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DEPENDENCE OF RING SIZE ON CONDITIONS IN CYCLIZATION OF 4-METHYLAMINOBENZOIC ACID BY DICHLOROTRIPHENYL-PHOSPHORANE

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Abstract – 4-Aminobenzoic acid was effectively coupled by dichlorotriphenylphosphorane to give cyclized aromatic amides with various ring sizes. Major compounds were trimer and hexamer. The ratios and yields of the compounds obtained by the reaction depended on the reaction conditions.

INTRODUCTION

Macrocyclic structures with a cavity are often seen in compounds that have molecular recognition abilities.[1] Calixarenes[2] and cyclodextrins[3] are examples that have been extensively studied. A feature of these classes of compounds is a structure constructed by a repeated monomer unit, which can easily be synthesized by a single step reaction from an appropriate monomer. The main reason why such cyclic structure can be easily constructed from a monomer is because the linkage places two monomer units in the same direction. In the course of our studies on the stereochemistry of aromatic amides,[4] we found that a cyclic structure could easily be constructed using conformational alternation by *N*-alkylation of aromatic amides from *trans* to *cis*.[5] For example, 3-methylaminobenzoic acids were coupled with themselves by a one-pot reaction using tetrachlorosilane to give a mixture consisting mainly of 3 – 6mer of the monomer.[6] While searching for a mild coupling reagent to couple a carboxylic acid with an *N*-alkylated aniline with low nucleophilicity, we found that dichlorotriphenylphosphorane, which has been used for synthesis of acid chloride,[7] was highly effective in the one-step cyclization from *N*-alkylated anilines and benzoic acids in which this reagent is used.[8] Here we report the effect of the coupling

reagent and the reaction conditions on the yield and ring size of the cyclized compound using 4-methylaminobenzoic acid by dichlorotriphenylphosphorane.

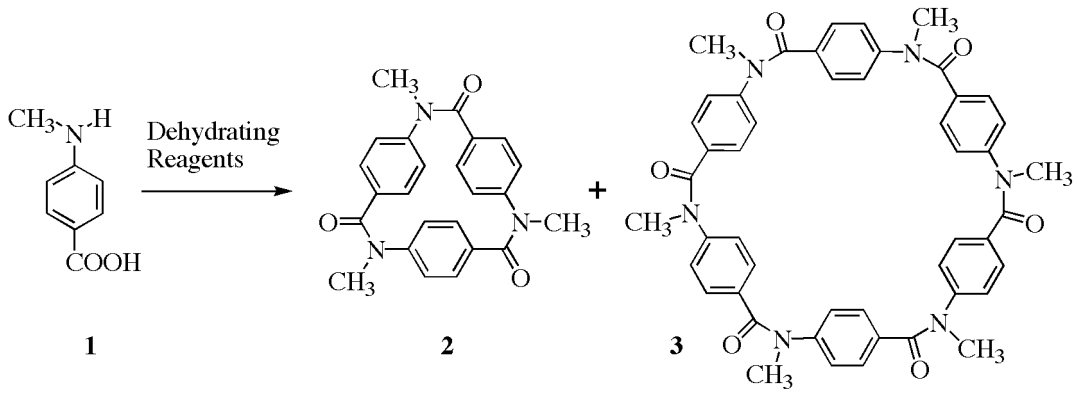
RESULTS AND DISCUSSION

Initially, we screened classical peptide coupling reagens[9] such as DCC and DCC with HOBt or HOAt in the cyclization of 4-methylaminobenzoic acid (Table 1), but obtained no cyclized amide in these reaction conditions (entries 1-3). The reaction using a peptide-coupling reagent for bulky or *N*-alkylated amino acid, PyBop[10] or CIP[11] gave only traces of a cyclic trimer at best (entries 4, 5), and HATU[12] gave none of cyclized compounds (entry 6). However, dichlorotriphenylphosphorane or dibromotriphenylphosphorane and pyridine produced cyclized amides with triphenylphophine oxide (entries 7, 8), in both cases giving almost the same amount of cyclic trimer and hexamer with a slight amount of cyclic tetramer; the best results from among these dehydrating reagents.

Next, we studied how conditions such as solvent, temperature and the presence or absence of additives in the cyclization using dichlorotriphenylphosphorane influenced the ring size of the cyclic amides obtained (Table 2). When $AgClO_4$ was added to the reaction conditions, the reaction became messy and no cyclized compound was observed (entry 1). When chloroform was used as the solvent instead of dichloromethane, more trimer and less hexamer were obtained (entry 2). With 1,1,2,2-tetrachloroethane, almost the same yield of trimer and less of the hexamer was obtained (entry 3). Heating was effective to proceed cyclization; the reaction in chloroform at reflux gave almost the same yield *without pyridine* (entry 4 *vs*. entry 2) and the reaction in 1,1,2,2-tetrachloroethane at 60 °C gave better yields both in trimer and hexamer *without pyridine* (entry 5 *vs*. entry 3). Finally, the highest yield of cyclic trimer was achieved at 120 °C in 1,1,2,2-tetrachloroethane (entry 6). In these cyclization reactions with heating, 2.4 equivalents of dichlorotriphenylphosphorane effectively completed the reaction, and surprisingly no other additives were needed.[8]

The reason why the yield of cyclic trimer and hexamer were much higher than those of other cyclic oligomers in the one-pot cyclization of 4-methylaminobenzoic acid could be because these conformations of the cyclic trimer and hexamer might be preferable in the cyclization, accounting for their crystal structures.[13,14] In the formation of the trimer, one conformation (the two terminal benzene rings located in *syn* conformation) out of the two possible conformations (*syn* or *anti*) is preferable in the

final amidation step. On the other hand, the chained hexamer at the final cyclization step could adopt the conformation where two open-ended trimers in *syn* conformation joined to each other at their ends.



