Synthesis of 'Crown Ether' Macrocyclic Bislactones Using Caesium Carboxylates of Pyridine and of Benzene Dicarboxylic Acids

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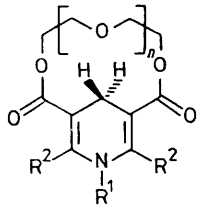
Summary The dicaesium salts of pyridine-3,5-dicarboxylic acids and of the benzene dicarboxylic acids react with the dibromides derived from a variety of polyethylene glycols to afford macrocyclic bislactones.

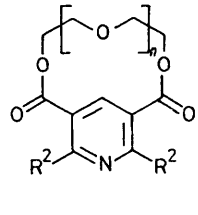
FOR some time we have been investigating the hydride donating abilities of 'Hantzsch' 1,4-dihydropyridines bridged through the carboxylic acid groups with a polyethylene glycol chain.[1] Enhanced hydride donating ability (towards phenacyl sulphonium salts) was found for (**1b**; $n = 3$). This compound was prepared from (**1a**), which was obtained in *ca.* 20% yield by a 'Hantzsch'-type ring closure.[1c] Attempts to extend this 'Hantzsch' approach to examples with $n=3$, which are needed for complexing ability–reactivity studies, have met with only limited success. Moreover, attempts to modify this approach to give dihydropyridines devoid of substituents at 2,6-positions (*i.e.*, **1c**), a change which should affect the redox potentials of the systems,[2] have shown little promise.†

To circumvent these problems, direct synthesis of the pyridines (**2a**,**b**) was considered *via* the readily available dicarboxylic acids.[3] Wang *et al.*[4] reported recently a versatile esterification method for preparing, in solution, amine protected amino-acids and peptides *via* reaction of the caesium carboxylates with reactive alkyl halides. Straightforward adaptation of this procedure to the reaction of pyridine-3,5-dicarboxylic acid and 1,11-dibromo-3,6,9-trioxoundecane (**3**; $n=3$) gave, in 85% yield, (**2b**; $n=3$) [equation (1)].



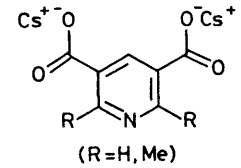
(1)

a; $R^1 = H$, $R^2 = Me$
b; $R^1 = R^2 = Me$
c; R^1 = alkyl, $R^2 = H$

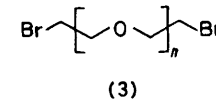


(2)

a; $R^2 = Me$
b; $R^2 = H$



(R = H, Me)



(3)

(2) + 2CsBr (1)

† Eisner and Kuthan (U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1) reported (experimental details not available) that methylpropiolate and tetramethylenehexamine provide 3,5-di(methoxycarbonyl)-1,4-dihydropyridine. We have been unable to reproduce this result.

TABLE

Entry	Carboxylate	M^+	n	Yield (%)[a]	Product	M.p. (°C)	Purification method[b]
A(i)	C_5H_3N-3,5-$(CO_2^-)_2$	Cs^+	3	75(85)	(**2b**; n=3)	94·5—96·5	1
A(ii)	"	Rb^+	"	45	"	"	"
A(iii)	"	K^+	"	15	"	"	"
A(iv)	"	Na^+	"	5	"	"	"
B(i)	"	Cs^+	2	20	(**2b**; n=2)	128—130	3
B(ii)	"	"	3	75(85)	(**2b**; n=3)	94·5—96·5	1
B(iii)	"	"	4	(90)[c]	(**2b**; n=4)	53—57	2
B(iv)	"	"	5	30	(**2b**; n=5)	oil	2
C	"	Cs^+	3	70	(**2a**; n=3)	90—92[1]	1
D	C_5H_3N-2,3-$(CO_2^-)_2$	Cs^+	3	d			
E	C_5H_3N-2,6-$(CO_2^-)_2$	Cs^+	3	d			
F	C_5H_4N-3-CO_2^-	Cs^+	3	90[e]	(**4**)	oil	2
G	C_6H_4-1,5-$(CO_2^-)_2$	Cs^+	3	60	(**5**)	95·5—97·0	1
H(i)	C_6H_4-1,2-$(CO_2^-)_2$	Cs^+	2	20	(**6a**)	91·5—93·5	5
H(ii)	"	"	3	d	(**6b**)	—	—
I(ii)	C_6H_4-1,4-$(CO_2^-)_2$	Cs^+	3	d	—	—	—
	"	"	4	10	(**7a**)	110—111	4
	"	"	5	20	(**7b**)	oil	4

