. Compounds (**4a**–**c**) or (**6b**) are obtained as brown solids. They are easily hydrolysed into their corresponding acids.
15. 6-(*N*,*N*-Diethylcarbamoyl)pyridine-2-methylcarboxylate (**4a**) IR (KBr) $\nu_{C=O} = 1680$ (CONEt$_2$), 1700 (COOMe) cm^{-1}. δ ^{1}H (CDCl$_3$): 3.29 (t, 3H), 3.38 (t, 3H), 3.52 (q, 2H), 3.55 (q, 2H), 3.96 (s, 3H), 7.58 (d, 1H), 7.75–7.88 (m, 1H), 8.12 (d, 1H). δ ^{13}C (CDCl$_3$): 14.3; 15.6; 41.8; 44.5; 46.3; 128.6; 131.1; 137.2; 143.1; 146.3; 163.1; 166.1. EIMS $m/z = 237.83$ (M+H)$^+$.
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17. 4-Chloro-6-(*N*,*N*-diethylcarbamoyl)pyridine-2-methylcarboxylate (**4b**) IR (KBr) $\nu_{C=O} = 1680$ (CONEt$_2$), 1700 (COOMe) cm^{-1}. δ ^{1}H (CDCl$_3$): 1.26 (t, 6H), 3.34 (q, 2H), 3.48 (q, 2H), 3.93 (s, 3H), 7.79 (s, 1H), 8.06 (s, 1H). δ ^{13}C (CDCl$_3$): 13.2; 14.6; 42.0; 43.7; 45.2; 127.1; 127.4; 147.9; 150.5; 157.4; 166.5; 168.8. EIMS $m/z = 271.13$ (M+H)$^+$.
18. 4-Bromo-6-(*N*,*N*-diethylcarbamoyl)pyridine-2-methylcarboxylate (**4c**): IR (KBr) $\nu_{C=O} = 1680$ (CONEt$_2$), 1700 (COOMe) cm^{-1}. δ ^{1}H (CDCl$_3$): 1.27 (t, 6H), 3.39 (q, 2H), 3.54 (q, 2H), 3.98 (s, 3H), 8.00 (s, 1H), 8.28 (s, 1H). δ ^{13}C (CDCl$_3$): 13.5; 15.3; 42.1; 44.3; 54.4; 128.6; 131.1; 137.2; 147.1; 154.3; 162.2; 165.9. EIMS $m/z = 316.29$ (M+H)$^+$.
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20. 4-Chloro-6-(3-oxo-3-phenylpropionyl)pyridine-2-carboxylic acid methyl ester (**6b**): IR (KBr) $\nu_{C=O} = 1725$ (COOMe), 1690 (COCH$_2$COPh) cm^{-1}. δ ^{1}H (CDCl$_3$): 3.71 (s, 5H), 7.10–7.29 (m, 3H), 7.72 (d, 2H), 7.86 (d, 1H), 7.85 (d, 1H). δ ^{13}C (CDCl$_3$): 54.9; 95.9; 126.9; 129.2; 129.4; 130.4; 134.8; 136.6; 148.5; 150.6; 155.9; 166.0; 182.9; 188.7. EIMS $m/z = 317.8$ (M$^+$). Anal. calcd for C$_{16}$H$_{12}$ClNO$_4$: C, 60.48; H, 3.81; N, 4.41; found: C, 60.42; H, 3.90; N, 4.32.