1 **2** **3**

Table 1

entry	conditions[a]	yield[b] **2**	yield[b] **3**
1	DCC (1.0 eq.), THF, rt, 24 h	n.d.	n.d.
2	DCC (1.0 eq.), HOBt (1.0 eq.), DIEA (1.0 eq.), THF, rt, 24 h	n.d.	n.d.
3	DCC (1.0 eq.), HOAt (1.0 eq.), DIEA (1.0 eq.), THF, rt, 24 h	n.d.	n.d.
4	PyBOP (1.0 eq.), DIEA (1.0 eq.), THF, rt, 24 h	trace	n.d.
5	CIP (1.0 eq.), DIEA (1.0 eq.), THF, rt, 24 h	trace	n.d.
6	HATU (1.0 eq.), DIEA (1.0 eq.), THF, rt, 24 h	n.d.	n.d.
7	Ph_3PCl_2 (2.0 eq.), CH_2Cl_2, 6 h, then pyridine, rt, 24 h	23 %	26 %
8	Ph_3PBr_2 (2.0 eq.), CH_2Cl_2, 6 h, then pyridine, rt, 24 h	18 %	22 %

a) 0.1 M. b) Isolated yield. n.d.: not detected.

Table 2

entry	conditions[a]	yield[b] **2**	yield[b] **3**
1	Ph_3PCl_2 (2.0 eq.), CH_2Cl_2, $AgClO_4$ (4.0 eq.), 1 h, then pyridine, rt, 24 h	n.d.	n.d.
2	Ph_3PCl_2 (2.4 eq.), $CHCl_3$, 6 h, then pyridine, rt, 24 h	32 %	14 %
3	Ph_3PCl_2 (2.4 eq.), $(CHCl_2)_2$, 6 h, then pyridine, rt, 24 h	22 %	6 %
4	Ph_3PCl_2 (2.4 eq.), $CHCl_3$, reflux, 4 h	31 %[c]	23 %
5	Ph_3PCl_2 (2.4 eq.), $(CHCl_2)_2$, 60 °C, 4 h	40 %	16 %
6	Ph_3PCl_2 (2.4 eq.), $(CHCl_2)_2$, 120 °C, 5 h	57 %	16 %

a) 0.1 M. b) Isolated yield. c) Ref. 8. n.d.: not detected.

CONCLUSION

Cyclic trimer and hexamer were effectively obtained by a one-pot coupling using dichlorotriphenylphosphorane as a dehydrating reagent. The ratio of the cyclic amides depended on the conditions, especially on solvents and temperature. We believe this phenomenon in the synthesis of macrocyclic aromatic amides is applicable to providing various sizes of functionalized cyclic aromatic amides.

EXPERIMENTAL

Analytical data and X-Ray crystallographical analysis of cyclic trimer (**2**) has been reported previously.[8,13]

General procedure for cyclization of 4-methylaminobenzoic acid using dichlorotriphenylphosphorane.

Procedure A (Table 1: entries 7, 8; Table 2: entries 2, 3): To a solution of 4-methylaminobenzoic acid (76 mg, 0.5 mmol) in dry solvent (5 mL) under argon was added dichlorotriphenylphosphorane (400 mg, 1.2 mmol) with stirring for 6 h. Then, pyridine (0.19 mL, 2.4 mmol) was added and the mixture was stirred at rt for 24 h. The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was washed with 2 N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and then evaporated to give a crude product that was purified by silica gel column chromatography (eluent: AcOEt : dichloromethane : MeOH = 28 : 70 : 2).

Procedure B (Table 2: entries 4-6): To a solution of 4-methylaminobenzoic acid (76 mg, 0.5 mmol) in dry solvent (5 mL) under argon, dichlorotriphenylphosphorane (400 mg, 1.2 mmol) was added with stirring and the mixture heated for several hours (see Table 2). The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was washed with 2 N HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and then evaporated to give a crude product that was purified by silica gel column chromatography (eluent: AcOEt : dichloromethane : MeOH = 28 : 70 : 2).

Hexamer (3): mp >300 °C; IR (KBr) ν= 2920, 1640, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.45 (s, 18H, CH_3), 6.79 (δ, 12H, *J* = 10.6 Hz, ArH), 7.02 (δ, 12H, *J* = 10.6 Hz, ArH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 38.5, 126.1, 130.1, 133.6, 145.9, 168.2; Anal. Calcd for $C_{48}H_{42}N_6O_6 \cdot 2H_2O$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.34; H, 5.36; N, 9.78; FAB-HRMS m/z found 799.3269, calcd for $C_{48}H_{43}N_6O_6$ m/z 799.3244; FAB-MS m/z 799 $(M+H)^+$.

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