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Preparation of substituted tris(2-pyridyl)methanol derivatives as mimics of the metal binding site of carbonic anhydrase.

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Abstract

A series of novel mono-substituted and symmetrically tri-substituted tris(2-pyridyl)methanols have been prepared in a one-step reaction from the corresponding 2-bromopyridines. Metal complexes of these compounds and their further functionalised derivatives are of interest as carbonic anhydrase (CA) mimics.

Keywords: Pyridines; Lithiation; Synthesis; Complexes.

Background

Recently, zinc (II) and cobalt (II) complexes of tripodal ligands containing nitrogen donor atoms have received much attention as possible carbonic anhydrase (CA) mimics. Tris-pyrazoyl borates [1], tris-imidazoylphosphines [2], tris-imidazoylcarbinols [3], and tris-iminocyclohexanes [4], have been investigated by various workers. We are interested in incorporating such tripodal ligands within larger arrays (particularly within dendrimers) to generate functional CA analogues and for this reason require ligands containing suitable substituents by which further functionality might be introduced. We were surprised to find that although tris-(2-pyridyl)methanol was first reported almost 50 years ago [5], with a few exceptions [6], substituted derivatives are almost unknown. In particular, no simple route exists to the symmetrically tri-substituted derivatives that we desired for our studies.

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Mono-substituted compounds[1]

By substituting functionalised 2-bromopyridines[2] into the procedure of Wibaut *et al* [5] we readily prepared a series of mono-substituted compounds in yields comparable to that reported for the unsubstituted compound (Scheme 1 and Table 1). This indicated that introduction of substituents had no detrimental effect on the yields obtained and also that the 2-lithio anions of the substituted pyridines could be generated without any complications.

Scheme 1

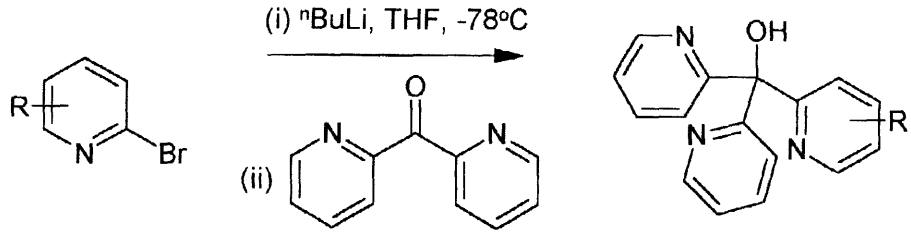

Table 1

Preparation of mono-substituted tris(2-pyridyl)methanols.

Entry Number	2-Bromopyridine	Isolated yield
1	R = H	38%[a]
2	R = 4-Me	46%
3	R = 5-Me	43%
4	R = 6-Me	55%
5	R = 4-(4',4'-dimethyloxazolin-2-yl)	40%
6	R = 6-Et	42%
7	R = 6-Ph	46%

[a] A yield of 41% has been reported in reference [7].

Symmetrically tri-substituted compounds

The preparation of symmetrically tri-substituted compounds is less straightforward. The only literature example is a 6,6',6"-tricyano derivative [6] prepared from reaction of cyanide with tris(2-pyridyl)methanol; this method is both low yielding and limited to a small range of possible substituents. A stepwise route could be adopted *via* preparation of the bis-substituted ketone from the 2-cyanopyridine [12] and 2-lithiopyridine and subsequent reaction with the substituted 2-lithiopyridine. For the unsubstituted system, all three steps are relatively low yielding - using the values reported in references [5], [7] and [12] we calculated that the overall yield for this

[1] All new compounds gave satisfactory ^{1}H NMR spectra, mass spectra and elemental analyses.

[2] 2-Bromopyridine and 2-bromo-5-methylpyridine were obtained commercially. The 4-methyl, 6-methyl and 6-ethyl derivatives were prepared from the corresponding amines via a diazotisation procedure [8]. The 6-phenyl compound was prepared from 2-phenylpyridine as reported in the literature [9]. The oxazolinyl derivative was prepared from 6-bromoisonicotinic acid [10] and 2-amino-2-methylpropan-1-ol using a literature procedure [11].

three step sequence would be in the region of 14%. While such a sequence may have greater versatility - for example, it would enable the preparation of systems bearing a different substituent on each of the three pyridine rings - it is a rather cumbersome synthesis when the symmetrically tri-substituted compound is required. We have therefore developed a procedure whereby tri-substituted compounds can be prepared in a one-pot reaction by treatment of a substituted 2-lithiopyridine with bis(trichloromethyl) carbonate (triphosgene)[3] (Scheme 2 and Table 2).