[a] Correct analytical data or exact mass determinations were obtained for new compounds unless otherwise stated. Spectral data agree with the proposed structures. Yields are of isolated product except when reported in parentheses in which case the yield was determined from integration of the ^1H n.m.r. spectrum of the crude reaction product. [b] See footnote ‡ in the text. [c] Material extremely difficult to purify; ^1H n.m.r., i.r., and mass spectral data are in agreement with the proposed structures. [d] Intractable mixture. [e] 24 h at room temperature; 2 equiv. of Cs salt.

The approach through the caesium salts has considerable generality as seen from the results listed in the Table. Cs^+ plays an irreplaceable role as compared with Na^+, K^+, and Rb^+ [Table, entries A(i—iv)] for the formation of (**2b**; n=3). Caesium is probably complexed more weakly than, for example, K^+ by (**2b**; n=3),[5] which suggests that it acts as a template in early stages of the ring closure.

As seen from the Table, this method can also be applied successfully to the benzene dicarboxylic acids. Yields have not been optimized for entries (G—I). Extensions of this method to the synthesis of other systems is currently being investigated as are the properties of these newly synthesized compounds.‡

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(4)

(5), *meta*
(6), *ortho*
(7), *para*

‡ The following general procedure is used. The bis-caesium salts are prepared following the described procedure (ref. 4). A well stirred heterogeneous mixture of the caesium salt (2 mmol) and the dibromide (2 mmol) in dimethylformamide (DMF) (150 ml, dried carefully before use) is held at 60—70 °C for 48 h. The temperature should not be allowed to go above 70 °C. The DMF is removed by distillation under reduced pressure and the residue is worked up by one of the following methods (listed in the Table).

Method 1: the residue is thoroughly extracted with Et_2O and the undissolved material is removed by filtration. The oil obtained after removal of the solvent is thoroughly extracted with boiling Pr^i_2O from which the product crystallizes on cooling. The procedure is repeated to obtain a maximum yield.

Method 2: the residue is thoroughly extracted with CH_2Cl_2 and the insoluble material is removed by filtration. The product is obtained from the CH_2Cl_2 extract by chromatography over silica gel (CH_2Cl_2–EtOAc, 40:60).

Method 3: Et_2O is used to extract the residue. After filtration and evaporation of the ether, the oil crystallizes on standing. Solid is filtered, washed with water and the washings are extracted with ether. After drying, the product is chromatographed over Al_2O_3 (CH_2Cl_2–EtOAc, 50:50). The combined products are recrystallized from water.

Method 4: the residue is extracted with Et_2O and the resulting oil is chromatographed over Al_2O_3 (Et_2O–EtOAc, 90:10). The product is recrystallized from Pr^i_2O.

Method 5: The residue is dissolved in dilute aqueous $NaHCO_3$ and is then extracted with Et_2O. Drying ($MgSO_4$) followed by removal of the ether leaves the crude product, which is recrystallized from MeOH–H_2O.

[1] (a) T. J. van Bergen and R. M. Kellogg, *J. Amer. Chem. Soc.*, 1976, **98**, 1960, 1962; (b) 1977, **99**, 3882; (c) *J.C.S. Chem. Comm.*, 1976, 965.
[2] K. E. Taylor and J. B. Jones, *J. Amer. Chem. Soc.*, 1976, **98**, 5689 and references cited therein.
[3] E. Brody and P. R. Ruby in 'Pyridine and Its Derivatives,' Pt. 1, ed. E. Klingsberg, Interscience, New York, 1960, p. 500.
[4] S-S. Wang, B. F. Gisin, D. P. Winter, R. Makofske, I. D. Kulesha, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, 1977, **42**, 1286 and references cited therein.
[5] R. M. Izatt, R. E. Terry, B. L. Haymore, L. D. Hansen, N. K. Dalley, A. G. Avondet, and J. J. Christensen, *J. Amer. Chem. Soc.*, 1976, **98**, 7620; R. M. Izatt, R. E. Terry, D. P. Nelson, Y. Chan, D. J. Eatough, J. S. Bradshaw, L. D. Hansen, and J. J. Christensen, *ibid.*, p. 7626; J. J. Dechter and J. L. Zink, *ibid.*, p. 845.