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SYNTHESIS OF DOUBLE-ARMED AZAOLIGOCYCLES BASED UPON HIGH PRESSURE AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

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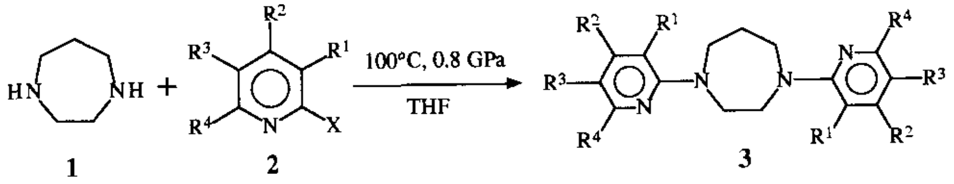
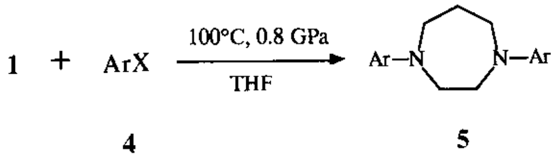
Abstract—A variety of double-armed azaoligocycles were prepared through high pressure S_NAr reactions (0.8 GPa, 100°C) of homopiperazine with five- and six-membered heteroaromatic halides, the yields being good to excellent when the halides are activated by electronic effects.

Some armed azamacrocycles have proved to exhibit specific binding and transport abilities for metal cations.[1] In contrast with armed azamacrocycles, azaoligocycles potentially possess specific binding and transport abilities particularly for metal cations of small size. Indeed, the 9-membered triazamacrocycle possessing pyridine-pendant arms has proved to be a Na^+ ion-selective ionophore.[2] Furthermore, heterocycles that are linked directly together, e.g. "linked heterocycles" often have valuable applications in agriculture and pharmacology.[3] Previously, we and Ibata's group have demonstrated that S_NAr reactions that normally proceed addition-elimination mechanism become practical when performed at high pressures.[4,5] Therefore, as an initial stage of our project on armed oligocycles as well as armed macrocycles that are directly connected with aromatic heterocycles, the high pressure S_NAr reactions were applied to bisheteroarylation of homopiperazine.

In a typical experiment, a mixture of homopiperazine (1, 4 mmol), halogenoheterocycle (2 or 4, 9.2 mmol), and triethylamine (13.3 mmol) was diluted with tetrahydrofuran in an 8 ml of polytetrafluoroethylene (PTFE) tube that was compressed to 0.8 GPa and heated to 100°C for 2-5 days. After evaporation of triethylamine and solvent, the resultant mixture was chromatographed on SiO_2. The results are summarized in Tables 1 and 2.





Among the 2-halogenopyridines, 2-fluoropyridine gave the best result (entries 1-3) being in accordance with the general rule that the relative reactivities with respect to S_NAr_{AE} displacement increase in the order Cl<Br<I<F.[6] 2-Chloropyridine was almost inert to 1 in refluxing toluene for 4 days, whereas 2-fluoropyridine with 1 gave the bispyridinohomopiperazine (3) in 12 % yield.

As expected in terms of mesomeric stabilization of Meisenheimer intermediate, the 2-chloropyridines (2) having an electron-withdrawing substituent at alpha or gamma position with respect to a leaving chloro atom produced the good yields of 3 (entries 4-7). In contrast, the process is slightly facilitated by an additional electron-withdrawing group beta to the chlorine (entries 7-9).

Reactivity increases in the diazines as compared with pyridines.[7] This is not the case for 2-chloropyrimidine (entry 10). 1 was inert to 5-bromopyrimidine in which both ring nitrogen atoms are located at beta position to the leaving group (entry 11).

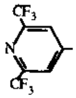
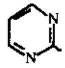
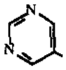
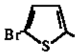
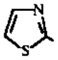
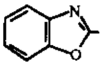
Because of their pi-excessive nature, halogenofuran and -thiophene are much less reactive than halogenopyridine. Indeed, iodo- and bromothiophene did not react under the present conditions (entries 12-14). Halogen atom in the 2-position of azoles is considerably activated toward S_NAr reactions by the neighboring nitrogen atom. Thus, 2-bromothiazole with 1 gave the double-armed azacycle (5) in

Table 1. Double-Armed Azaoligocycles **3**

Entry	Halogenopyridine **2**					Reaction Time	Yield of **3**	mp
	R^1	R^2	R^3	R^4	X	(d)	(%)	(°C)
1	H	H	H	H	Cl	4	57[a)]	67-68
2					Br	4	96	
3					F	4	100[b)]	
4	H	H	CF_3	H	Cl	4	89	133-134
5	H	H	NO_2	H	Cl	2	84	262-264
6	CF_3	H	Cl	H	Cl	4	84	oil
7	H	CF_3	CF_3	H	Cl	4	51	207-208
8	H	CF_3	H	CF_3	Cl	3	55	87-88

a) Only a trace amount of the product was obtained in refluxing toluene for 4 days. b) A 12% yield of the product in refluxing toluene for 4 days.

Table 2. Double-Armed Azaoligocycles **5**

Entry	Halogenoheterocycles **4**		Reaction Time	Yield of **5**	mp
	Ar	X	(d)	(%)	(°C)
9		Cl	4	58	242-243
10		Cl	4	44	96-97
11		Br	5	0	——
12		Br	5	0	——
13		Br	5	0	——
14		I	4	0	——
15		Br	4	92	66-67
16		Cl	4	69	207-208

92 % yield (entry 15); the sulfur atom may cause additional stabilization of the Meisenheimer intermediate by involvement of its d-orbitals.

Studies on transport properties of these armed azaoligocycles and related ionophores are envisaged.

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