Scheme 2

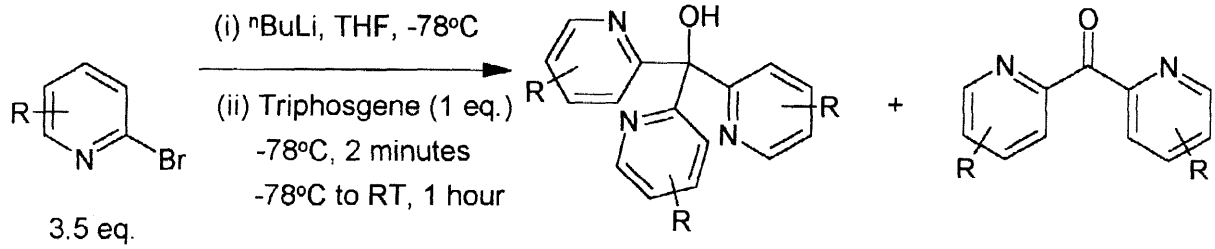

Table 2

Preparation of symmetrically tri-substituted tris(2-pyridyl)methanols.[4]

Entry number	2-Bromopyridine	tris(2-pyridyl)methanol yield[a]	bis(2-pyridyl)ketone yield[a]
8	R = H	16%	[b]
9	R = 4-Me	16%	24%
10	R = 5-Me	24%	28%
11	R = 6-Me	14%	52%
12	R = 4-(4',4'-dimethyloxazolin-2-yl)	16%	20%
13	R = 6-Et	12%	61%
14	R = 6-Ph	12%	40%

[a]All values are isolated yields.

[b]Not isolated.

Six tri-substituted derivatives were prepared. In each case, a significant amount of the bis(2-pyridyl)ketone was also formed. In general, compounds containing 6-substituents resulted in lower yields of tris(2-pyridyl)methanol which we attribute to steric factors, but higher overall yields of isolated products which we attribute to a reduction in competing addition reactions at

[3] The use of other carbonyl equivalents diethyl carbonate and 1,1'-carbonyldiimidazole (CDI) resulted in no isolable amounts of either tris(2-pyridyl)methanol or bis(2-pyridyl)ketone.

[4] **Sample Procedure (Entry 10):** To a solution of 5-methyl-2-bromopyridine (2.029 g, 11.80 mmol) in dry THF (10 mL) at -78°C under N_2 was added a solution of nBuLi (1.6M in hexanes, 8.85 mL, 14.2 mmol) dropwise over 10 minutes. After stirring for 5 minutes at -78°C, a solution of triphosgene (1.00 g, 3.37 mmol) in dry THF (2 ml) was added over 1 minute. Stirring was continued at -78°C for 2 minutes before removal of the cold bath. After the mixture had warmed to room temperature, 2N H_2SO_4 (5 mL) was added and shaken well. The organic layer was separated and further extracted with 2N H_2SO_4 (4 x 5 mL). The combined acidic extracts were neutralised (40% aqueous KOH) and extracted with diethyl ether (4 x 50 mL). The combined ether extracts were dried (Na_2SO_4), filtered and evaporated. The crude oil was purified by flash chromatography on silica gel eluting with a 3:1 CH_2Cl_2 / acetone mixture to give tris(2-(5-methylpyridyl))methanol (0.252 g, 24%) and bis(2-(5-methylpyridyl))ketone (0.200 g, 28%).

the pyridine C-6 position. Use of a greater excess of the 2-lithiopyridines did not appear to improve the yield of tris(2-pyridyl)methanols. Both compounds were purified and isolated via flash chromatography on silica gel. The substituted ketones provide a useful intermediate in the preparation of mixed-substituent tris(2-pyridyl)methanols. It seems likely that the final reaction between the ketone and 2-lithiopyridine is the limiting step and is consistent with the relatively low yields in Table 1 and the literature [7].

The new ligands prepared are currently being used in our investigation of CA mimics. In particular, compounds containing 6-substituents are of interest because they enable the simulation of the hydrophobic cavity of the enzyme where the metal co-ordinating site is isolated from the bulk solvent as well as preventing dimerisation reactions that lead to inactive species [4, 13]. Further elaboration of the substituents will lead to incorporation of the ligands into macromolecular structures that simulate the larger scale environment of the active site in the enzyme.

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